Hoyle Leigh · Jon Streltzer
Editors

Handbook of Consultation-Liaison Psychiatry

2nd Edition

Springer

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For Vinnie and Sheila

Preface

This *Handbook of Consultation-Liaison Psychiatry* is intended for psychiatrists, psychiatry residents, primary care physicians, medical students, and all members of health care professions who are interested in psychiatric approaches to patients in medical settings and with medical conditions.

The practice of consultation-liaison psychiatry must be practical and flexible. It has to provide immediate management of an agitated or suicidal patient, it has to deal with gravely ill patients wishing to sign out against medical advice, and it has to deal with an impasse in communication between the patient and the doctor. The consultation-liaison psychiatrist must be knowledgeable and comfortable in dealing with serious as well as not-so-serious medical diseases.

The consultation-liaison setting is widely recognized as an ideal site for training not only for psychiatry residents but also for medical students, primary care residents, and allied health professionals. It is, of course, the primary training site for fellowship training in consultation-liaison psychiatry (psychosomatic medicine). This handbook is intended to be a practical guide for all of them.

The recent designation of *psychosomatic medicine* as a subspecialty of psychiatry has stimulated interest in the interface between psychiatry and medicine. What is the relationship between consultation-liaison psychiatry and psychosomatic medicine? The field of psychosomatic medicine was never intended to be specific to psychiatry or any one discipline. Indeed, in many countries, psychosomatic medicine is most closely identified with other specialties of medicine. Consultation-liaison psychiatry is the clinical application of psychiatry and psychosomatic principles in medical and surgical settings. Consultation-liaison psychiatry is, indeed, a specialty in its own right, with a unique field of knowledge and specific clinical skills beyond that of general psychiatry. This book attempts to describe that knowledge base in a practical and useful manner consistent with the clinical orientation of consultation psychiatry. As discussed in Chap. 1, consultation-liaison psychiatrists have a strong interest in "mind-body" medicine, but it is our belief that "consultation-liaison" psychiatry best denotes the type of practice we describe in this book.

In Chap. 4, we list the common reasons for consultation request and their immediate management. This chapter serves as a portal from which diagnostic syndromes branch out for further evaluation and treatment. Chapter 5, dealing

with psychiatric evaluations in the emergency setting, emphasizes the importance of *the patient's story*, which is a must in understanding the patient.

We believe that *diagnosis* is essential in understanding and treating the illness. In Chap. 7, we discuss the concept of psychiatric diagnosis in some detail, and show that psychiatric conditions are a continuum of evolutionarily adaptive phenomena, and that major psychiatric syndromes are best conceptualized as final common pathway syndromes reflecting a brain dysfunction. In medically ill hospitalized patients, symptoms of anxiety, depression, and psychosis may develop due to or be complicated by the added stress of illness and hospitalization. We adopt DSM-5 classification and nomenclature, which is far less categorical than DSM-IV, and recognizes that major psychiatric conditions are not mutually exclusive but can coexist, especially those with multiple contributions from both genetic influences, developmental influences, and medical diseases and substances. New chapters on adjustment disorders, PTSD, obsessive-compulsive disorders, dissociative disorders, and delirium and neurocognitive disorders have been added as well as a chapter on psychopharmacology in the consultation-liaison setting. Many chapters, especially chapters on psychiatric diagnosis, ethical issues, depression and bipolar disorders, heart disease and depression in the acute setting, among others, have been rewritten or extensively revised to reflect newer discoveries and insights.

Most of this book is written by the editors who have been involved in teaching consultation-liaison psychiatry for more than four decades.

More specialized chapters are written by international experts in the field and provide depth and variety.

This book is primarily for those who are interested in general psychiatry in general hospitals. Although some "subspecialties" in consultation-liaison psychiatry are covered in this book, others such as psychooncology, psychodermatology, and so forth are not included. Covering all areas relevant to CL psychiatry would render the book unwieldy and thus less useful as a clinical guide.

A major development in the USA since the publication of the first edition of the *Handbook* is the implementation of the Affordable Care Act, which encourages the integration of primary care and psychiatry, especially in the outpatient setting. The editors and three contributors, Drs. Lipsitt, Powsner, and Nair, have performed workshops on teaching psychiatry to primary care physicians at the annual meetings of the American Psychiatric Association for more than a decade. A chapter on the *integrated care model* with primary care is added in this second edition.

Advances in genetics, epigenetics, neuroscience, and neuroimaging are rapidly being incorporated in psychiatry. The effects of specific psychotherapy in specific brain areas are being investigated with functional brain imaging, and, soon, receptor-specific and gene-specific designer drugs may revolutionize psychopharmacology. Specific gene x environment interactions are being investigated that may reveal exactly how such interactions, with the

added ingredient of current stress, may result in health or resilience. Consultation-liaison psychiatry is ready to integrate these developments in caring for our patients in the general medical setting.

We are indebted to our students and colleagues who have stimulated and encouraged us to write this second edition of our book. We are grateful to Ms. Janice Stern of Springer for her support in all phases of this endeavor.

Fresno, CA, USA — Hoyle Leigh
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Part I

General Principles and Approaches: Nature, Evolution, and Practice of Consultation-Liaison Psychiatry

Nature and Evolution of Consultation-Liaison Psychiatry and Psychosomatic Medicine

1

Hoyle Leigh

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1.1 Definition

Consultation-liaison (CL) psychiatry refers to the skills and knowledge utilized in evaluating and treating the emotional and behavioral conditions in patients who are referred from medical and surgical settings. Many such patients have comorbid psychiatric and medical conditions, and others have emotional and behavioral problems that result from the medical illness either directly or as a reaction to it and its treatment.

Psychosomatic medicine refers to the study of "mind–body" relationship in medicine. Investigators in psychosomatic medicine have historically been interested in the psychosomatic aspects of medical patients, and were pioneer practitioners of CL psychiatry.

1.2 Ancient Civilizations

Imhotep, court physician and architect to King Djoser (2630–2611 BCE) of Egypt, built the Step Pyramid in Sakkhara, Egypt, some 4500 years ago, as a medical instrument to keep the king's body through eons until his soul returned, a truly "psychosomatic" instrument. This pyramid is the oldest pyramid still standing, and Imhotep was deified as god of medicine. Ancient Chinese and Indian medicine was inherently "psychosomatic" in that the psyche and the soma were seen to be intrinsically interconnected. In Chinese medicine, excesses or deficiencies in

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seven emotions—joy, anger, sadness, grief, worry, fear, and fright—were commonly considered to cause disease (Rainone 2000). In Vedic medicine, certain personality components were considered to reside in particular organs, for example, passion in the chest and ignorance in the abdomen, and powerful emotions may cause peculiar behavior.

Hippocrates (470–370 BCE) was perhaps the first physician to systematize clinically the notion that psychological factors affect health and illness. In a famous, what might now be called "forensic psychiatric" opinion, Hippocrates defended a woman who gave birth to a dark-colored baby on the grounds that her psychological impression on seeing an African was sufficient to change the color of her fetus (Zilboorg 1941). Hippocrates was an excellent clinical observer of psychiatric manifestations of medical disease as shown by his detailed descriptions of postpartum psychosis and delirium associated with tuberculosis and malaria (Zilboorg 1941). Hippocrates condemned the prevailing view of epilepsy as a "sacred" disease, holding that it was a disease like any other. Though his theory of the "wandering uterus" underlying hysteria lacked scientific foundation, Hippocrates' humoral theory of disease anticipated present-day neurotransmitters. His emphasis on climate, environment, and lifestyle in health and illness, together with his awareness of the role of psychological factors in physical health and his belief in biologic/physiologic explanations of pathogenesis, entitle him to the title of not only the father of medicine but also the father of psychosomatic medicine and the biopsychosocial approach.

With the descent of the Dark Ages, a tyrannical religious monism attributing mental and physical illness to witchcraft, and divine retribution stifled scientific inquiry. A textbook for the diagnosis (torture) and treatment (execution) of witches was the *Malleus Maleficarum* (The Witch's Hammer, 1487) written by two Dominican monks, James Sprenger and Henry Kramer, and prefaced with a bull from Pope Innocent VIII.

1.3 Mind–Body Philosophy Through the Nineteenth Century

The Hippocratic tradition in medicine was revived with the Renaissance and nourished by the Enlightenment. The French mathematician and philosopher René Descartes (1596–1650) proposed that the human body was like a machine, subject to objective investigation, while the soul or mind was a separate entity that *interacted* with the body in the pineal gland and that it was in the domain of theology and religion. This *mind–body dualism* facilitated the scientific study of the body at the expense of such studies of the mind. A number of competing and complementary theories, briefly described below, have been proposed since then to attempt to explain the nature of mind and body/matter.

Benedictus de Spinoza (1632–1677), a Dutch lens crafter and philosopher, proposed a monism called *double aspect theory*, that is, the mental and physical are the two different aspects of the same substance, which in his view was God. Gottfried Wilhelm Leibniz (1646–1716) proposed *psychophysical parallelism*, that is, mind and body exist in parallel harmony predetermined by God from the beginning. *Immaterialism*, as advocated by George Berkeley (1685–1753), declared that existence is only through perception of the mind, that is, the body is in the mind. On the opposite pole is *materialism*, which holds that matter is fundamental and that what we call mind is a description of a physical phenomenon. Julien Offroy de la Mettrie (1709–1751) advocated that human souls were completely dependent on the states of the body and that humans were complete automata just like animals as proposed by Descartes.

Epiphenomenalism, proposed by Shadworth Holloway Hodgson (1832–1912), an English philosopher, postulates that the mind is an epiphenomenon of the workings of the nervous system. Mind and emotions, being epiphenomena, cannot affect the physical, just as a shadow cannot affect

a person. Thomas Henry Huxley (1825–1895) popularized this view and placed it in an evolutionary context. *Double aspect monism*, proposed by George Henry Lewes (1817–1878), postulates that the same phenomenon, if seen objectively, is physical, and, if seen subjectively, is mental. William Kingdon Clifford (1845–1879) coined the term *mind-stuff theory*. In this theory, higher mental functions, such as consciousness, volition, and reasoning, are compounded from smaller "mind-stuff" that does not possess these qualities, and even the most basic material stuff contains some "mind-stuff" so that compounding of the material stuff would produce higher order "mind-stuff." This theory holds psychical monism—mind is the only real stuff and the material world is only an aspect in which the mind is perceived.

In spite of strong monistic trends, the major trend in medicine and psychiatry through the nineteenth and twentieth century has remained dualistic and interactional, that is, how the mind affects the body and vice versa. Johann Christian Heinroth (1773–1843) coined the term *psychosomatic* in 1818 in the context of psychogenesis of physical symptoms. Psychosomatic relationship in the form of hypnosis was demonstrated and exploited by Anton Mesmer (1734–1815), though he mistakenly claimed it to be magnetic in nature ("animal magnetism"). Hypnosis was revived as a subject of medical investigation, diagnostics, and treatment by two competing schools, one at the Salpetriere Hospital in Paris headed by the neurologist, Jean-Martin Charcot (1825–1893), and the other at the university in Nancy, France, led by the internist, Hippolyte Bernheim (1840–1919). Charcot believed that hypnotizability was a result of brain degeneration in hysteria, while Bernheim and the Nancy school (including Ambroise-Auguste Liebeault and Pierre Janet) believed that psychological suggestion underlay the hypnotic phenomena.

1.4 Psychoanalytic Theory

Sigmund Freud (1856–1939) learned hypnosis to treat hysteria under Charcot. Freud gave up hypnosis in favor of free association, and with this tool systematically investigated and proved the psychogenesis of somatic symptoms by reversing them with successful treatment. Franz Alexander (1891–1964) was a student of Sigmund Freud who emigrated to the USA and founded the Chicago Institute of Psychoanalysis in 1932. Alexander psychoanalyzed patients suffering from a variety of somatic illnesses, and formulated that there were seven diseases that were particularly psychosomatic: essential hypertension, peptic ulcer, thyrotoxicosis, ulcerative colitis, neurodermatitis, rheumatoid arthritis, and bronchial asthma. He postulated that specific psychological conflicts were associated with specific autonomic activation, resulting in psychosomatic disease (e.g., in peptic ulcer, repressed dependency needs stimulate gastric secretion causing ulceration). This is called the *specificity theory* of psychosomatic medicine. Flanders Dunbar (1902–1959), a contemporary of Alexander, believed that psychosomatic illnesses were associated with certain personality profiles and constellations rather than specific conflicts.

Peter Sifneos and John Nemiah (1971, 1973, 1996) proposed that psychosomatic disorders arose as a result of a difficulty in describing or recognizing one's own emotions, a limited fantasy life, and general constriction in the affective life, which they called *alexithymia*. The concrete mode of thinking associated with alexithymia is called *operational thinking* or *pensée opératoire*. Alexithymia is postulated to be related to primitive defenses of denial and splitting, and may be associated with a disturbance in cerebral organization.

Psychological defense mechanisms have been shown to be essential in modulating psychophysiologic arousal to stress.

During the latter half of the twentieth century, through the work of various investigators, specificity theory gave way to a field model of psychosomatic medicine in which biological constitution interacts with environment in the development of personality, which, in turn, interacts with current stress in health and disease (Mirsky et al. 1957; Leigh and Reiser 1992).

1.5 Studies on Stress

The American physiologist Walter Cannon (1871–1945) investigated the physiologic activation associated with the *fight–flight reaction* and the role of homeostasis in physiology. Hans Selye (1907–1982) systematically studied stress that led to the elucidation of the *general adaptation syndrome* through the activation of the hypothalamic–pituitary–adrenal (HPA) axis. Later in the twentieth century with the development of psychoneuroendocrinology and psychoimmunology, there has been an explosion of knowledge on the relationship between stress and all aspects of the human organism.

1.6 Biopsychosocial Model and Integrative Medicine

George Engel (1913–1999), a well-known psychosomatic investigator, coined the term *biopsychosocial model* (Engel 1977), as an alternative to the prevailing disease model in medicine that he called the biomedical model. While recognizing the contributions that the biomedical model made to the development of modern medicine, Engel objected to the "dogma" of the biomedical model on the grounds that it is reductionistic, mechanistic, and dualistic. Utilizing a general systems theory approach, the biopsychosocial model proposes that psychosocial factors influence the pathogenesis of all diseases. The biopsychosocial model has found wide acceptance among psychiatrists and medical educators.

In late twentieth century, the terms *behavioral medicine* and *integrative medicine* appeared. Behavioral medicine is practically indistinguishable from psychosomatic medicine except that, in treatment modalities, it tends to incorporate more behavioral techniques such as biofeedback. Integrative medicine strives to incorporate within the biopsychosocial model approaches derived from nonorthodox medicine such as *alternative* and *complementary* medicine.

1.7 Evolution, Evolutionary Medicine, Memes

Charles Darwin (1809–1882) showed that species evolved through the process of natural selection (*The Origin of Species,* 1859). With modern advancements of genome analysis, it is now possible to calculate just how closely specific species are related. For example, humans and chimpanzees share almost 99 % of the genes. An evolutionary perspective of human illness is shedding light on why illnesses arise. As natural section confers advantage to traits only up to the reproductive age, healthy traits in the post-reproductive period are not selected for. The human body probably evolved so that it was best adapted for the Stone Age, when most adults died in their youth. With the prolongation of human life that came with the progress of civilization and medical advances, the human body is living long past what it was adapted for (Nesse and Williams 1996). The Stone-Age adapted human body may be ill-adapted for modern life, with its abundance of food, lack of physical exercise, and mental stresses, especially in the post-reproductive age. Evolutionary perspectives also may explain why certain genes that may cause vulnerability to potential mental illness, such as panic, may be adaptive under certain conditions found in evolutionary history (e.g., survival value, as in an overly sensitive smoke-detector).

Richard Dawkins, in his book *The Selfish Gene*, postulated a second replicator comparable to the gene, the *meme*, which is information that is replicated through imitation (Dawkins 1976). Later, memes are recognized as being cultural replicators, which may be stored outside of brains such as books and electronic media. Memes are considered to be like cultural DNA, containing cultural information that undergoes Darwinian natural selection.

Leigh extended the concept of memes as information contained in the potentiated neural connections in the brain, which may be absorbed from culture or generated from experience

(memory) or from genes (Leigh 2010). Leigh proposed that the environment does not affect genes directly, but mediated through these memes, and gene x meme x environment interaction is important in health and pathogenesis (Leigh 2012a, b). See Chapter 7 for more on this. According to this view, what we call "mind" is the brain's processing of the memes. As both genes (making up "body") and memes (making up "mind") are replicating packets of information that can be translated into codes (e.g., binary code), the distinction between the mind and body seems to be reduced to that of patterns.

1.8 Modern Psychosomatic Medicine

Advances in molecular genetics and imaging technology have elucidated the role of genes in our constitution, brain morphology, and behavior. Psychoneuroendocrinology and psychoneuroimmunology have elucidated the mechanism by which stress affects the human organism. Health and illness is now conceptualized as a result of the interactions among genes, early environment, personality development, and later stress (see Chap. 7). This interaction is in no small measure influenced by salutary factors such as good early nurturance and current social support. It is also clear that all illnesses are the results of this interaction, that there is no subset of illnesses that are any more psychosomatic than others. Nevertheless, the term *psychosomatic* continues to be used to denote studies and knowledge that place particular emphasis on psychosocial factors in medical illness.

Some consider *psychosomatic medicine* to denote an interdisciplinary approach that includes internists, oncologists, psychologists, etc., in contrast to *consultation-liaison psychiatry*, which is clearly a field within psychiatry.

There are a number of national and international "psychosomatic" organizations such as the American Psychosomatic Society, Academy of Psychosomatic Medicine, European Society of Psychosomatic Medicine, and International College of Psychosomatic Medicine, and "psychosomatic" journals such as *Psychosomatic Medicine, Psychosomatics, Journal of Psychosomatic Research,* and *Psychotherapy and Psychosomatics. General Hospital Psychiatry, International Journal of Psychiatry in Medicine,* and *Psychosomatics* are mainly consultation-liaison psychiatry journals. Most of the organizations and journals are interdisciplinary, participated in by members of various specialties and professions. In Europe and Japan, there is often a department of psychosomatic medicine in medical schools, apart from the psychiatry department. Such psychosomatic departments mainly deal with patients with psychophysiologic disorders, and may use complementary medicine techniques such as yoga and meditation.

In the USA, the term *psychosomatic medicine* is often used interchangeably with consultation-liaison psychiatry, and most CL psychiatrists practice in general hospital settings evaluating and treating psychiatric, emotional, and behavioral problems of medical patients. Research in the emotional aspects of specific medical patients gave rise to such fields as psychonephrology, psycho-oncology, and psychodermatology.

1.9 Consultation-Liaison Psychiatry Training and Psychosomatic Medicine as a Subspecialty

In the early part of the twentieth century, formal training in CL psychiatry began in a number of general hospitals, most notably at the University of Rochester under George Engel's direction and at the Massachusetts General Hospital (MGH) under Thomas Hackett's direction. Other notable training sites included University of Cincinnati, Montefiore Hospital–Albert Einstein Medical College in New York, and Yale–New Haven Hospital. The Rochester model was psychodynamically oriented, and trained both psychiatrists and internists in "liaison psychiatry." Liaison psychiatry emphasized the educational role, and the trainee was assigned to be a member of the primary medical team including making rounds together. The MGH model, in contrast,

emphasized the consultation aspect of training. The training programs were usually one to 2 years in duration. The CL training programs thrived during the 1960s and 1970s with the support of the National Institute of Mental Health and James Eaton, then head of its education branch. With the advent of managed care, however, "unbillable" liaison activity has faded to a large extent.

In 2003, the American Board of Psychiatry and Neurology (ABPN) approved the issuance of certificates in psychosomatic medicine. The Academy of Psychosomatic Medicine, an organization of CL psychiatrists, had been advocating the recognition of a subspecialty for CL psychiatry for some time. The executive summary of the proposal submitted to the ABPN states:

This application is in response to the growing body of scientific evidence demonstrating the high prevalence of psychiatric disorders in patients with medical, surgical, obstetrical, and neurological conditions, particularly for patients with complex and/or chronic conditions ("the complex medically ill"), and the critical importance of addressing these disorders in managing their care. [Psychosomatic medicine] psychiatrists would, therefore, constitute a group of individuals in psychiatry who have specialized expertise in the diagnosis and treatment of psychiatric disorders/difficulties in complex medically ill patients.

Obviously, this is a description of CL psychiatry. It is ironic that psychosomatic medicine, rather than CL psychiatry, is now recognized as a subspecialty of psychiatry as this designation leaves nonpsychiatric "psychosomaticists" in a Neverland.

1.10 Postscript: The Mind–Body Relationship Revisited in the Light of Modern Physics

The advances in medicine during the past several decades have been largely due to the elucidation of the mechanisms of pathogenesis based on genetics, the role of stress, and functional morphology. At a philosophical level, the *psyche* of psychosomatic medicine is understood as a label for brain function, particularly of the prefrontal cortex. While this Newtonian conceptualization of the mind works at a heuristic level, developments in modern physics may require us to reexamine this epiphenomenologic view of the mind.

Sperry (1969, 1980) proposes that mental phenomena have dynamic emergent properties arising from cerebral excitation, which are different from and more than material brain processes. Once generated from neural events, the higher order mental patterns and programs have their own subjective qualities, and progress, operate, and interact by their own causal laws that cannot be reduced to neurophysiology. Popper and Eccles (1981) maintain that mental processes are emergent relative to physical processes but believe in a dualism where the relationship of the brain to the body is that of the computer to the programmer, with the self-conscious mind playing a superior interpretive role.

Software written in binary language is both patterns of magnetic or optical properties as well as information, as defined with the interacting entity (without interaction there is no communication and no information). How do these entities become interactional (communicational)? Such interaction may be inherent in nature, as matter and antimatter "know" to annihilate each other upon encounter. Psychological awareness, although a subset of communication (interaction), might arise as an emergent phenomenon in a complex system of lower level interactions. Perhaps, as a critical mass of uranium will start a chain reaction, a "critical mass" of "proto-awareness" might result in a series of events leading to what we call awareness. To the extent that humans can hardly guess at the experience of "awareness" of beings such as photons, electrons, or, for that matter, dogs and chimpanzees, a true description of others' awareness may be an impossible task. Nevertheless, whether mental or physical, information is exchanged at all levels of organization in the cosmos.

Modern quantum theory presents us some intriguing notions of the mind. Quantum mechanics places the conscious observer at the center of reality. It is a quantum theory maxim

that "no phenomenon is a phenomenon unless it is an observed (or recorded, resulting in some irreversible change) phenomenon." Until observation has occurred, reality exists only as potentials or probabilistic waves. At the instant of observation, however, the wave function collapses into a reality according to the orthodox Copenhagen interpretation (Bohr 1958), or the universe splits into a number of possible universes according to the many worlds theory (Everett 1973; Wolf 1988). Consciousness, though arising as a result of brain processes, may be regarded as a cosmic process of creation (as the choices it makes are not locally determined but cosmically inherent) that produces events or reality (Stapp 1993). Such events, or the observation-induced collapse of the wave function into particles, seem to supersede the barriers of space-time.

Einstein proposed an experiment that tried to show what he considered to be a failing in quantum theory: Suppose two particles arising from an interaction are flying apart at the speed of light. According to quantum theory, if one quality of the particle is observed at a later time (say, a particular spin to the left) at one place by observer A, another observer B, observing the other particle (say, 20 light years away from observer A) must observe the complementary quality that is being observed by A. As it is purely by chance that A would observe the spin to the left, until the moment of observation of A, the spin of B is indeterminate. But once A is observed, B's spin can be nothing but "right," which Einstein considered to be "spooky action at a distance" at speeds faster than light—the Einstein–Podolsky–Rosen (EPR) paradox (Einstein et al. 1935). Later reformulation of the EPR experiment (Bell's inequality; Bell 1964) that was carried out by Aspect et al. (1982) proved the quantum theory predictions over Einstein's objections. It should be pointed out, however, that the quantum theory predictions do not presuppose "communication faster than light." It simply shows a cosmic connectedness or unity beyond space-time separation. One way of looking at this is to consider the two particles not to be separate at all, but a part of a whole (a single wave). This is compatible with modern superstring and Membrane or M-theories (Greene 2004).

In playing a role as to when and how observation is done, a series of conscious choices influence the way reality occurs (wave function collapses), or biases the number of split-off universes in a particular direction and therefore the probability that observers will find themselves in a universe in the chosen direction (in a many-worlds interpretation).

In this regard, it may be useful to ponder the role of the *observing physician* in the diagnosis and treatment of disease and in patient care. Will the act of diagnosis result in a collapse of the wave function? What is the role of a patient's *will* (or *choice*) *to live*, which may arise out of an interaction between the patient and the physician or the family and friends?

The practice of medicine may truly be a creative process. The interaction between the physician and the patient creates new paths of reality for both participants.

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The Function of Consultation-Liaison Psychiatry

2

Hoyle Leigh

Contents

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2.1 Introduction: The Dual Roles of the Consultation-Liaison Psychiatrist

There are two sets of dual interrelated roles that a consultation-liaison psychiatrist plays—consultation and liaison, and consultant and psychiatrist.

2.1.1 Consultation and Liaison

The term, consultation-liaison psychiatry, consists of the two primary functions—that of a psychiatric specialist providing expert advice on the consultee's patient and that of a liaison or link. Historically, the *liaison* function indicated that the psychiatrist was stationed in, and worked as a member of the medical team. Currently, the term has been expanded to indicate the educational, and facilitative function of the consulting psychiatrist, i.e., the linkage the psychiatrist provides the consultee between medical and psychiatric knowledge and skills on the one hand, and the facilitation of communication and understanding that the psychiatrist provides between the patient and the health care personnel. Thus, the liaison function is inherent in the comprehensive approach utilized by the psychiatric consultant to the patient and the health care system. Furthermore, increasingly, the liaison function includes administrative/legal services required of the consultant such as determination of decision making capacity, conservatorship, and involuntary hospitalization.

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2.1.2 Consultant and Psychiatrist

The CL psychiatrist is both a consultant and a psychiatrist, i.e., he or she has two masters, the requesting physician (consultee) and the patient. The obligation to the requesting physician often extends to serving the interests of the health care facility, and of society at large. Sometimes this duality leads to an internal conflict, such as in situations when the perceived interest of the patient conflicts with the desires of the consultee, the needs of the hospital, or of society (See Sect. 2.4, below).

CL psychiatry developed mainly in teaching hospitals with psychiatric residency training programs. There is usually a psychiatric consultation-liaison service in major teaching hospitals consisting of one or more full or part-time faculty, one or more psychiatry residents rotating to it, and, perhaps other staff and trainees, e.g., resident rotating from another specialty (most commonly internal medicine or family practice), medical student, psychiatric nurse, social worker, psychologist. Such CL services generally serve several explicit and implicit functions, i.e., *clinical, educational, administrative, and research*. In medical settings without a formal CL service, one or more full or part-time psychiatrists may be hired or designated to be a consultant for defined times. Such CL psychiatrists' function may be limited to the clinical and administrative functions.

2.2 Clinical Function: Consultation vs. Referral

The consultant's primary clinical function in an acute general hospital is to facilitate the *medical* treatment of the patient since that is the primary reason why the patient is in the hospital. In this sense, *consultation* should be distinguished from *referral*, usually seen in outpatient settings and chronic care facilities. In referral, the psychiatrist is asked to take over the psychiatric care of the patient if indicated, while in consultation, the psychiatrist renders an opinion or advice to the requesting physician. In addition to such advice and opinion, the requesting physician usually, and implicitly, requests collaborative care of the patient if indicated, which forms the basis of the direct rendering of treatment by the CL psychiatrist. Except in emergencies and psychotherapy inherent in diagnostic interview and facilitation of communication through meetings and phone calls with members of family and staff, direct treatment of patients including ordering medications should be with the explicit acknowledgement and cooperation of the consultee so as to prevent a diffusion of responsibility for direct care.

2.3 Educational Function

The liaison part of consultation-liaison psychiatry largely denotes its educational function. Education is for patients, requesting physicians, nursing staff, patient's families and friends, and the health care system. Examples of liaison education include teaching the psychological needs of patients based on their personality styles (see Chap. 25), the immediate management of psychiatric conditions (Chap. 4), use of psychotropic drugs (Chap. 8), determination of capacity to consent to procedures (Chap. 10).

The CL Service in teaching hospitals has formal educational functions in addition to the liaison function. They include the teaching of various trainees including psychiatric residents, residents from other departments such as internal medicine and family medicine, medical students, nursing and social work students, psychology interns, etc. The consultation-liaison setting is particularly well suited to teach medical students and primary care residents the aspects of psychiatry that would be most relevant to any physician. Members of the CL team may also give lectures and seminars or participate in the grand rounds of other departments as a part of the formal teaching function. A survey of primary care training programs showed that about 60 % of psychiatry departments provide didactic courses, 36 % participate in case conferences, and 15 % participate in joint rounds with primary care training programs (Leigh et al. 2006).

In the outpatient setting, the integrative care model (see Chap. 9) establishes formal teaching and supervision of mental health workers as a main function of the CL psychiatrist.

2.4 Administrative Function

The administrative functions of the CL psychiatrist are often mandated by either the government or the institution and often involve coercive measures such as emergency hold and involuntary hospitalization. Institutional rules usually mandate that an acutely suicidal or homicidal patient has to be evaluated by a psychiatrist, who will decide whether the patient should be placed on an emergency involuntary hold and be transferred to a psychiatric facility when medically stable. The CL psychiatrist may be required to evaluate a patient with suspected dementia and apply for a conservatorship.

The Risk-Management Department of the health care institution relies on the CL psychiatrist to evaluate patients' capacity to sign out against medical advice, to refuse medical/surgical procedures, and for general behavioral problems that disrupt the facility's function.

At times, the mandated administrative function may interact or interfere with the clinical function of the consultant, such as an emergency hold disrupting rapport with the patient. These conflicts can usually be resolved with skillful communication, but the CL psychiatrist must recognize and be comfortable with the multiple roles inherent in the function.

2.5 Research Function

The CL setting provides unique opportunities for research in the interface between psychiatry and medicine. Much of psychosomatic research in the twentieth century was done by CL psychiatrists. The CL setting gave rise to such subspecialty fields as psychonephrology, psychooncology, psychoimmunology, psychoendocrinology, and psycho-obstetrics and gynecology.

The role of psychiatric intervention in medical utilization has also been a productive field of research, and has provided evidence that psychiatric intervention actually reduces the cost of health care (Katon et al. 2005; Wells et al. 2005). In primary care settings, a collaborative care model in which the primary care physician works closely with a care manager (mental health worker) supervised by a CL psychiatrist is shown to be more effective than care as usual (Huijbregts et al. 2013).

This type of collaborative care with stepped up specialized care when needed is expected to be increasingly utilized with the implementation of the Affordable Care Act (ACA). (Unutzer et al. 2013; Unutzer and Park 2013a, b)

Affordable Care Act, aka Obamacare, promotes new programs and tools, such as health homes, interdisciplinary care teams, co-location of physical health and behavioral services, and collaborative care. (Mechanic 2013; Sorrell 2013) This provides fertile new venues for exciting research for the CL psychiatrist.

As the gene–brain–environment interaction becomes better understood, the CL setting may provide unique opportunities to study the role of epigenetics interacting with development in the selection or sequence of organ dysfunction (e.g., the subgenual cingulate cortex and the intestines, See Chap. 7) (Leigh 2011).

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The Why and How of Psychiatric Consultation

3

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3.1 Vignette

The reason for the psychiatric consultation simply stated, "Behavioral problem. Please evaluate."

When the consultant called the requesting physician, she said, "I don't really know what the problem is, but the nurses seem to be upset about the patient. The patient just had an MI but is doing OK. I think he may be a little depressed though because he is so quiet." When the consultant spoke with the nursing staff, the night nurse had written that the patient was observed crying in the middle of the night. Upon interview, the consultant was able to diagnose a recurrent major depression.

3.2 The Nature of a Psychiatric Consultation

Why is a psychiatric consultation generated? Specialty consultations are requested to obtain expert opinion in diagnosing and treating conditions that fall in the specialty area. As psychiatry deals with a vast area of human experience including cognition, emotion, and behavior, it is often difficult to know the exact reason for referral as the Vignette illustrates. Psychiatric consultation, like any other consultation, is not the primary reason for the patient's hospitalization or contact with the health care system, and not a few patients may be surprised that a psychiatric consultation has been requested. Primary physicians may also be reluctant to request a

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psychiatric consultation because of the perceived stigma. Therefore, requesting a psychiatric consultation on a patient requires a certain amount of motivation on the part of the referring physician. This motivation is often generated by a strain in the health care unit consisting of the doctors, the nursing staff, and allied professionals around the patient. Common causes of such strain are anxiety, communication difficulties, behavioral problems, and administrative/legal requirements.

While some consultations are generated at the patient's request, most psychiatric consultations arise out of discomfort on the part of one or more health care personnel, and recognizing this discomfort or strain is an essential part of a successful consultation. It is the consultant's job to ameliorate the strain so that the health care personnel can proceed to provide medical care without impediment.

As discussed in Chap. 2, the consultant serves two masters—the requesting physician/health care system (consultee) and the patient. The primary role of the consultant is to provide expert advice to the consultee so that medical/surgical treatment can be successfully rendered. A secondary role may be to provide direct psychiatric care for the patient with the consultee's agreement. In a collaborative care model, such as in medical homes, the consultant may supervise the ongoing mental health care provided by either the mental health care manager or the primary care physician (Croft and Parish 2013; Huang et al. 2013)

The psychiatric consultant is often the face of psychiatry in the health care facility. It is through her/him that the nonpsychiatric physicians form an impression about psychiatry, and, hopefully, learn psychiatric approaches and techniques. The educational function of the consultant psychiatrist, as discussed in the previous chapter, is an integral part of the practice of CL psychiatry.

3.3 How to Do a Consultation

3.3.1 Receive a Consultation Request

Most health care institutions have formal mechanisms for requesting a consultation—computerized request, written request, fax, e-mail, telephone, etc. Informal requests may also be made either by phone or by button-holing. While informal consultations, especially when urgent, are often attended to, it is a good idea to insist on a formal consultation request as well.

3.3.2 Talk to the Referring Physician and Clarify the Consultation Request

Consultation requests are often vague and sometimes misleading (as in the Vignette), usually because the consultee lacks the vocabulary of psychiatry. The consultee is aware of the discomfort of the strain mentioned above, but has difficulty putting it into words. Thus, it is critical that the consultant seeks out the consultee, usually by phone, and asks him/her to provide additional information about the consultation, particularly what the consultee would like from the consultant. It is a good idea to ask the referring physician to be sure to let the patient know to expect a psychiatric consultant, and, if possible, to introduce the consultant to the patient.

3.3.3 Determine the Scope of Consultation

The consultant should be able to determine the probable scope of the consultation after speaking with the referring physician, i.e., whether it is an emergency management of an agitated or acutely suicidal patient, a focused consultation about a specific question, i.e., the patient's ability to sign out against medical advice, to consent to a surgical procedure, a comprehensive evaluation of the patient in assisting with diagnosis, etc.

Even though the question asked by the consultee may sound focused and simple, at times the consultant can facilitate the medical treatment through a comprehensive understanding of the patient and facilitation of communication, e.g., a patient may decide to stay rather than sign out against medical advice after a question and answer period between the patient and her responsible physician, which was arranged by the consultant.

In general, the narrower the scope of consultation, the quicker should the consultant respond to the referring physician.

3.3.4 Review the Chart

The chart of the patient should be reviewed prior to seeing the patient. Most recent progress notes and nurses' notes should provide information about the patient's recent and current status. Medication orders, and more specifically, medications actually administered, should be reviewed, especially for any recent additions or changes that might contribute to the patient's changed mood or mental status. Laboratory and imaging findings should be reviewed for possible metabolic/structural causes of the psychiatric syndrome, as well as to determine which additional lab tests may be indicated. Reviewing chart notes from prior admissions, if available, may provide a perspective by which to put the patient's current medical and mental status in perspective. Old records may even have previous psychiatric consultation notes that can be very informative.

Talking with the nurse who is directly taking care of the patient can yield important information not only about the patient but also about visitors and patient's interactions with the staff. Furthermore, talking with the nursing staff allows them to discuss their impressions of the patient, and any difficulties they may be having in management. Nurses appreciate a doctor who is interested in their input. Their tolerance for deviant behavior will increase when the consulting psychiatrist shows interest. This alone may improve patient–nurse interactions.

3.3.5 Interview the Patient

The consultant should have a reasonable idea about the strain that resulted in the consultation, and the areas to focus in evaluating patient by the time she/he interviews the patient. Before interviewing the patient, privacy should be sought as much as possible—in many cases this may be drawing the curtains around the patient, or, in a private room, closing the door. If there are visitors with the patient, it is in general a good idea to ask them who they are, and then ask them to wait outside for a few minutes while the consultant talks with the patient. The consultant should not identify herself/himself as a psychiatrist until the visitors have left. An exception to this is when the patient's cognitive function is known to be impaired. Under those conditions, the visitors may remain with the patient's permission, and can provide valuable history and additional information.

Once some semblance of privacy has been obtained, the consultant should introduce self as a psychiatrist, and ask the patient whether he/she was expecting one. If not, the consultant should explain that the patient's primary doctor asked a psychiatrist to consult for a comprehensive evaluation—which may be for anxiety, depression, mood changes, memory problems, hallucinations, etc. The consultant should reassure the patient that many medical conditions and medications, as well as the stress of being in the hospital, can cause such problems and they can be managed effectively.

The initial interview should ordinarily take not more than 30 min, and should identify the patient's current concerns, the presence of major or minor psychiatric syndrome and its history, past history of psychiatric problems, family history, the family and occupational situation of the patient, and current mental status. In general, if the patient is obviously confused or delirious, a mental status exam (cognitive exam) may be performed in lieu of history, which may have to rely on collateral sources. When a patient is not obviously confused, the mental status exam may be performed for 5 min or less at the end of the interview, which can be prefaced by first asking the question, "How is your memory lately?", followed by, " I'd now like to ask you some questions to assess your current memory and concentration."

3.3.5.1 The Mental Status Examination

The mental status consists of the following components: (1) appearance, (2) levels of consciousness and orientation, (3) status of the communicative

facilities (speech and movement), (4) content of thought, (5) affect and mood, (6) cognitive processes (attention, concentration, comprehension, memory, perception, thinking logical thoughts, abstraction, judgment). Mental status examination usually refers to cognitive examination, and should be distinguished from mental status, of which cognitive status is a subset. For patients with cognitive deficits, cognitive tests such as the Mini-Mental Status Examination (MMSE) is useful in quantitatively determining the extent of cognitive deficit, and when used serially, in documenting changes in cognitive function (see Chap. 4 for MMSE).

Appearance. Appearance is an excellent indicator of the sum total of a patient's mental status at a given point. Body build should be first noted, i.e., medium, slender, emaciated, moderately obese, morbidly obese, etc. Sloppy, disheveled appearance often signifies self-neglect or preoccupation and distraction. Flushed appearance and the smell of alcohol on the breath, combined with characteristic drunken behavior, point to the diagnosis of alcoholic intoxication. Pale, emaciated appearance accompanied by malodorous and sloppy dress may indicate the presence of depression or cachexia. Some patients with a lesion in the nondominant hemisphere of the brain may dress only one side of the body, completely oblivious to the presence of the other side (hemineglect, hemiagnosia). Such patients may pay attention only to one half of the visual field. Notations on appearance should include observations on the general impression made by the patient (e.g., sloppy, neat), including any unusual features (e.g., completely shaved scalp, unusual bodily habitus, dress).

Levels of Consciousness and Orientation. Awareness of self and environment constitutes consciousness in the mental-status examination. Consciousness may be subdivided into content of consciousness and arousal. The sum total of mental functions, including the ability to remember and to think, comprises the content of the consciousness, while the appearance of wakefulness and response to stimuli form the bases of inference concerning arousal. The content of consciousness is largely a function of the cerebral hemispheres, while the state of arousal is largely a function of the reticular activating system in the brain stem (Boly et al. 2008; Boveroux et al. 2008; Lapitskaya et al. 2013)

Arousal: Levels of consciousness may be classified as follows:

Hyperalert state: Increased state of arousal in which the patient is acutely aware of all sensory input. Anxiety and certain central nervous system stimulants can cause this state.
Normal degree of alertness.

Dullness and sleepiness: May be due to fatigue and insomnia, as well as to sedating medications (as either primary effect or side effect). Metabolic derangements due to disease can also result in dullness and sleepiness, such as in uremia and hypercalcemia.

Clouding of consciousness: A state of reduced wakefulness in which periods of excitability and irritability often alternate with periods of drowsiness. Illusions, especially visual, may occur, and the patient is often startled. Mild to moderate toxic states, withdrawal states, and metabolic derangements can cause this.

Confusional states: In addition to clouding of consciousness, there is consistent misinterpretation of stimuli and shortened attention span. There is disorientation at least to time and often to place. Memory is often poor, and the patient appears perplexed. This is a more severe degree of clouding of consciousness.

Delirium: When used to denote a particular and often fluctuating level of consciousness, delirium may include a florid state of agitation, disorientation, fear, misperception of sensory stimuli, and, often, visual hallucinations. The patients are often loud, talkative, and suspicious and are sometimes completely out of contact with the environment. The degree of contact may vary. Delirium usually occurs in moderately severe toxic states and metabolic derangements of the

central nervous system, including withdrawal from central nervous system depressants such as alcohol and barbiturates.

The term delirium is often used to denote all reversible organic brain syndromes due to metabolic encephalopathy (see Chap. 12). When used in this sense, delirium is in contrast to dementia, which implies chronic and irreversible changes in the brain. Agitation and florid psychotic picture may be lacking in patients with delirium in this broader sense; that is, the patient with reversible confusion and disorientation may be placid and drowsy rather than agitated. In delirium, there is evidence of abnormal neural connectivity and a hyperdopaminergic state (Caplan 2012; Choi et al. 2012)

Stupor: In this state, the patient is unresponsive to stimuli unless their application is very strong and repeated. Usually caused by diffuse cerebral dysfunction.

Coma: Complete unresponsiveness to stimuli. Even strong and repeated stimuli cannot arouse the patient. This occurs in severe dysfunction of the brain, such as serious intoxication or severe head trauma.

Content of consciousness: *Orientation* refers to the person's consciousness of the orienting markers, such as correct awareness of time, place, person and situation. Impairment of orientation results in confusion. The orientation of a patient is determined by asking questions such as: "What day of the week is it today?" "Where are you right now?" "What is your name?" "Why are you in the hospital?" In case of insufficiency in the cerebral cortical functions for any reason (most often due to metabolic derangement of the brain or neuronal destruction), orientation may be impaired to varying degrees. Impairment of orientation usually occurs in the order of time, place, situation, and person. In hospitalized patients, disorientation as to date is not uncommon, perhaps due to the change in daily schedule following hospitalization, distractions by the medical procedures, and other disruptions in the patient's usual routine. In the absence of delirium, however, most patients are oriented to the month and year if not to the exact date. Orientation as to person, especially to the patient's self, usually is not impaired until the very latest stage of cognitive impairment, although the patient may often forget the names of others, especially those persons encountered recently. Disorientation to the self despite relatively normal mental-status examination in other areas strongly suggests a dissociative syndrome rather than an organic brain syndrome such as delirium or dementia.

Status of Communication Facilities (*Speech and Movement*).

In assessing the communicative facilities of a patient, one should consider the integrity of the apparatuses, the effect of learning and psychological state, and the content of the communication.

Integrity of apparatuses. The organs related to speech and movement should be assessed. Weakness of the tongue or facial muscles may produce dysarthria (difficulty in articulating words). Hemiplegia may cause the patient to gesticulate with only one hand. A painful lesion in the mouth may force the patient to be verbally noncommunicative. Deafness may result in nonresponse to a question.

Disorders of language (*aphasia*) caused by brain lesions may be present. Aphasia should be distinguished from dysarthria; the former is due to problems with language itself at the brain level, while the latter refers to difficulty in articulation. In aphasia, written language as well as verbal speech is affected. Aphasias may be roughly classified into expressive (Broca's or motor) and receptive (Wernicke's or sensory) types. Expressive aphasia is related to lesions of the motor speech (Broca's) area in the dominant frontal lobe of the brain. The patient with expressive aphasia has major difficulties in translating thoughts to symbols; thus, what the patient wishes to express may come out in a distorted form or not at all. The patient is usually aware of this distortion or difficulty in his/her own speech and, for this reason, is usually reluctant to speak (or write). Receptive or sensory aphasia is due to lesions of the sensory speech (Wernicke's) area of the dominant temporal lobe. In this condition,

the patient has difficulties in comprehending language, including their own speech. Thus, the patient's speech may be garbled, but they may not be aware of the problems with speech. Unlike patients with expressive aphasia, those with the receptive form are usually fluent, although often incomprehensible to others. There are varying combinations and subtypes of aphasias. For example, in conduction aphasia, there is a disconnection between the Broca's and Wernicke's areas, and thus the patient is unable to repeat what the examiner says to the patient.

Effect of learning and psychological state. Given intact apparatuses for communication, the form of communication often depends on the patient's psychological state and the effect of learning. The effect of learning determines the language in which the patients will express their feelings and thoughts as well as the fluency and facility of the language. For example, middle-class patients are more likely to use grammatically correct syntax. Some patients may use dialects or culturally specific expressions. The current psychological state also determines speech and nonverbal communication. A euphoric patient is more likely to be effusive, verbose, and flamboyant; a depressed patient may be uncommunicative and withdrawn.

Content of communication. What the patient is communicating forms the content of communication. The content of communication often reveals the patient's psychological state, for example, themes of hopelessness and death in depressed states, and bizarre contents in psychotic states. Extreme suspiciousness and ideas of persecution may indicate paranoid psychosis.

Affect and Mood: In current usage, *mood* denotes the subjective feeling/emotion of the patient (euthymic, sad, happy, depressed, euphoric, etc.), while *affect* refers to the way the emotion is expressed (normal range, flat, obtunded, labile, appropriate, inappropriate, etc.). In another, common usage, *affect* refers to feeling and is synonymous with emotion, while *mood* refers to prevailing and relatively enduring emotional tone. Mood can be documented by observation and direct questioning. By observation, one can see whether the patient's affect is appropriate or inappropriate relative to the topic of conversation (does the patient smile while talking of sad events?) and whether it is stable or labile. Labile affect, as manifested, for example, by laughing one minute and crying the next, may be indicative of organic brain dysfunction, in which case there will be additional signs of cognitive difficulties. Flat affect means the absence of any display of affect and is often a negative symptom of schizophrenia or is associated with extreme use of isolation as a defense mechanism (Chap. 19). Direct questions about affect might be "How do you feel right now?" and "Do you feel anxious?" Physiological signs such as sweating, rapid heart rate, and facial expressions also reveal affective states. Family, friends, and relatives of the patient may also provide useful information concerning the patient's mood.

Cognitive Processes. These are the processes that determine the content of consciousness. The processes include attention, perception, memory, concentration, comprehension, abstraction, logical thinking, and judgment. Diminution in the function of any of these areas may indicate the presence of pathology in the cerebral cortex or limbic system. It should be noted, however, that what is important is a decrease in function from the premorbid state and not necessarily the absolute level of functioning, since the absolute levels of abstract thinking, comprehension, and other processes may be determined by background and by long-term variables such as constitutional endowment, educational level, and habitual functional level, as well as by illness. For example, cerebral pathology is more probably present in a college professor who cannot remember the names of the past five presidents than in a blue-collar worker with a tenth-grade education who evinces the same inability.

The cognitive processes can be tested both indirectly and directly. Indirectly, inferences can be made concerning the patient's memory, judgment, concentration, comprehension, and other abilities by asking the patient to describe the present illness and his personal history. Does the

patient remember the dates (or years) of graduation from schools, marriage, and other significant events? Does the patient comprehend the nature of her/his illness and the proposed procedures? Does he/she remember what has been told him by the physicians? Does she/he seem to be aware of the possible risks and complications?

Direct tests of cognitive processes. In introducing direct tests of cognitive processes, it may be helpful to explain that they evaluate memory, concentration, and so forth and so are useful in evaluating possible mental effects of medications, procedures, and the illness itself. For example, sedating medications may need to be reduced if the patient is found to be too drowsy or if concentration is diminished. This type of reassurance may put the patient at ease about possible errors they may make and gives the testing a medical context.

A. Orientation. When doing a direct cognitive testing, it is useful to ask questions concerning orientation first. The questions may be "What day is today? What is the date (or day of the week)?" If the patient does not know, then "What month is it now?" "What year?" may follow. Mild disorientation as to time (e.g., not knowing the date) is common even among normal persons, but severe disorientation (e.g., not knowing the month and year) is indicative of a cognitive disorder. "Where are you right now? The name of this place?" These test orientation as to place. If the patient does not know, then he may be asked "Are you in a hospital, a hotel, or a supermarket?" The patient may know that he/she is in the hospital (or a doctor's office), but may not know the name of the hospital or clinic, which indicates a milder degree of dysfunction than not knowing the nature of the place or confusing it with somewhere else, such as a hotel room. The situation may be inquired simply, "What brings you here?" The next question (orientation as to self) might be "What is your name?" As discussed previously, dysfunction in orientation proceeds in an orderly manner from time to place to situation to person. In fact, except in cases of very severe brain disease, orientation as to self is usually well preserved. Of course, a delusional patient may have a distorted orientation as to self, for example, "I am Napoleon Bonaparte."

B. Memory, attention, concentration, comprehension. Presidents: "Who is the President of the United States now?" If the patient answers correctly, continue asking "Yes, and before him?" until four or five names have been given correctly. This tests recent memory and information of the patient. Most patients with average high-school education can remember four or five recent presidents.

Calculations: Asking the patient to do simple calculations can test the patient's ability to attend to and comprehend the physician's instructions and to concentrate and utilize immediate memory. "How much is 15 plus 17?" "25 minus 7?" If the patient has difficulty, an easier calculation involving single digits should be tried. Unlike additions and subtractions, simple multiplications, such as 4 times 6, are easier tasks, since they involve primarily long-term memory (which is resistant to decay) and comprehension of the instructions. Thus, if the patient can do 4 times 6 but not 15 plus 17, then one might wonder whether the patient has difficulties with concentration and immediate or recent memory but not with remote memory and comprehension (indicating possible brain dysfunction). On the other hand, if the patient has difficulties with both, low educational level or mental retardation might be suspected.

If there is reason to suspect difficulties on the basis of simple calculations, serial 7 s and digit span might be done. Serial 7 s are done by asking the patient to subtract 7 from 100 and to keep subtracting 7 s from the results. This tests sustained attention and concentration as well as short-term memory. If serial 7 s are too difficult for the patient, serial 3 s may be tried. For example, "Could you count backwards from 20 by 3 s?" Digit span is tested by asking the patient to repeat a number of random digits, not including zero, such as 5-7-2-8-6. Digit span backward is tested by asking the patient to repeat in reverse order the numbers that you gave the patient. For example, "If I say 1-2, please say 2-1" This tests

primarily short-term memory and concentration. Most patients without brain dysfunction can do at least six digits forward and four digits backward. Failure to repeat 6 digits forward strongly suggests cognitive impairment. In contrast, the ability to repeat 5 numbers backward is very unlikely in the presence of brain dysfunction.

Memory, especially recent memory, is very sensitive to dysfunction of the brain. The hippocampus is involved in the coding of recent memory into the long-term memory mechanisms. Any metabolic derangement of the hippocampus and the cerebral hemispheres can result in problems with memory. When memory dysfunction is suspected, the registration, retention, and recall of memory can be tested by the following steps: First, ask the patient if he/she remembers your name. If the patient does not remember it, repeat your name and ask the patient to repeat it (immediate memory: registration and immediate recall). Then, tell the patient that you will mention three objects that you are asking them to remember, as you will ask again in a few minutes. The objects may be items such as "apple, penny, and table". Tell the patient to repeat the names of the three objects immediately. In about 5 min or so, ask the patient if he/she remembers your name; also, the names of the three objects (recent memory: retention and recall). The patient may be able to remember only one or two objects (diminished recent memory). If the patient cannot recall the names at all, ask the patient "Please say 'yes' if any of the objects I name now is one of the objects I named before. If the patient can identify the articles but could not remember them, it may indicate the presence of retention but difficulty with recall.

C. Abstraction. Similarities: This tests the ability of the patient to categorize objects on the basis of the similarities. For example, "What is the similarity between a cat and a dog?" The patient may answer "They are both animals" (a good abstraction) or "They both have legs" (a concrete response). In case of the latter, you might ask "Then how about a dog, a cat, and a snake?" At this point, the patient may be able to abstract and say "They are all animals." Proverbs: If I told someone, "Don't judge a book by its cover", what am I trying to say? "Don't cry over spilt milk," etc. Proverb interpretations are most subject to influences of educational level, cultural background, and language. For example, those from non-English-speaking cultures may have great difficulty in abstracting English-language proverbs. A concrete response in tests for abstraction may indicate possible brain dysfunction, low educational level, low intelligence, or formal thought disorder, as in schizophrenia. An idiosyncratic or bizarre response may indicate an unusual way of thinking, as in psychosis. For example, "What is the similarity between a cat and a dog?" "They are both my enemies." "What does the proverb, 'People who live in glass houses shouldn't throw stones' mean?" "That means that even if you have enough money to buy a glass house, you should not throw away money. Stones are gems, you know, which cost a lot of money."

D. Logical thinking and judgment. Patients with brain dysfunction may show varying degrees of difficulty with judgment. Judgment means the ability to act appropriately in social and emergency situations. Many questions concerning judgment also involve the ability to think logically. For example, "If you were in a crowded theater and happened to discover fire and smoke coming from the ceiling, what should you do?" A good answer would be "I would tell the usher or manager." If the patient replies "I would yell 'Fire'," the physician might ask "If you yelled 'Fire,' what would happen?" The patient with intact logical thinking may then say "I guess that would cause panic … perhaps I should not yell 'Fire'." Other judgment questions include "What should you do if you found an envelope with an address and a stamp on it on the street?" Patients with personality disorders without organic brain dysfunction may give idiosyncratic or inappropriate responses to judgment questions. For example, an impulsive patient may say "I would try to put out the fire by throwing my can of soda on it."

E. Perception. The patient's perception can be tested by first observing whether the patient seems to be aware of the tester's presence and whether the patient seems to be responding to visual or auditory hallucinations (e.g., carrying

on a conversation). Then, the patient can be asked questions such as: "Have you ever had any experiences of hearing things or seeing things that others couldn't see or hear?" "Any experiences of things changing shape or becoming distorted?"

F. Delusions and paranoid thinking. A delusion is an idea firmly held by a patient that is not corroborated by reality. Delusions may be grandiose ("I am God"), persecutory ("Everybody is out to get me"), or depressive ("Worms are eating my brain out"). Some delusions involve diseases, such as: "I know I have cancer, no matter what the tests show." The term "paranoid" is often used to describe patients who have persecutory ideas or delusions.

The presence of delusions is usually manifested by the content of the patient's communications. Delusion formation is a process by which perceptions are put into some kind of perspective. Thus, strange bodily sensations, due to whatever cause, may be attributed to "poisoning" and continuing presence of anxiety to "people spying on me." Obviously, when cognitive processes are not functioning optimally, and when the anxiety level is high (such as in a hospitalized patient with preexisting cognitive difficulties due to poor blood supply to the brain), the risk of delusion formation is greater; it is easier to misperceive stimuli or attribute confusing stimuli to a cause unrelated to reality (e.g., "The doctors are trying to kill me so that they can give my kidneys to someone else").

In addition to indicating the possible presence of cognitive difficulties, delusions give clues concerning the emotional state of the patient. For example, persecutory delusions are associated with anxiety, grandiose delusions with euphoria, and depressive delusions with a depressive syndrome.

Once initial interview is concluded, the consultant proceeds to the next steps:

3.3.6 Obtain Collateral Information

After interviewing the patient, obtaining collateral information from the spouse, significant others, families and friends can provide valuable information. The consultant should obtain permission from the patient to speak with available collaterals whenever feasible. If the patient is severely cognitively impaired, or the patient refuses to give permission, still the consultant may speak with collaterals as long as they are aware that the patient is in the health care facility, and as long as the consultant only obtains information and does not divulge information about the patient.

3.3.7 Diagnose the Consultation: The Syndrome, The Patient, The Environment

After reviewing the reason for consultation, patient's history, family history, information from collaterals, lab, vital signs and physical exam data, the consultant is in a position to make a comprehensive diagnosis of the consultation itself. Such a diagnosis may include primarily *a systems strain*, e.g., a personality or opinion conflict between the health care professional(s) and the patient (see Chap. 10). When the patient shows evidence of a psychiatric condition, the consultant develops a differential diagnosis leading to a working diagnosis of the psychiatric syndrome, its interaction with the medical condition, and an understanding of the patient as a person dealing with the medical and psychiatric condition. Such an understanding will include an understanding of the patient's developmental history, childhood, recent, and current stresses, as well as the patient's coping ability and psychosocial assets. Differential diagnosis of the psychiatric syndrome should be from general to specific, e.g., psychotic syndrome secondary to drug use, psychotic syndrome secondary to delirium secondary to multiple metabolic causes—electrolyte imbalance, increased serum ammonia. Very often, the psychiatric syndrome may represent multiple possible contributing etiologies, e.g., major depression which may be a recurrence of existing unipolar depression, plus the effects of chronic alcohol abuse, plus secondary to hepatic failure, plus cocaine withdrawal. (See Chap. 7 for further discussion of psychiatric diagnosis).

3.3.8 Provide Diagnosis and Recommendations

The proof of the pudding of a psychiatric consultation is how informative it is and how implementable the recommendations are. The most effective way of conveying the recommendations is to speak with the referring physician directly, either face to face or on the phone, so that the referring physician may be able to ask questions and interact with the consultant. The consultant should communicate to the consultee the findings and diagnosis clearly and concisely, without using unnecessary psychiatric jargon, and discuss alternative treatments and recommendations. The recommendations should be presented very concretely, and specify who is to do what. For example, "I recommend olanzapine 10 mg po hs on a regular basis for the patient's psychosis, plus lorazepam 1–2 mg IV q 4 h prn for agitation. Please tell the nursing staff to orient the patient each time they do any procedure with the patient such as taking the vital signs—they should say, I am nurse so and so and I am going to take your blood pressure."

The written consultation note should be concise and, above all, comprehensible, without obscure abbreviations or jargon. The note should contain, as a minimum, the reason for referral, brief history and mental status, relevant labs, working diagnosis, and specific concrete recommendations.

3.3.9 Consultation Interventions

In the course of psychiatric consultation, the consultant, ipso facto, provides intervention through an empathic interview process, and through supportive psychotherapeutic elements inherent in a psychiatric interview. In addition, the consultant may provide immediate relief of agitation through listening and reassurance, and when indicated, with stat medications. There may be need for an involuntary hold if the patient is considered to be dangerous to self or others and is in need of psychiatric hospitalization.

The consultant may find it advisable, at times, to arrange an ad hoc nurses meeting, meeting with the patient's family, or a meeting of the patient, referring physician, the consultant, and others to facilitate communication and/or plan a course of action.

The consultant may also perform specialized procedures such as lorazepam interview when indicated (see Chap. 34).

3.3.10 Follow-Ups

At least one follow-up visit is recommended for all initial consultations whenever feasible. A follow-up visit is valuable to determine any changes either as a result of the treatment recommendation or of the disease process. In delirious patients, the fluctuation in mental status during follow-up visits may be diagnostic. When a patient no longer requires follow-up, but is still in the health care system, the consultant should sign off and communicate it to the referring physician.

Note: A Computerized Psychiatric Consultation Database with Forms, Reports, and Queries, which is a Microsoft Access Database application, is available free of charge for download from Springer. This database was developed by Hoyle Leigh, MD and is used at the Community Regional Medical Center, Fresno, CA. It is made available "as is" with the explicit understanding that it will be used for clinical and academic purposes only, and it is without any warranty. It is usable only as an application of existing Microsoft Access database.

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Common Reasons for Psychiatric Consultation

4

Hoyle Leigh

Contents

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The most frequent emotions, behaviors, and symptoms that patients exhibit that draw the attention of the health care professional and result in a psychiatric consultation request are the following:

1. Depression and Suicidal Behavior
2. Altered states of consciousness/delirium
3. Anxiety and agitated behavior
4. Psychotic symptoms
5. Suspected psychogenic physical symptoms
6. Patient behavior generating strong feelings in staff or splitting staff
7. Addiction and pain problems

This chapter discusses the immediate evaluation of these common reasons for consultation request, their immediate management, and how to proceed from there (Table 4.1).

4.1 Depression

The term, depression, is commonly used to denote both simple depressed affect as well as the depressive syndrome, which is a clinical significant psychiatric condition that requires careful evaluation and treatment. *Depressed affect* refers to subjective feelings of sadness, feeling blue, feeling like crying, or being "down in the dumps," which may be accompanied by a sad expression, tearfulness, and either psychomotor retardation or psychomotor agitation. Depressed affect is a normal response to loss and threatened loss. When such feelings persist, often without any obvious cause, and are accompanied by physiologic signs such as sleep disturbance (insomnia or hypersomnia), anorexia, fatigue, constipation, loss of libido, cognitive symptoms such as inability to concentrate or memory disturbance, low self-esteem, guilt feelings, hopelessness, helplessness, and suicidal ideations, then the depressive syndrome should be suspected, for which definitive treatment may be imperative (see Chap. 15). Suspected depression and/or suicidal ideation is the most common reason for psychiatric consultation request in a general hospital, followed by altered mental status (delirium).

Table 4.1 Common reasons for psychiatric consultation request in a general hospital

Year	2012	2011
Suspected Depression and/or suicidal ideation	356 (28 %)	325 (27 %)
Depression	176 (14 %)	166 (14 %)
Suicide attempt or ideation	80 (14 %)	159 (13 %)
Delirium	255 (20 %)	259 (22 %)
Diagnosis by Consultant		
Mood disorder	335 (26 %)	245 (20 %)
Delirium:	238 (19 %)	231 (19 %)
Total:	1,275 (100 %)	1,197 (100 %)

From CL Database, UCSF Fresno/Community Regional Medical Center

4.1.1 Suicidal Behavior

A common reason for psychiatric consultation is suicidal behavior—either suicidal ideation or suicidal attempt. *Suicidal ideation* refers to thoughts about suicide that a patient expresses spontaneously or upon questioning. Such thoughts may be active ("I want to kill myself") or passive ("I wish I were dead," "I wouldn't mind if I died"), and may be vague thoughts or actual plans.

Suicide is the 10th leading cause of death in the USA, resulting in 36,909 lives lost in 2009. The top three methods used in completed suicides were firearm (51 %), suffocation (24 %), and poisoning (17 %) (CDC). Approximately 3 % of the general population has suicidal ideation each year, and about 0.4 % attempt suicide. About 20–30 % of people who have suicidal ideation make plans, and about 30 % of those who plan make a suicide attempt (Kessler et al. 2005).

Actual plans usually require an immediate involuntary psychiatric hospitalization (see Sect. 4.1.2.8). The underlying, potentially treatable psychiatric conditions should be evaluated as discussed below (see Sect. 4.1.2.1).

There are several quantitative scales to assess the seriousness of suicidal ideation and suicidal attempt, which may be helpful in evaluating and documenting the evaluation of suicidality. They include Columbia Suicide Severity Rating Scale (C-SSRS), Harkavy–Asnis Suicide Survey (HASS), InterSePT Scale for Suicidal Thinking (ISST), Scale for Suicide Ideation (SSI), Sheehan

Suicidality Tracking Scale (STS), Suicidal Behaviors Questionnaire-Revised (SBQ-R), and Beck Suicide Ideation Scale (BSI). Among the more commonly used scales which may be downloaded below, C-SSRS has been endorsed by the FDA for tracking suicidality in pharmaceutical trials (Gassmann-Mayer et al. (2011)).

Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al. 2011): http://cssrs.columbia.edu/docs/C-SSRS_1_14_09_Baseline.pdf

Sheehan Suicidality Tracking Scale (Coric et al. 2009): http://emmlprofessionals.com.au/images/resources/Mental%20Health/7_Sheehan_Suicidality_Tracking_Scale_(STS).pdf

Modified SSI (Miller et al. 1991): http://160.40.50.57/EXPO/images/5/50/MSSI.pdf

4.1.2 Suicide Attempt

Psychiatric consultation is often automatic in patients admitted because of a suicide attempt. The mode of attempt may range from a mild overdose (e.g., 10 aspirin tablets) to stabbing or gunshot. An immediate consideration in evaluating a suicide attempt is whether the patient is able to provide information or is delirious or comatose. If the patient has an altered state of consciousness, treatment and management of that condition takes first priority. Collateral information from relatives, friends, or a suicide note may be invaluable in determining the patient's preattempt state of mind, seriousness of intent, and stressors. Unless the consultant is convinced that the patient is no longer suicidal, post-attempt patients should be placed on suicide precautions, which would include close observation by a sitter. An emergency involuntary hold may be necessary if the patient is unwilling to stay in the hospital for necessary treatment.

4.1.2.1 Evaluation of the Attempt

1. Demographics of the patient
   (a) Single, divorced, widowed, or living alone are risk factors.
   (b) Caucasian, older males are more at risk of completed suicide, and females are at higher risk of a suicide attempt.
   (c) Are there supportive persons—significant others relatives, friends, community, church?
   (d) Are there ethnic/cultural factors in the suicide attempt (e.g., social alienation, ostracism, shame)?
2. Seriousness of attempt
   (a) How lethal was the mode? Gunshot, stabbing, hanging, and drowning are in general more serious than a drug overdose, but even in an overdose, taking a whole bottle of pills (empty bottle found nearby) is more serious than taking half or less. A bizarre mode points to a psychotic diagnosis (e.g., setting fire to self, drinking Drano).
   (b) What was the likelihood of help from others? Was the patient alone? Did the patient inform anyone about the attempt? Where was the attempt made? When was it made?
   (c) What did the patient have in mind—to die or to escape? What ideas did the patient have about what would happen after he/she died? Is there a psychotic quality, for example, delusional or bizarre quality to the ideas, or any evidence of hallucinations, for example, commanding voices? Did the patient wish to be relieved of physical pain (more serious)?
   (d) Was it planned? If so, how long, how thoroughly? Was there an obsessive-compulsive quality (more serious)?
3. Medical and psychiatric history of the patient
   (a) Presence of a chronic (especially painful) medical condition (increases risk)
   (b) Past history of suicide attempt (increases risk, also helpful in diagnosis)
   (c) History of psychiatric illness, especially depression, mania, psychosis, schizophrenia, substance use including alcohol, PTSD, anxiety and panic, borderline personality, antisocial personality

Table 4.2 Lifetime mortality from suicide in discharged hospital patients

Bipolar disorder	20 %
Unipolar depression	15 %
Schizophrenia	10 %
Alcoholism	18 %
Borderline personality	10 %
Antisocial personality	10 %

From Mann 2002

4. Family history
   (a) Any psychiatric disorder, especially bipolar disorder, depression, schizophrenia?
   (b) Any suicide?
5. Current Mental State

4.1.2.2 Determination of Underlying Condition

On the basis of the evaluation of the above factors, the consultant should be able to determine tentatively the underlying condition(s) for the suicidal behavior/ideation. It should be recognized that suicide per se is not a psychiatric condition; however, it is often associated with underlying psychiatric conditions that may be amenable to treatment (Table 4.2).

4.1.2.3 Situational Precipitating Factors

These factors include interpersonal/family conflict, occupational stress, occupational loss or failure, anomie, and altruistic motive. *Anomie*, first described by the French sociologist, Emile Durkheim, refers to a sense of loss of definition when something that provided an anchor or purpose in life has disappeared, either through successful attainment (e.g., passing an examination) or loss (e.g., someone the patient cared for, or a cause with which the patient was passionately involved). A more common situational factor for suicide is a personal failure, either to achieve a goal or to maintain a status, which Durkheim named "egoistic suicide." Durkheim also described suicides with an altruistic motive, such as an elderly person contemplating suicide so as not to be a burden to his family. A situation of special concern is a patient with a serious medical condition, such as Alzheimer's disease or Huntington's disease, who may choose suicide. If situational factors are present, they should be carefully evaluated. How are the factors affected by the suicide attempt? Are they resolved, the same, or worse? What are the possible avenues of resolution?

4.1.2.4 Intoxication and Altered State of Consciousness

Such states increase the impulsiveness and acting out behavior, and up to 50 % of successful suicides are intoxicated at the time of death (Moscicki 2001).

4.1.2.5 Depressive Syndrome

Depressive syndrome is suspected when depressive affect (sadness, feeling blue or down in the dumps) or, in more severe cases, apathy is associated with other symptoms, such as sleep disturbance, anhedonia, inability to concentrate, anorexia or overeating, guilt feelings, recurring suicidal ideation, hopelessness, helplessness, lowered self-esteem, and social withdrawal, especially if there is a history of previous such episodes or a family history of depression (See the first section of this chapter and Chap. 15).

If a depressive syndrome has been diagnosed, one has to determine whether it is unipolar or bipolar. A history of manic or hypomanic symptoms in the absence of substance use, including feeling full of energy and not needing sleep for nights, feeling "on top of the world," getting involved in many projects at once, and going on spending sprees, point to bipolar illness, as well as atypical depression (hypersomnia, eating more). Suicidality may come without any prodrome in bipolar illness and may be extremely severe. A family history of bipolar illness and suicide should increase the index of suspicion for bipolar illness. (See the first section of this chapter for more on suicidality).

4.1.2.6 Psychosis

When suicidal behavior is particularly bizarre, or accompanied by psychotic symptoms (see

above), then psychosis may be suspected as an underlying condition (see Chap. 19). Examples of bizarre suicidal behavior include embracing a hot stove or setting oneself on fire.

4.1.2.7 Borderline Syndrome or Borderline Personality Disorder

Borderline personality patients show a pattern of stormy interpersonal relationships and a tendency to see others as all good or all bad (*splitting*), which assessment may change suddenly without apparent reason, often accompanied by substance abuse problems, feelings of emptiness, and previous suicide attempts and self-cutting behavior. Sometimes the cutting behavior of borderline patients is not with the intention of dying, but rather to relieve tension (see Chap. 25).

At least 75 % of patients with borderline personality engage in suicidal behaviors, particularly, wrist cutting and overdose of medications. About 10 % eventually commit suicide, representing up to one third of completed suicides (Black et al. 2004; Pompili et al. 2004). Borderline patients who also have major depression, substance abuse, and previous history of suicide attempts are at particular risk for suicide.

4.1.2.8 Management of Suicide Attempt/Ideation

Managing a patient with suicide attempt/ideation involves two considerations:

1. determination of the need for immediate measures to protect the patient, and
2. treatment/resolution of the underlying condition. If the patient is considered to be actively suicidal, he or she may need constant observation and psychiatric hospitalization when medically stabilized, under involuntary emergency certificate if necessary. Treatment of the underlying conditions, in such cases, would be implemented in the psychiatric inpatient setting.

If the patient is not actively suicidal, then treatment of the underlying conditions should be planned, either on an outpatient or inpatient basis, depending on the severity of the underlying condition and the availability of resources (Table 4.3).

Table 4.3 Psychiatric disorders underlying suicide attempts

Disorder	Percent
All disorders	90
Major Psychiatric Disorders	
Anxiety disorders	70–74
Affective disorders	60–74
Major depression	40
Bipolar disorder	20–30
Alcohol abuse	20–45
Other drugs	4–15
Stress-related and somatoform disorders	26
Eating disorders	13
Schizophrenia and nonaffective psychosis	5
Impulse control disorder including conduct disorder	5–33
Personality Disorders	46
Anxious	21
Anancastic (obsessive-compulsive)	19
Paranoid	15
Histrionic	13
Dependent	13
Emotionally unstable	11
Dissocial	5
Schizoid	5
Borderline	55
Co-existing Medical Diseases	45
Presence of Major Stressors	62

4.2 Altered States of Consciousness/Delirium/ Cognitive Impairment

Clouding of consciousness is characterized by impaired ability to think clearly and to perceive, respond to, and remember stimuli. *Delirium* is a state of disturbed and fluctuating consciousness with psychomotor changes, usually restlessness or drowsiness, and transient psychotic symptoms. *Obtundation* is a state in which patients are awake but not alert and exhibit psychomotor retardation. *Stupor* is the state in which the patient, although conscious, exhibits little or no spontaneous activity. Stuporous patients may be awakened with stimuli but have little motor or verbal activity once aroused. *Coma* is the state of unarousable unresponsiveness. A comatose patient does not exhibit purposeful movements.

In light coma, patients may respond to noxious stimuli reflexively, but in deep coma, there is no response even to strongly noxious stimuli. The Glasgow Coma Scale (GCS) is commonly used in identifying the degree of impairment. A GCS score of 8 or below indicates coma (see Appendix 1 at the end of chapter).

Psychiatric consultation is often requested to evaluate altered mental states (AMS). As comatose and stuporous patients do not respond verbally, the immediate approach to such patients is to recognize and treat the underlying medical condition, and to provide physical protection and supportive measures. When the patient presents with delirium or improves to a delirious state, the psychiatric consultant may be of great service in evaluating and managing the condition (see Chap. 12).

Cognitive impairment may be seen in both delirium and dementia (See Chaps. 12, 13, and 33). It is often useful to document the cognitive impairment serially to determine whether the impairment is improving, declining, or stable. Mini-Mental Status Examination (MMSE) and the Montreal Cognitive Assessment are two commonly used tests to document the current cognitive state of the patient (see Appendices 2 and 3).

4.3 Anxiety and Agitated Behavior

Anxiety refers to an emotional state of dread and apprehension, with or without an easily identifiable stressful situation (see Chap. 13). *Fear* refers to anxiety specifically tied to an object or situation, for example, fear of hospitalization. A *phobia* is an irrational fear of a usually harmless object or situation, such as cats (ailurophobia) or open spaces (agoraphobia). *Panic* refers to the intense anxiety experienced when one finds oneself suddenly thrust into a severely feared or dangerous situation, for example, waking up in a room engulfed in fire. Autonomic (usually sympathetic) arousal is usually associated with anxiety spectrum syndromes. Thus, there is often tachycardia, increased blood pressure, rapid breathing, sweating, dry mouth, gastrointestinal disturbance (diarrhea or constipation), and urinary frequency.

As a phenomenon, agitated behavior indicates increased restless motor activity, usually accompanied by hyperarousal and an internal sense of anxiety. When agitated behavior is accompanied with confusion, hallucinations, or delusions, delirium or psychosis should be suspected.

4.3.1 Situational Factors

Mild degrees of anxiety and agitation are commonly seen in stressful situations such as hospitalization and as a result of an internal psychological conflict. Such conflict may be conscious, as in feeling ambivalent about making a decision, or unconscious, as when some trigger awakens a repressed painful memory or an unconscious conflict. An example may be the approaching of the anniversary date of a significant loss.

A common trigger for anxiety and agitation in the health care setting is inadequate communication between the patient and health care team, especially when patients feel they are not listened to or when they misunderstand the diagnosis and treatment.

4.3.2 Psychiatric Syndromes and Anxiety

Anxiety and agitation are common symptoms of almost all psychiatric syndromes. They are very commonly seen in depression, in which patients may alternate between psychomotor agitation and retardation, as well as in bipolar disorders, both in the manic and the depressive phases. Anxiety disorders, including posttraumatic stress disorder, are usually accompanied by agitation during some phase of the illness. Both anxiety and agitation are commonly seen in psychosis including schizophrenia, schizoaffective disorder, delusional disorder, and others. Certain personalities and personality disorders are prone to

Table 4.4 Causes of anxiety/agitation

Symptom	Stress	Cause
Anxiety/agitation	Stress identifiable	Adjustment Disorder/PTSD
		Specific object/situation: phobia social anxiety, performance anxiety
		No specific object/situation
	Stress not identifiable	Panic present: panic disorder
		No panic: generalized anxiety disorder
		Substances (side effect, intoxication, withdrawal)
		Prescribed
		Recreational
		Medical disease present
		R/o secondary to medical condition
		Another major psychiatric syndrome present (e.g., schizophrenia)

anxiety/agitation. Patents with borderline personality syndrome may become anxious and agitated when they feel mistreated by staff; patients with an obsessive-compulsive personality are often agitated when the staff is not as exacting and orderly as they expect the staff to be; patients with a narcissistic personality may be particularly sensitive to any evidence of slight or lack of respect, and histrionic and dependent patients may be sensitive to any perceived lack of attention and caring (see Chap. 25 for more on patients' personalities.)

4.3.3 Intoxication and Withdrawal

Intoxication and withdrawal from both prescribed and recreational drugs often cause anxiety, agitation, and delirium, as do various medical/surgical conditions. Thus, an important part of the diagnostic workup of severe anxiety and agitation is a urine and blood drug screen and blood levels of suspected substances including alcohol. Of particular importance in the consultation-liaison setting is patients who had been dependent on alcohol who find themselves acutely hospitalized. Such patients may develop delirium tremens within days of hospitalization unless a benzodiazepine detoxification schedule or other measures to prevent/treat alcohol withdrawal are implemented upon ascertaining the alcohol history (see Chap. 20 on Substance Use Problems).

4.3.4 Immediate Management of Agitation

Acute agitation is often a medical-psychiatric emergency requiring immediate treatment to reduce the potential for harm both to the patient and to the staff. An acutely agitated patient may need to be physically restrained. If an intravenous (IV) line is not already in place, an intramuscular injection of haloperidol 1–2 mg may be given stat, and an additional lorazepam 1–2 mg IM may be needed. Once an IV line is in place, lorazepam 1–5 mg may be given for immediate management of agitation. At this point, the clinician should assess the patient's medical condition to determine whether there are risk factors for torsades de pointes due to haloperidol's QTc interval$_c$ prolongation effect. The risk factors include female gender, cardiac disease, hypokalemia, concomitant medications that may prolong QTc (almost all psychotropic drugs prolong QTc, especially thioridazine, ziprasidone, and citalopram as well as methadone), and familial long QT syndrome (Justo et al. 2005). In general, if the QTc is below 450 ms, any antipsychotic including haloperidol can be safely used; if QTc is between 450 and499 ms, antipsychotics should be used with

caution, and if QTc is above 500 ms, then they should be avoided. In using haloperidol, the major risk factor, however, is use of exceedingly high doses. There is rarely a problem when normal doses are used. If such risk factors are present, continuing use of lorazepam IV may be indicated (1–5 mg q 2–4 h). Lorazepam, however, is highly likely to increase confusion in a medically ill patient who has any degree of cognitive dysfunction (Breitbart et al. 1996) and may also depress respiration. In addition to lorazepam IV, immediately dissolving olanzapine (Zydis) 5–10 mg may be given if the patient is willing, or olanzapine 5–10 mg may be given IM, to be repeated every 2–4 h up to 20–30 mg per day (Table 4.4).

If risk factors for torsades de pointes are not present, haloperidol 1–5 mg IV (depending on the degree of agitation and the size of the patient) every 1–4 h may be needed until the patient is reasonably calm. Then, the patient may be given the effective dose of haloperidol every 4–6 h. In severe agitation associated with delirium, large doses of haloperidol may be used without significant extrapyramidal side effects as long as it is given intravenously. For most delirium, keeping the dose low, in the range of 1–6 mg per day, leads to rapid improvement if medical causes of the delirium are not ongoing. Haloperidol IV at high doses, however, may lower the seizure threshold and may also cause QT prolongation in some patients, and if other risk factors are present, it may lead to torsades de pointes. Electrocardiogram monitoring should be done on high-dose IV haloperidol patients. In contrast to IV, oral and IM doses of haloperidol exceeding 1–2 mg may be associated with extrapyramidal side effects, requiring the use of benztropine or diphenhydramine.

If the patient is willing to take oral medication, immediately dissolving forms of second-generation psychotics may gradually be substituted for IV haloperidol, for example, Zyprexa Zydis 5 or 10 mg po hs, plus IV haloperidol 1–2 mg q 4 h prn for agitation. Lorazepam 1–2 mg IV may be added to the haloperidol if the patient is so agitated that inducing sleep might be desirable, but in patients with delirium and dementia, benzodiazepines may cause paradoxical agitation due to suppression of the frontal lobe function and are well known to increase cognitive dysfunction (Kraemer et al. 1999).

If the presumptive reason for the agitation is alcohol withdrawal, lorazepam (intermittent lorazepam may increase the chances of developing delirium tremens; see Chap. 20) rather than haloperidol may be used, followed by instituting an alcohol withdrawal schedule (See Chaps. 12 and 20). If the presumptive underlying cause is phencyclidine (PCP) intoxication, haloperidol and phenothiazines should be avoided and the agitation should be controlled with lorazepam.

Psychologically, the staff should approach a delirious patient calmly, and avoid any behaviors that might be interpreted as being threatening, including standing or sitting too close to the patient. The patient should be oriented each time the staff approaches, for example, "I am your nurse, Susan, and you are in University Hospital. I am here to take your temperature and give you an injection for your infection."

Agitated patients should be in a quiet room if possible, and there should be someone to observe the patient at all times.

4.4 Psychotic Symptoms: Delusions, Suspiciousness, Hallucinations, and Disturbances with Reality

Delusion refers to an irrational and persistent conviction or belief that is not shared by the community, which considers it to be not based on reality. Delusions may be, among others, persecutory, grandiose, pessimistic, simple, complex, or bizarre. Delusions or excessive suspiciousness may be symptoms of psychosis, delirium, dementia, or personality disorders. *Hallucination* refers to an internally generated perception, that is, a perception without external sensory input. Hallucinations may be visual, auditory, tactile, olfactory, gustatory, or kinesthetic. Visual hallucinations, especially in the absence of auditory

hallucinations, should be considered to be organic (delirium, dementia, substance-induced, secondary to a medical disease including neurologic disease, such as Charles Bonnet syndrome) unless organic causes are completely ruled out. Auditory hallucinations of voices coming from outside the head, two voices conversing with each other, giving a running commentary on the patient, or giving orders to patients (command hallucinations) are more likely to be symptoms of schizophrenia. Olfactory and gustatory hallucinations are often associated with the aura of seizure disorder, and tactile and kinesthetic hallucinations may be associated with substance use (e.g., cocaine bug). *Illusions*, in contrast with *delusions*, refer to misidentifying sensory input, for example, seeing a gallows instead of an intravenous pole. Illusions are common in delirium. Derealization, where reality does not feel real, and depersonalization, where the person does not feel real, are dissociative symptoms that may be normal under stressful conditions, substance-induced, part of borderline personality syndrome, posttraumatic stress disorder (PTSD), or psychosis.

In general, any of the psychotic symptoms above calls for the ruling out of delirium, drug intoxication/withdrawal states (including prescribed medications), and medical conditions causing psychiatric symptoms (see Table 7.1 in Chap. 7). See Chap. 19 for further discussion of psychosis.

4.5 Suspected Psychogenic Symptoms

Psychiatric consultation may be requested when a patient's physical symptoms are suspected of being psychogenic. Such suspicions are aroused when no organic pathology underlying the symptoms is found, or when the symptoms are considered to be out of proportion to the pathology. When the symptoms involve the somatosensory nervous system, such as blindness, aphonia, "glove-like" anesthesia, convulsions, or paralysis of a limb, conversion disorder is suspected. When the symptom is primarily pain, chronic pain syndrome is suspected. When the patient is preoccupied with symptoms that might point to a disease, for example, heart disease, hypochondriasis may be suspected.

Since Slater's (1965) landmark 10-year follow-up study of patients diagnosed with hysteria (conversion disorder) in which over 50 % were found to have clear neurologic or psychiatric conditions, it is generally recognized that a large percentage of patients diagnosed with conversion or psychogenic physical symptoms have serious neurologic or psychiatric illnesses. However, there has been a steady decline in misdiagnosis of conversion disorder since the 1970s (29 % in the 1950s; 17 % in the 1960s; 4 % in the 1970s–1990s), which may be attributed to both better diagnosis due to the development of better diagnostic tools such as brain imaging (Stone et al. 2005).

4.5.1 Evaluation of Suspected Psychogenic Symptom

A thorough medical and neurologic workup including laboratory testing and imaging studies is a must. Especially of note is that multiple sclerosis is the most common neurologic condition misdiagnosed as conversion disorder. Many physical symptoms that may have an organic basis may be exaggerated or precipitated by psychological factors ("psychological overlay"). Stresses, interpersonal relationships, and psychological conflicts may contribute to the amplitude of distress associated with a physical symptom.

Thus, whether or not tissue pathology is present, a careful psychiatric examination is also warranted to identify environmental stressors, interpersonal relationships, personality style and psychological conflicts, as well as the patient's relationship with the health care system.

Specialized techniques such as hypnosis and lorazepam interview may be conducted to further elucidate unconscious factors that may underlie the symptom (see Chap. 34).

The following is an algorithmic approach for further evaluation:

4.5.1.1 Suspected Psychogenic Symptom After Complete Medical/Neurologic Workup

1. One or several somatosensory symptoms: conversion (functional neurologic symptom) disorder
2. Many symptoms in many organ systems: somatic symptom (somatization) disorder
3. Chronic pain disproportionate to tissue pathology: Somatic symptom disorder with predominant pain (chronic pain syndrome)
4. Preoccupation with a disease: Illness anxiety disorder (hypochondriasis)
5. Preoccupation with a body part: body dysmorphic disorder

4.6 Patient Behavior Generating Strong Feelings in Staff or Splitting Staff

The consultation request arising for this reason is often not explicit, or may sound like something else entirely, for example, "Pt refuses meds; please evaluate" or "Pt disruptive; please evaluate." It is only when the consultant actually speaks with the requesting physician that the reason becomes clearer. The physician may indicate that the patient is difficult, refuses to have a particular nurse attend to him/her, or is inconsistent in complying with simple requests such as allowing blood to be drawn. One finds that the staff members taking care of the patient are often divided; some are more sympathetic to the patient while others are angry with the patient. Such patients are often seen by staff to be demanding, entitled, and unstable. The consultant may notice nonverbal cues from the consultee that he/she dislikes the patient.

The most important consideration in dealing with such patients is that the goal of psychiatric consultation is to allow optimal medical care. Patients with this type of behavior and problems often have borderline personality disorder or traits (see Chap. 25). Though others see such patients as being unstable, for the patients it is others and the external world that is inconsistent and constantly changing. For the patients, people whom they believed loved them suddenly turn against them and behave hatefully. Such patients also have the predisposition to see neutral reality as being hostile. Educating the staff that the patient has a personality trait/disorder that cannot be resolved during an acute medical hospitalization is an important first step. An even-handed, objective, explicit, and firm expectations agreed upon by everyone concerned can be helpful.

4.7 Addiction and Pain Problems

Patients who are suspected of having chronic pain and addiction to pain/prescription drugs (see Chap. 22) often generate frequent consultation requests, especially if the referring physicians believe the psychiatric consultant is skilled in these areas.

Appendix 1: Glasgow Coma Scale (GCS)

The GCS results in a score between 3 and 15, with 3 being the worst and 15 the best. It is composed of three parameters—best eye response, best verbal response, best motor response—as given below:

Best eye response (1–4)

1. No eye opening
2. Eye opening to pain
3. Eye opening to verbal command
4. Eyes open spontaneously

Best verbal response (1–5)

1. No verbal response
2. Incomprehensible sounds
3. Inappropriate words
4. Confused
5. Orientated Best motor response (1–6)

1. No motor response
2. Extension to pain
3. Flexion to pain
4. Withdrawal from pain
5. Localizing pain
6. Obeys commands

Note that the phrase "GCS of 11" is essentially meaningless, and it is important to break the fig-

ure down into its three components, such as "E3V3M5 = GCS 11." A GCS of 13 or higher correlates with a mild brain injury, 9–12 is a moderate injury, and 8 or less a severe brain injury. (From Teasdale G, Jennett B, Murray L, Murray G. Glasgow coma scale: to sum or not to sum. Lancet 1983 Sep 17;2(8351):67 8, and available at http://www.trauma.org/scores/gcs.html).

Appendix 2: Mini-Mental State Examination (MMSE)

Orientation	Score to be added up
What is the year, month, date, day of week, season?	5
Where are we? Country, State, City, Hospital, Floor	5
Registration	
Give the names of 3 objects, then have pt repeat all 3	3
Attention, Concentration, Calculation	
Serial 7 s for 5 answers	5
Recall	
After 5 min, ask for the 3 names of objects	3
Language	
Name two objects shown (e.g., watch, pen)	2
Repeat "No Ands Ifs or Buts"	1
3 Stage command "Take this paper in your right hand, fold it in half, and put it on the bed next to you" 1 point for each done correctly	3
Write on paper "Close your eyes," give it to pt, ask pt to do what it says	1
Please write a sentence on this paper (must have subject and a verb)	1
Visuomotor Function	
Copy two intersecting shapes(e.g., two pentagons, a hexagon and a pentagon)	
The total number of angles should be correct and they must intersect	1
	30

Adapted from:

Folstein MF, Folstein SE, McHugh PR. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189–98.

Appendix 3: Montreal Cognitive Assessment (MOCA)

This test and instructions may be downloaded from http://www.mocatest.org/

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Psychiatric Consultation in the Emergency Setting

5

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Contents

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5.1 Overview

Consultants may be called to an emergency department for a variety of reasons. Most requests are like those from a general hospital ward. However, two issues are notable: a broader definition of psychiatric emergencies and greater concern about patient rights. These issues stem from an emergency department's lack of a buffer from its surrounding community: patients come as they are, whether pushed, or just so inclined, whether in crisis, or just avoiding clinic appointment delays. There is little or no time for patients and emergency department staff to come to any understanding. In this absence of a traditional physician–patient relationship, consultants may be forced to change their usual approach.

Psychiatric emergencies now include patients who are depressed, disorganized, odd, or acting badly for no obvious gain. Psychiatric emergencies traditionally meant patients going berserk: yelling, screaming, likely to hurt themselves or others. The newer, broader definition follows in part from a better appreciation of the morbidity of untreated psychiatric illness. And it follows in part from a fear of liability for homicidal public violence, perhaps as part of a suicide attempt. Ever since the Columbine High School massacre, Americans have become leery of any adolescent talk or behavior suggesting depression or self-destructive urges. Widely publicized shootings at schools (Sandy Hook, Virginia Tech), workplaces (Fort Hood, Accent Signage), and public events (Tucson, Aurora) have further increased public fears of mental illness (Follman et al. 2012).

Concern for the patient's right to accept or refuse medical treatment is another frequent trigger for emergent consultations. Old attitudes were simpler: "If you want treatment, walk in: if you don't want treatment, walk out." Such attitudes are very fitting for a country of frontiersmen. However, there are few frontiersman left, and more urbane citizens worry that the complexities of medical treatment will elude anyone whose cognitive capabilities are impaired, by mental or by medical illness. Psychiatric consultants find themselves cast as arbiters of medical choice.

An emergency department setting does entail other specific issues: time constraints, incomplete histories, overt patient intoxication, admission screening, ambiguous patient status, shifting treatment personnel. Moreover, some emergency departments expect their psychiatric consultants to assume responsibility for cases, though these consultants may have neither dedicated nursing staff nor dedicated psychiatric beds. General hospital consultation skills are helpful in an emergency department, but when assuming responsibility for cases, good inpatient treatment skills can become critical.

Because psychiatric consultation to an emergency department has so much in common with consultation to general medical and surgical wards, this chapter focuses on the areas of divergence. The nature of patients coming to emergent psychiatric attention is the first topic. Then, a clinical vignette is presented for purposes of discussion throughout this chapter. Discussions of medical clearance, evaluation, and treatment follow.

5.1.1 Expulsion from the Social Matrix

People end up in an emergency department because they have been expelled from their social matrix. Almost everyone lives in some sort of community, some social matrix. Neighbors, if not immediate family members, surround most people as they begin their day. Working people travel to another segment of their matrix for part of the day. There are usually other places to eat, shop, or find entertainment. There are different people in different segments of each matrix, different expectations in different segments. However, there are expectations, there are limits on behavior; failure to meet expectations, failure to abide by limits, leads to expulsion.

Suicidal comments commonly lead to expulsion. Family and friends were probably more encouraging and tolerant in the past. These days they may worry about murder-suicides or another school/workplace/public massacre. They often push patients to psychiatric attention.

Some patients do come on their own. They complain they are anxious, overwhelmed, or depressed, even suicidal. However, only a fraction come on their own, truly believing that no one around them is concerned. And many of them first seek care in a clinic or office setting (only to discover a scarcity of treaters).

Criminal behavior usually results in transport to jail—a hardened, closed segment of the social matrix. Only a small fraction of these people come to psychiatric attention. On the other hand, expulsion for unacceptable behavior that serves no obvious criminal gain, or is just odd, usually results in transport to emergency psychiatric attention. One patient was brought to our emergency department for waving a snow shovel at passing cars. He had not actually hit a car or driver. But there was very little snow on the ground and no conceivable purpose to his actions. Eventually, we located his mother who told us that he suffered from schizophrenia, had stopped taking his medication, and wandered away from home. (We returned him to his caregivers in a nearby state.)

Communities could make other arrangements for their strangely behaved: a local mental health center could operate an around-the-clock intake service. However, these days, managers abhor the labor costs associated with around-the-clock service. Hospitals, police departments, fire departments, and fast food restaurants are the only around-the-clock operations found in most communities. Of these, only hospitals and police feel obliged to deal with disturbed patients. It would take major changes in health care funding to make mental health center economics more amenable around-the-clock service: even the ACA, the Affordable Care Act is unlikely to effect such a transformation (HHS).

5.1.2 Vignette

Psychiatry was called to consult on a middle-aged, married, Caucasian woman with no formal psychiatric history. Her husband brought her to our emergency department Monday evening because she could not walk, again. Generally healthy, even athletic, she first had trouble walking a few weeks ago, after a pet was lost during a family outing. The pet was eventually found. However, there have been some continuing financial stresses, and she was very ambivalent about a recent, milestone birthday.

She first complained of leg weakness on the day after their outing. Her husband took her to a small hospital near home. The workup was unrevealing. She was released. She suffered a recurrence a few days later, which led to an admission and an extensive workup (including magnetic resonance imaging and lumbar puncture). All tests were normal.

About a week has passed since discharge. Neither patient nor husband could describe any other unusual events. Staff at the first hospital faxed all available test results to us. Her blood count, sedimentation rate, glucose, and a few other easily obtained lab tests were rechecked. There seemed to be very little possibility of any rapidly progressive or new disease; no abnormalities were found.

Patient and husband were cooperative. Both were concerned about her inability to walk, both were a bit exasperated that there was no diagnosis. Her husband eventually became tired of all the time spent waiting around our hospital; he went home to relieve their baby sitter. Our patient seemed a bit subdued, affect a bit flat, but otherwise entirely normal. No other stresses or conflicts were elucidated. Family history revealed no mental illness and no neurologic illness.

The emergency medicine staff initially requested psychiatric consultation, but later suggested that this patient be moved from their area to our locked unit (within the emergency department). No one believed she was a safety risk. Since space was not tight in our medical area, transfer was delayed for a few hours for a trial of oral lorazepam. She was given 1 mg along with the suggestion that her weakness was likely due to stress, for which lorazepam might be helpful. She was also told that if she could not walk, she would have to be admitted to the psychiatry department, since we could find no reason to admit her to a medical service. (All of this was communicated in a very matter-of-fact manner.)

After about 90 min, the patient was reexamined and was now able to move her feet a bit. After about 2 h, she could stand on her own. When called, her husband sounded tired, but willing to fetch her, provided she could walk to use the bathroom on her own. This was relayed to her. About 20 min later she felt ready; she walked 20 ft to the nearest bathroom. She was discharged with a referral to a psychiatric clinic near her home.

5.2 Evaluation

5.2.1 Medical Clearance

The above vignette raises a number of issues in emergency department consultation. First and foremost is the issue of medical clearance. Colleagues talk of patients being medically cleared as if it were a routine process like being disinfected or immunized. Unfortunately, it has more in common with security clearance, a process of looking into someone's history for clues of disloyalty or past criminal behavior that might lead to future security breaches or outright spying. There is no reliable lie detector, no reliable medical illness detector. There is no simple collection of medical tests to ensure the absence of medical illness affecting mental function or behavior (Allen et al. 2005; Lukens et al. 2006; Shah et al. 2012; Zun and Emembolu 2010).

The odds of a mental illness being due to a general medical condition are reduced if a patient's urinalysis is benign and blood tests are all within normal limits (white blood cell count, hematocrit, glucose, blood urea nitrogen, creatinine, and electrolytes). That leaves thyroid disease and liver disease untested, and even testing for those leaves very pertinent conditions like multiple sclerosis and B12 deficiency untested. The list goes on and on. Multiple sclerosis, vasculitis, even Wilson's disease are all possible, although uncommon, in a previously healthy adult. As our vignette demonstrates, a thoughtful workup for acute neuromuscular disease ranges far beyond anything reasonable in an emergency department; it used to take a 2-day medical admission.

Viewed from another perspective, our patient's extensive workup demonstrates that most adults who report they have been healthy are in fact healthy, at least as far as simple blood tests reveal. Medical history, vital signs, and physical examination are the most useful steps to detect medical illness causing psychiatric symptoms.

What about uncooperative patients, or those very disturbed patients who cannot give a coherent medical history? They represent a true challenge for emergency medicine physicians and psychiatrists alike. The history still provides the most helpful information, though it may have to be obtained from ambulance staff, police, friends, family, and old records. The physical exam gives a clue about trauma, systemic illness, and recent living conditions. For elderly patients, urinalysis may reveal unsuspected urinary tract infection. For younger patients, alcohol breath testing, finger-stick glucose measurements, and urine toxicology screening are the laboratory tests most likely to provide a clue about their acute behavioral disturbances.

5.2.2 EMTALA—Emergency Medical Transfer and Active Labor Act

EMTALA (part of COBRA, the Consolidated Omnibus Budget Reconciliation Act of 1986) has made medical screening exams mandatory for hospital emergency departments, regardless of chief complaint (American Academy of Emergency Medicine 2006). Free-standing psychiatric walk-in clinics, even some attached to medical clinics, would not normally perform physical exams, check vital signs, or draw blood for laboratory tests. Nonetheless, EMTALA mandates medical screening in an emergency department. Patients with only psychiatric complaints are not exempt. Luckily, EMTALA's requirement is not detailed, so a short examination, expanded only based on a patient's physical complaints, seems appropriate.

5.2.3 Psychiatric Evaluation

5.2.3.1 Overview

Once emergency department clinicians have concluded that their patient's complaints are not principally due to medical illness, psychiatric

evaluation becomes the main task. Psychiatric evaluation in an emergency department is very similar to psychiatric evaluation on a medical or surgical service. The primary difference is in the nature of a patient's story. Consultation for a medical patient requires an understanding of the patient's medical history and treatment with particular attention to aspects that affect brain function and to aspects that resonate with prior psychological experiences. On the other hand, psychiatric patients arriving in an emergency department usually have no medical illnesses and no active treatments.

5.2.3.2 The Story

The story, critical to a psychiatric patient's arrival in an emergency department, is the story of their expulsion from their social matrix. Did they do something dangerous? Did they say something? Who became concerned? Is this a change? How long has this been happening? If this information is not available, consultation must proceed cautiously, if at all. Occasionally, the available information is misleading. Ex-boyfriends and ex-girlfriends have been known to falsify reports to the police of odd or dangerous behavior. Their hapless victims arrive in our emergency department, quite surprised. Once calm, they can usually provide some collateral source of information to support their request to be released.

The story is also critical because symptoms and diagnosis do not always determine treatment. A patient may hear voices, telling him he is no good, telling him that he ought to die, but he hears them chronically and ignores them. If such a patient walks into an emergency department, on his own, for an intractable cough, he may need testing for tuberculosis, but he does not need psychiatric admission. However, another patient with exactly the same complaints, sent from jail because he has been banging his head bloody on cell bars, likely needs psychiatric admission.

A patient's history should make sense as a story. The patient in our vignette might have recounted something like this: "Things have been tough around our house since my company relocated out of state. I had a good job, but my husband's work pays more, and he's got a lot of seniority, we couldn't afford to move. Problem is, I haven't been able to find work. I haven't got any special skills. Money's been tight. I was fretting about the cost of our camping trip. Then our dog ran away. I couldn't stand it. As soon as we found the dog, I insisted we go home. I couldn't sleep. I was so weak the next day."

Such a story would make perfect sense as part of our vignette. It offers an entirely plausible sequence of events. Its wording provides a nice linguistic connection to our patient's symptom. Alas, no such recitation was part of either our patient account or her husband's.

Patients occasionally offer stories that make no sense from a psychological or social perspective: "Everything was fine till today. This evening I couldn't walk. Why do you keep asking me how I'm getting along with my family?"

A patient might suddenly become lame, without any change in his or her life, but not based on psychological issues. Such a story only makes sense if the untold prologue goes something like this: "Ms. Jones had a small ventricular septal defect that was never documented. She failed to keep an appointment for an echocardiogram years ago, ordered by a physician who heard a murmur. Ms. Jones believed her health was fine. She complained that their local cardiologist wanted a new car, that's why he recommended a fancy test."

Some stories require detective work. Patients occasionally say: "I've always been depressed. Been that way my whole life. Today's no different. Couldn't take it anymore. I came to the emergency department." This is not a story. As children, even these patients would never have accepted the equivalent bedtime story: "The prince was riding around his kingdom. He turned into a frog. The end." It falls to a consultant or emergency department staff to call the patent's friends or family in search of an undisclosed offense toward an undisclosed witch.

Some stories never achieve coherence. Our lame patient's vignette makes unsatisfying human drama. No doubt, both husband and wife omitted some critical details. Was there a dispute, an affair? It was never revealed to us. Treatment had to proceed with a nonspecific intervention.

5.2.3.3 Social Review of Systems

A social history and a developmental history can be very helpful for emergent psychiatric evaluation. The challenge is to stay on task, to understand why a patient has been extruded from their social matrix, why they have been extruded today. Reducing social history to an inventory of substance use, or reducing developmental history to a timeline of infant milestones, is not informative. It is more helpful to think in terms of patients' progress and their place in society: a review of their social systems. Did the patient start poor and later climb the corporate ladder? Was the patient born into riches, but slipped into a life on the streets and in homeless shelters? These contrasting trajectories suggest different diagnostic possibilities, though either patient might initially come to our attention as a man found wandering by the police.

For the social review of systems, first come questions about our patients' start in life. What was their family of origin like? Where did the patient grow up: in a ghetto, a rough-scrabble rural area, a wealthy suburb? Modern American demographers would opine that the mother's zip code at the time of the patient's birth provides a good clue. However, it is friendlier to ask: "Where were you born? Where did you grow up? What did your parents do for a living?" Indeed, many patients will talk at length about childhood, their family, friends, accomplishments, and disappointments, yielding everything needed to understand their current crisis.

Knowing the patient's starting point in life, we can then ask what kind of school they attended, how far their education progressed. These answers round out our picture of the patient as a child; they give us a sense of how he or she performed at society's first task: being a student. Traditional developmental milestones are not very helpful in evaluating adults in an emergency department; if they were not successful at walking, talking, and toilet training, they would probably arrive from a supervised living arrangement, complete with a report on their disabilities (see Sect. 5.5.1).

Next come questions about young adult challenges: work, military service, finding a spouse. Now, it may turn out that the patient succumbed to schizophrenia or substance abuse at this critical stage, which changes our expectations. Or the patient may have had a more benign life, in which case we can ask how she or he did relative to their parents.

Finally come questions about current social function: home, work, family. These are traditional elements of a social history, but more meaningfully seen as part of a lifelong social trajectory. Inquiring about hobbies may provide a benign entree to critical information. Some hobbies involve activities and exposures to solvents with orthopedic or neurologic sequela. Even descriptions of quieter hobbies may yield a wider range of affect. And asking about hobbies provides a natural segue to questions about guns and weapons available to the patient.

Questions about alcohol, tobacco, and substance abuse often fit better with questions about past psychiatric history than about social history. Americans increasingly view addictions as a type of psychiatric illness. It is only physicians who have been trained to think of a social history as "no tobacco," or "three to four beers per week."

Local variations and newer substances of abuse present a challenge for emergency department clinicians and consultants. Oblique references to "bath salts" or "K2" may provide an important clue about a patient's substance misuse (Volkow 2011). The term "bath salts" is a ploy, a packaging trick to avoid the attention of authorities, sort of like calling a pistol a hammer or rifle a walking stick. "K2" contains synthetic marijuana like substances. It is not so subtly named after the earth's second highest mountain. These and other local favorites may or may not be detected by local urine tests.

5.2.3.4 Traditional Review of Systems

A review of systems (ROS), in the traditional sense, is a useful addition to the psychiatric evaluation. It can serve as a wrap-up, or a short review of the patient's medical history, head to toe, system by system. It helps ensure that a consultant understands the patient's condition.

An ROS can also be very useful to psychiatrists reimbursed by Medicare and other payers

following the Centers for Medicare and Medicaid Services (CMS) 1995 and 1997 Documentation Guidelines for Evaluation and Management Services (Centers for Medicare and Medicaid Services 2006). The CMS guidelines divide a physician's chart note into components, which are then tallied according to a complicated scoring system. This process has been termed "bullet counting" in honor of the bullet points adorning the many computer slide presentations used to explain this system. For a history of present illness (HPI) to rate as an extended HPI, as obtained by many consultants, an ROS must be included (or there must be accurate documentation of time spent on counseling and coordination of care).

Whatever the motivation, it does not hurt to recast the usual psychiatric concern for neurovegetative signs into a broader view of a patient's physiology: anorexia and constipation into questions about general gastrointestinal function, anergy into questions about endocrine function, etc. Recording a patient's answers in the form of an ROS can improve both the consultant's understanding of a case as well as the billing office's rating of a case.

An ROS can also serve the mental status examination (MSE). After questioning patients about eye trouble, ask them to identify three objects of decreasing size. It is not as accurate as using a reading chart, but does provide a quick test of language as well as vision. This maneuver also leads to a test of immediate memory: ask patients to name the objects again, without prompting. Finally, toward the end of the MSE itself, ask once again for the names of the objects, yielding a measure of delayed recall.

5.2.3.5 Mental Status Examination

A formal MSE is a critical task for psychiatric consultants in an emergency department. It is second in importance only to a patient's history for diagnosing psychiatric illness and for distinguishing psychiatric illness from general medical conditions. Even when psychiatric diagnosis seems obvious, a formal MSE provides assurance that other serious conditions do not go unnoticed. For example, a schizophrenic patient brought to an emergency department for bizarre behavior should not be lethargic and disoriented; ingestion or head trauma is a more likely cause of such symptoms in this setting.

The cognitive portion of the MSE is the critical component in an emergency setting. Unfortunately, cognitive testing often receives short shrift: physicians write "A&O×3" (alert and oriented in three spheres) when they have ascertained only that their patient is alert and responds to very simple questions. Consultants can add much by clearly documenting a patient's level of alertness, and then asking, and documenting explicitly, a patient's response to questions about their name, their location, and today's date. Along with these responses, consultants should document whether or not a patient remembers three objects after a few minutes, and the patient's ability to spell a five-letter word backward. These six components are, arguably, the irreducible minimum of an MSE.

Risk for violence is another major concern in emergency department consultations: is this patient a danger to himself or others? Some would argue that this is the most critical aspect of an MSE. However, it is rare for a patient's violent inclinations to become evident solely during an MSE. Comments about suicide or homicide are usually included in the chief complaint or reason for consult. Common practice requires some documentation of a patient's suicidal or homicidal thoughts with an MSE; however, if these are serious considerations, they warrant explication within the HPI.

Unfortunately, form and wording of questions receives short shrift in busy emergency departments. National efforts to reduce suicide have triggered some consults simply because a patient tried to honestly answer his literal interpretation of questions like "have you ever thought of killing yourself." It is hard to know whether staff asking this misspoke, were misunderstood, or failed to follow up by asking "what put you in that state of mind?" That could yield an explanation like "we were watching *The* Last Samurai on NetFlix." This would allow evaluation of the patient's belly pain to proceed apace without psychiatric input.

Consultants would do well to review the actual tone and form of their own questions around

sensitive topics. Consider "any reason anyone would think you were going to cause trouble? hurt yourself or anyone else?" It is deliberately ambiguous. It avoids asking a patient to directly admit contemplating suicide or homicide: sins in most religions. It simultaneously allows a patient to mention behaviors that have worried friends/family. Of course, it is an obvious opening to discuss violent thoughts if even if no one else is aware yet, e.g., "no, but I've been spending a lot of time cleaning my service revolver."

Deafness may not normally be considered a topic for the MSE, but it occasionally confounds psychiatric consultation. Fast-paced, noisy emergency environments increase the odds that a patient who is hard of hearing will be mistaken for a patient who is disorganized or bizarre. Psychiatrists should have a high index of suspicion when consulted about older patients who are reasonably groomed, without history of psychiatric treatment, and who are alert but give nonsensical answers. Such patients can seem quite fine, and begin their interactions normally enough. They recognize the attempt to converse; they just cannot hear the words. Once this problem is recognized, there are often obvious solutions (quiet examination room, amplifier, writing, etc.).

A complete MSE has a number of other components; psychiatrists rarely fail to comment on mood, affect, hallucinations, and such. These are all useful, and certainly should be recorded. However, it is the cognitive portion and inclinations to violence that merit special attention during consultations in an emergency department.

5.2.3.6 Physical Examination

Under certain circumstances, the physical examination becomes important to psychiatric evaluation in an emergency department. If a psychiatric consultant is expected to be responsible for the physical examination and medical care of patients in an emergency department, that needs to be very clearly understood, along with guidelines for transferring complicated medical care back to an emergency medicine physician.

In addition to a critical role in detecting major medical illness, physical examination may yield objective evidence about a patient's mental state. Dirt, untreated sores, ragged fingernails, and odor are physical findings that augment traditional psychiatric evidence that a patient is confused, distracted, or disorganized.

Old neck and wrist scars can support a history of prior suicide attempts. Fresh, deep wounds suggest a greater risk than superficial scratches.

Physical findings may also be of legal importance. Failure to document physical injuries from a suicide attempt may cast doubt on the overall psychiatric evaluation, for example, when a patient challenges an involuntary commitment or a judge considers appointing a conservator.

5.2.4 Diagnostic Considerations

Diagnostic considerations are quite similar in both emergency departments and general hospital wards. Both settings can host a full spectrum of psychiatric problems, ranging from chronic mental illness to side effects of research protocols. However, some problems are more common in one setting than the other. Acute schizophrenic exacerbations are more common in emergency departments. Delirium is more common in medical and surgical units. Still, the diagnostic efforts remain more alike than different.

Separating traditional mental illness from mental illness due to a general medical condition is a diagnostic challenge that warrants extra attention. From an emergency department, patients are often transferred to very different facilities based on diagnosis. Transfer may be to a psychiatric hospital with little capacity to treat conventional medical illness. Or admission may be to a general hospital with no psychiatric wards. Sending patients to the wrong institution can cause significant morbidity and cost.

This challenge to differentiate psychiatric from medical illness is often posed to consultants in a short clinical vignette: "A man was brought by his family because he'd been acting oddly; they became worried and brought him to our emergency department because they did not know what else to do." A subtle tone may hint that the consultee is really quite uncertain what to

do. Guidelines follow to help direct diagnostic attention. They are based on my experience in urban settings; thus a priori diagnostic probabilities could be different in other locales. These guidelines assume basic triage findings have not been contributory, such as vital signs, finger-stick glucose, alcohol breathalyzer, inspection for head trauma. These guidelines serve as a starting point for further investigation.

Two critical pieces of data must be available: 1) Onset or time course, 2) Age

Past history, medical and psychiatric, is the next most important information. Friends and family are often the best source of this information when there is suspected mental illness.

So we must elaborate on our vignette: A 66-year-old retired businessman was brought by his wife because Saturday morning he suddenly started talking to someone who was not there. He has never seen a psychiatrist. His internist is following his high blood pressure.

An alternate elaboration might go as follows: A 22-year-old college student was brought by his parents because they noticed that Saturday morning he was talking to someone who was not there. He had been out very late Friday night with friends. He has never seen a psychiatrist and has generally been in good health.

Neither of these patients is likely to be suffering from new-onset schizophrenia, although, theoretically, both could be. More likely, the older patient has had a stroke; the younger patient has ingested some illicit substance. Careful neurologic exam, and perhaps neuroimaging, are part of the initial workup for the older patient. Urine toxicology screening is an immediate part of the workup for the younger patient. These sorts of considerations above are expanded in the guidelines below.

5.2.4.1 Convenient Categories

5.2.4.1.1 Onset

Acute	<48 h
Subacute	<1 month
Gradual	<6 months
Insidious	6+ months

5.2.4.1.2 Age

Children	birth to 12 years
Teens	13–16
Young adults	17–25
Adults	26–64
Elderly	65+

5.2.4.1.3 Likely Etiologies

Acute onset (unlikely to be a traditional psychiatric illness)
- Children: infection, unrecognized ingestion, trauma
- Teens: ingestion (intentional or not), infection, trauma
- Young adults: same as for teens, but ingestions are almost always substance abuse; be alert for meningitis/encephalitis depending on living situation
- Adults: same as for young adults, but add central nervous system (CNS) vascular events, and ingestions include prescription drug side effects, other iatrogenic effects, including hypoglycemia, and prescription drug misuse
- Elderly: infection (urinary tract) and CNS vascular events most likely, otherwise same as for adults

Subacute (anything is possible)
- Children: endocrine, metabolic, infection, seizures, subdural (trauma), tumor
- Teens: drugs, otherwise same as younger children
- Young adults: differential is very broad, anything from lupus to schizophrenia may first manifest itself
- Adults: most psychiatric illness would have already declared itself; but infections and inflammatory disease loom larger over this time span, and tumor becomes a possibility
- Elderly: same as for adults, but effects of drug changes, drug buildup, congestive heart failure all add to the picture

Gradual (psychiatric illness becomes more likely)
- Children: family conflicts, developmental abnormalities, environmental, other
- Teens: drugs, family conflicts, pregnancy, psychiatric
- Young adults: psychiatric, drugs, autoimmune

Adults: psychiatric, drugs, HIV, tumor
Elderly: dementia, cerebrovascular accident (CVA), B12 deficiency, normal pressure hydrocephalus

Insidious (psychiatric illness remains quite possible)
Children: family conflicts, developmental abnormalities, environmental, other
Teens: drugs, family conflicts, psychiatric, pregnancy
Young adults: psychiatric, drugs, autoimmune
Adults: HIV, tumor, psychiatric, drugs
Elderly: dementia, CVA, B12 deficiency, normal pressure hydrocephalus

In general, acute changes in behavior or mental status suggest medical illness or ingestion. Gradual or insidious onset reduces the odds of acute medical illness (infection, infarction), but does NOT rule out inflammatory process (lupus), endocrine disease (thyroid), or tumor. Workup for slower onset changes is likely to include brain imaging, thyroid testing, HIV testing, and the center's preferred tests to rule out autoimmune disease; however, this may not really be appropriate in an emergency department itself.

Based on the above lists of rough diagnostic probability, the following tests can be considered (keeping in mind emergency department time limitations).

GLU: Glucose, since not all diabetics give a clear history, yet may be taking hypoglycemic agents

U/A: Urinalysis for the elderly, since delirium or cognitive impairment can be seen with otherwise asymptomatic urinary tract infection; a chest X-ray for relatively asymptomatic pneumonia is an option

WBC: White blood cell count, as a second test for otherwise asymptomatic infection in the elderly and in young patients

EtOH & U-Tox: Alcohol breath testing and urine toxicology screening for ages 13–64 (can be selective); substance abuse is often omitted (or denied) when patients give a history

LFT: Liver function tests, for clues about covert alcohol use, poisoning, and drug side effects

BUN/Cre: Blood urea nitrogen and creatinine may reveal early kidney disease

ESR: Erythrocyte sedimentation rate along with C-reactive protein can be helpful if negative; can essentially rule out infectious or inflammatory illness

CT/MRI: Brain imaging with computed tomography or magnetic resonance imaging may prove helpful in patients of ages 26–64; old strokes and atrophy are often seen in older patients, but not helpful in making decisions about a particular emergency department visit

LP: Lumbar puncture should be considered if there is any question of central nervous system infection

A number of commonly ordered tests are rarely helpful. Electrolytes are almost never a cause of behavioral disturbance unless there is a history of eating disorder, drinking, or polydipsia. (Hyponatremia is occasionally a side effect of SSRIs in the elderly.) Normal BUN and Cre and the absence of any suggestive history should be sufficient, likewise for serum calcium, magnesium, and phosphorus. Thyroid testing is very rarely helpful, unless a patient has a history of thyroid dysfunction, and results are rarely available in a reasonable time frame. (In my experience, uremia is a better mimic of major depression than is thyroid disease, and internists usually diagnose thyroid disease long before patients come to psychiatric attention.) Venereal Disease Research Laboratory (VDRL) or fluorescein treponema antibody (FTA) testing for syphilis, along with B12 and folate testing for nutritional deficits, should be considered in puzzling cases. However, these are also unlikely to be available in a timely fashion.

5.3 Treatment

Distractions and time pressure can make emergency department treatment difficult: it is a noisy, busy place. Conventional wisdom holds that the only real options are "treat or street," that is, admit for inpatient treatment or discharge to the street. In truth, simple-minded approaches are a bigger distraction than the noise and activity. Accurate evaluation facilitates efficient treatment, whether or not a patient requires admission. Less-than-thoughtful evaluation risks complications and morbidity.

5.3.1 So-Called Agitated Patients

So-called agitated patients are repeated tests of each consultant's ability to make careful psychiatric evaluations in an emergency department. Luckily, the majority of agitated patients can settle down, can be *de-escalated* without physical force (Richmond et al. 2012). Trained staff, careful planning, and thoughtful facility design are important factors before a consultant arrives. The American Association for Emergency Psychiatry's *Project BETA* articles offer various suggestions to reduce the need for physical restraints and forced medications (Holloman and Zeller 2012). Their emphasis is on training staff to de-escalate patients as early as possible. This can be as simple as agreeing with a patient that it is a shame his freedoms to drink and dance nude in public have been constrained. It then often helps to offer a snack and sympathetic comments, or even an apology for the delay in getting through a busy emergency department. This can avoid the unfortunate angry, drunken fight between patient and staff.

Teaching emergency department staff to use appropriate tactics and to invest extra effort initially, can yield significant saving in total time and effort. This can also minimize the sequela of forcible patient management: injuries, needle sticks, and resentment. The most basic tactics to teach are respectful etiquette and simple helpfulness. A certain number of patients will rise to meet the implicit social expectation; a larger number will respond to implicit service even if they are not really there for food and water.

Staff training can help resist urges to insist patients *calm down*, *shut up*, *sober up*, and *behave*. An authoritarian tone will escalate many patients. Treatment areas may need to be rearranged, giving patients room to move, and walk around, maybe watch TV. Implicit restrictions only add to a patient's irritability.

Emergency department staff and consultants do well to meet agitated patients more than half way: even the angry and upset may have some goals in concert with staff, if only quick discharge. Explicitly pursuing areas of agreement first, though not quite routine protocol, may enlist some cooperation and reduce patient frustration.

When accentuating the positive does not work, a show of force by clinical and security personnel may work for another significant fraction of the patient population. The goal is to make expectations about safe behavior clear. Avoid interchanges like *if you do this then we'll have to …* which may be taken as a challenge to up the ante. That will still leave an occasional, unmanageable patient that requires physical restraints (Rund and Hutzler 2004) unless local authorities and ambulance crews all agree to send combative patients elsewhere.

Faced with an unmanageable, agitated patient, many clinicians reflexively order a mixture of tranquilizers. "Five-two-and-one" is a favorite combination: haloperidol 5 mg, lorazepam 2 mg, and benztropine 1 mg. Few clinicians even wait for registration to confirm patient identity and computerized records to report known allergies; luckily, true allergies are rare to haloperidol or lorazepam or benztropine. Fewer clinicians yet, even in quiet moments, seriously consider the need for benztropine when haloperidol is given with lorazepam. Benzodiazepines are a second or third-line treatment for parkinsonian side effects; I have never seen dystonia after one injection of haloperidol with lorazepam. Medication is not the first line of defense against violent or dangerous patients. Table 5.1 lists some times to consider (Drugdex 2006; Eli Lilly 2006; Pfizer 2005).

Only anesthetic agents begin to work quickly enough to stop a truly raging patient. Realistic wild-animal shows (e.g., National Geographic) show chemical dart guns being used from a distance, preferably from a truck. Raging rhinos can cover a lot of ground in the minutes required for modern opiates to take effect. (Difficulties ventilating rhinos in the wild make succinylcholine an unattractive option.) (Table 5.1).

The inevitably delayed effect of psychiatric medication is yet another reason to try de-escalation tactics whenever possible. Meantime, pharmaceutical companies are pursuing new antipsychotics/tranquilizers. Inhaled medications

Table 5.1 Peak and half-life for commonly used drugs

Peak	Half-life	Drug (intramuscular route)
1–3 h	12 h	Lorazepam (Ativan)
1 h	2–5 h	Ziprasidone (Geodon)
30 min	30 h	Olanzapine (Zyprexa)
20 min	21 h	Haloperidol (Haldol)
10 min	4 h	Fentanyl (Sublimaze)
2 min	1 min	Succinylcholine (Anectine)

might provide faster results: tests of inhaled loxapine showed some measurable effect in just 10 min, at least in a company sponsored study (Lesem et al. 2011). Inhaled loxapine under the name Asasuve™ was approved by the FDA in FDA 2012 (NDA 022549). Further testing may or may not demonstrate true clinical utility with agitated patients: an inhaler requires patient cooperation and loxapine's mechanism of action is the same as haloperidol.

Once a patient is physically safe, it is time to carefully review what is known and what can be determined by exam, perhaps even by interview. (A small number of patients do settle down once restrained.) Thoughtful clinicians consider a number of possibilities: Is this patient intoxicated? Is there evidence of head trauma? Is this patient already taking a sedative? Is this patient known to respond to some specific treatment? Noncompliance/nonadherence is a common cause of relapse; if patients will accept an oral dose of their routine medication, recovery will be underway.

Keep in mind that patients, their families, and our colleagues are all human; in a crisis they may fail to report critical information. One very large, very paranoid, and then very combative patient required the efforts of eight staff to subdue him. Only afterward did his mother reveal that he had jumped out a second-story window—that was the real reason she had finally brought him to the emergency department. Initially, she had only mentioned he was acting "differently" for a few days. Given his obvious, initial anxiety, the triage staff slotted him directly for psychiatric evaluation without any check for trauma. You can imagine the staff's anxiety on discovering that the patient they had just wrestled into restraints was at risk for a broken neck. Luckily, there were no fractures and the patient's phencyclidine eventually lost its hold on his thinking.

At the time of this writing, there is no diagnosis of "agitation disorder" or "agitation disorder not otherwise specified" in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (APA 2013). Indeed, there is not even an entry for "agitation" in the index to DSM-5. This could all change. Until then, there is no official approval for the concept of drug treatment of an "agitated" patient. We can recognize and keep clear in our minds that we do treat some patients before we are certain of their diagnosis. Careful consideration of a given patient's diagnostic possibilities allows careful choice of treatment, even if it is a combination of drugs (Alexander et al. 2004; Allen et al. 2005; Andrezina et al. 2006; Battaglia et al. 1997; Breier et al. 2002; Breitbart et al. 1996; Broderick et al. 2002; Brook et al. 2000; Eli Lilly 2006; Food and Drug Administration 2001, 2006; Martel et al. 2005; Pfizer 2005; Preval et al. 2005; Scahill et al. 2005; Tesar 1996; TREC Collaborative 2003).

5.3.2 Alcohol Withdrawal and Sedative/Hypnotic Withdrawal

Most alcohol withdrawal is either directly reported by patients themselves or strongly suggested by histories of alcohol abuse. There are no special considerations in an emergency department; it is best to treat before overt delirium tremens or seizures are manifest.

It is a little more common in an emergency department for patients to claim, "I'm just always anxious." They may hope to keep their addiction a secret. They may hope for a benzodiazepine prescription and then to be on their way. One trainee was thus misled by an entirely pleasant, middle-aged woman who promptly seized when the attending arrived to examine her.

Sedative/hypnotic withdrawal is essentially identical to alcohol withdrawal. Unfortunately, finding a suitable dose of replacement can be a challenge; patients frequently minimize or

exaggerate their daily use. There may be some advantage in sticking with whichever agent the patient normally takes.

It is important to differentiate among the sedating agents. Withdrawal from agents that affect γ-aminobutyric acid (GABA) receptor complexes leads to symptoms of alcohol withdrawal (benzodiazepines, barbiturates, alcohols). Agents that work elsewhere (antihistamines, antipsychotics) do not treat alcohol withdrawal; indeed, antihistamines can aggravate matters by lowering seizure thresholds. Agents not traditionally considered sedatives (opiates, antidepressants) can independently cause sedation in emergency department patients, further complicating evaluation and treatment.

In my experience, the most common errors in the treatment of alcohol withdrawal are failure to diagnose until quite advanced, and failure to give adequate doses of benzodiazepines. It is easy to dismiss anxiety and mildly elevated vital signs in a middle-aged accident victim, but remain alert for symptom progression and a history of alcohol use. Though standard doses of benzodiazepine (e.g., diazepam 5 to 10 mg) are usually effective, some patients need a lot more (Mayo-Smith et al. 2004).

5.3.3 Anxiety

Patients in an emergency department may be anxious for a wide variety of reasons. Making treatment even more difficult, their physical problems may not be fully known at the time a psychiatric evaluation is requested. A patient going into shock might report "anxiety," a "nervous, queasy feeling," especially if he is already in psychiatric treatment. This requires the consultants to an emergency department to carefully review vital signs, physical findings, and test results, some of which may not yet be integrated into a complete diagnosis.

When anxiety is a manifestation of physical illness or preexisting psychiatric illness, the first course of action should be to treat the underlying problem. Then, check for improvement or worsening. Reflex administration of a benzodiazepine may cloud the picture.

Fear is more common than one might guess, at least based on emergency department conversations. People often prefer Freud's use of anxiety, a psychological signal of inner conflict, to fear, a central nervous system signal of potential mortality (or morbidity). Nevertheless, patients in an emergency department may have very real reason to be afraid, and it may fall to a consultant to point this out.

Fear may respond to facts, family presence, and general reassurance. If these and other simple maneuvers fail, be alert to pain as a critical underlying factor. Pain and fear are supra-additive. Likewise, a little attention to analgesia may yield large improvements. Lastly, fear responds to benzodiazepines, but at a cost in alertness, cognition, and memory.

Anxiety disorders themselves, particularly panic disorder, may present and be first diagnosed in an emergency department. A panic attack is likely to respond to a benzodiazepine, which is a reasonable, immediate intervention. That then leaves the rest of the medical workup (e.g., thyroid tests, which are not immediately available), and psychiatric follow-up (i.e., overall condition, side effects). Unlike medical ward consultation, there may be no option to see a patient again the next day. Practical limitations in follow-up care are an important constraint on emergency department treatment recommendations.

Recommending an antidepressant to treat an anxiety disorder may not be simple in an emergency department. The FDA (2005) has issued warnings on suicidality in patients treated with antidepressants. These warnings might make it seem negligent to prescribe an antidepressant without first establishing follow-up care.

A short, trial course of benzodiazepines is a common intervention, but one that can lead to problems in an emergency department. If quick psychiatric follow-up is not available, it is no longer a clinical "trial"; there is no trained professional to evaluate results. A more pernicious problem is well known to emergency medicine clinicians—developing a reputation as a facility that dispenses benzodiazepines. If local addicts discover that panic is treated with a week's worth

of Xanax, then there will be a lot of panic attacks to be treated. This does not mean that prescriptions for benzodiazepines should never be dispensed, just that more care is required than in a controlled environment like a medical ward.

Addicts raise other anxiety-related treatments issue in an emergency department. Crack/cocaine and stimulant users may arrive very anxious, due to intoxication. They can be overtly paranoid. A benzodiazepine will usually help. However, be aware that some stimulant abusers do not actually have any sedative tolerance, and may become very sedated. Low-dose antipsychotics may also be helpful. Avoid giving α-adrenergic antagonists in the face of stimulant intoxication as they can increase demands on cardiac output.

5.3.4 Catatonia

The underlying mechanisms of catatonia remain unknown. For emergency department purposes it is reasonable to assume it represents overwhelming anxiety or fear, causing a patient to freeze like a deer in the headlights. This matches the clinical impression that a catatonic patient is awake and alert, not comatose or lethargic. It also leads to use of a benzodiazepine as an immediate intervention. Lorazepam 1 mg IM or IV is usually effective within an hour. Other benzodiazepines should work just as well. Oral doses can be effective but take longer (2 h or longer).

Keep in mind that catatonia is a sign of some other process, likely an affective disorder with psychotic features. Treatment of the underlying process is necessary to prevent recurrence. Repeated attempts to temporize with a benzodiazepine are likely to fail.

5.3.5 Conversion Disorder (Functional Neurological Symptom Disorder)

Conversion disorder is an irritation to emergency departments. Other patients who can be shown to be free from physical ailments are not a problem; emergency department staff members are quite happy to rule out myocardial infarction (so long their patients are reasonably cooperative). The underlying problem with conversion disorder is that these patients are not relieved, rarely grateful, and often cannot leave because their symptom is paralysis. A consultant's real challenge may be to get the patient out.

Conversion disorders were apparently quite common among Charcot's patients; they helped spur Freud's development of psychoanalysis. Unfortunately, in urban emergency departments, patients with conversion disorder rarely show much insight or response to interpretation. Some are quite willing to talk, but usually make no connection among affects, anxiety, and physical (dys)function. Many reveal no clear conflict or recent stressor.

Emergency department treatment often devolves to very general interventions: reassurance that there's no evidence of serious medical illness, suggestions that their physical symptoms are likely to remit on their own, encouragement to continue regular activities as much as possible. Patients who show any interest in counseling or any acceptance of the idea that stress might be a significant issue can be referred to a mental health professional. Be alert that some patients may react quite negatively to any implication that their symptoms are all in their head.

When reassurance and referral fail, consultants can recommend a benzodiazepine, for example, lorazepam 0.5–1.0 mg orally (or parenterally). Before the discovery of benzodiazepines, earlier generations of psychiatrists would use a barbiturate. It is hard to know whether sedation, anxiety reduction, or cognitive dulling is key. Placebo injections are rarely helpful. In any case, after 1 to 2 h, there may be sufficient improvement to allow discharge.

Refractory cases may have to be admitted to a psychiatric facility. Few medical or surgical services will accept a patient whose diagnosis is conversion disorder. Inpatient psychiatric services are a bit more tolerant, and refractory cases may prove to have an underlying psychotic illness.

Pseudo-seizures may not be good cases to treat with a benzodiazepine. An apparent response to benzodiazepine administration may confuse

both staff and patients. Luckily, these patients usually stop seizing, and then accept outpatient follow-up. Those who do not may have to be admitted to a psychiatric service.

5.3.6 Intoxication

Intoxication per se has not traditionally been considered a psychiatric problem. However, consultees may request psychiatric help for particularly bizarre intoxicated patients. And in some facilities psychiatry does take primary responsibility for substance abuse disorders. So some guidelines may prove useful.

Opiate intoxication and benzodiazepine intoxication are the only two types that can be reversed. Naloxone (Narcan) is an injectable opiate antagonist. Flumazenil (Romazicon) is an injectable benzodiazepine antagonist. Both entail significant risks. They are effective, though their half-lives are short compared to most drugs of abuse. Flumazenil can induce seizures in patients who are dependent on benzodiazepines (a significant population in an emergency department). Naloxone treatment can lead to immediate withdrawal, including severe agitation, vomiting, diarrhea, and cramps.

Cocaine and stimulant intoxication cannot be reversed. It may be moderated with a sedative or an antipsychotic. Be wary of medications causing peripheral vasodilation and thus increased cardiac demand (e.g., α-adrenergic blockers).

Hallucinogens cannot be reversed. As with stimulants, a sedative or antipsychotic may be a useful temporizing agent.

Alcohol intoxication cannot be reversed. Anecdotal remedies for reducing alcohol levels upon exiting a pub have yielded no reliable approach; likewise for efforts to reduce aftereffects the next morning. Medical professionals have not fared any better. However, medical and law enforcement professionals have discovered some approaches that increase morbidity and mortality. Benzodiazepines can augment alcohol's suppression of respiratory drive, even though they themselves have very little effect. Droperidol can lead to sudden death (FDA 2001). Rapid osmolar changes from IV fluids can lead to central pontine myelinolysis. These therapeutic pitfalls suggest the primary goal should be simply to keep staff and patient safe until the patient is sober.

Haloperidol can be tried to render alcoholics less agitated until they have metabolized their alcohol. Be aware that haloperidol is a butyrophenone, like droperidol, and has been reported to cause arrhythmia when given IV (torsades de pointes). Alternatively, a high potency phenothiazine (e.g., fluphenazine) would be just as effective or ineffective. Low-potency phenothiazines, and certainly antihistamine sedatives, risk lowering seizure thresholds.

5.3.7 Major Depression

It is quite unfortunate that antidepressant treatment entails risk of suicide during the 3 or 4 weeks required for full effect. Major depression, episodes of depression in bipolar disorder, and postpartum depression may present first to an emergency department. Once the diagnosis is made, it is very tempting to prescribe an antidepressant and send the patient home, just as our medical colleagues do with antibiotics for infections. However, the FDA (2005) clearly publicized the risk of suicidality, if not suicide itself.

Arranging reliable follow-up is now the biggest challenge when starting patients on antidepressants. Follow-up must be available, and there must be good reason to believe the patient will actually go for follow-up. Odds are less than 50% that patients will keep a psychiatric clinic appointment that is simply scheduled for them (some clinics and practitioners do not accept appointments unless patients call on their own). This suggests that a family member or friend should be involved to ensure appointments are kept, and perhaps to bring the patient back if symptoms worsen.

All of the above can seem quite frustrating to consultants. However, the current situation is much improved from the days when only tricyclic and monamine oxidase inhibitor antidepressants were available. Back then, patients could

return to an emergency department dead, or near death, accompanied by an empty pill bottle bearing the prescribing psychiatrist's name.

If reliable follow-up treatment can be arranged, the choice of an antidepressant should be given to the follow-up clinician, who must deal with the complications. Most clinicians start with a selective serotonin uptake inhibitor.

5.3.8 Mania

Mania's treatment may be considered in three phases: immediate, episodic, and long-term prophylaxis. Floridly manic patients usually trigger a request for psychiatric intervention. Their diagnostic possibilities are similar to any inpatient consultation request, although there may be more pure mania in an emergency department population and more stimulant intoxication. Immediate treatment of uncomplicated mania can begin with almost any sedative; benzodiazepines continue to be a favorite.

Manic patients may require a lot of sedation immediately, and some will require an antipsychotic. In an otherwise healthy manic, any sedating antipsychotic would likely work by itself. Chlorpromazine (Thorazine) has a long track record. Olanzapine (Zyprexa) is a new favorite, along with Ziprasidone (Geodon). All three are available in parenteral forms; all three have their drawbacks. Chlorpromazine injections can be locally irritating and require a relatively large injection volume (only available in 25 mg/mL solutions). Olanzapine must be reconstituted before injection and has a long half-life. Ziprasidone carries a precaution about QTc prolongation, which may be difficult to check in a floridly manic patient; that is, avoid use in the presence of other drugs known to prolong QTc, in the presence of arrhythmia, or in the presence of electrolyte abnormalities. All of this contributes to the continued popularity for combination therapy with haloperidol plus lorazepam (Allen et al. 2005).

While most patients respond to any of the above approaches, it is safest to use a medication that has helped the patient in the past. Using a previously successful medication reduces the odds of a new, adverse drug reaction, and makes a start toward treatment of the episode itself.

Clearing an episode of mania is not easy. It usually takes days or weeks. Sedatives alone are unlikely to succeed. An antipsychotic or a drug such as lithium, also effective for prophylaxis, is usually needed. Unfortunately, none of the proven prophylactic agents are likely to be effective quickly enough for emergency department purposes; manic patients must usually be admitted to a psychiatric service.

Unfortunately, restarting patients on lithium or valproic acid (Depakote and others) requires attention to potentially severe side effects. Lithium can destroy renal function: check (baseline) blood urea nitrogen (BUN) and creatine (Cre). Valproic acid has direct liver toxicity and affects hematopoiesis; do (baseline) liver function tests (LFTs) and complete blood count (CBC). Serum levels of both should be monitored. It is usually safe to give one or maybe two doses without test results. That allows restarting treatment but delaying blood drawing until after the patient is a bit more cooperative.

5.3.9 Psychosis

Treatment of psychotic patients in an emergency department is essentially the same as their treatment on a medical or surgical service. (Here we mean psychotic in the restricted sense of a patient suffering from a psychotic spectrum disorder, e.g., schizophrenia.) Treatment is simplified by the fact that most psychotic patients presenting to an emergency department are physically healthy, and many are suffering recurrence of an established mental illness, with an established treatment regime. They will respond to a resumption of their usual medications.

Two caveats are in order: some psychotic patients have serious medical illness, and some do not actually need treatment at all (at least not any new or additional treatment).

It seems emergency department staff members are inclined to assume that any apparently psychotic person who appears healthy is

physically healthy. Statistics would support their contention: most such patients do not need any emergent medical attention. However, an occasional psychotic patient will prove to have diabetic ketoacidosis or even internal trauma (e.g., splenic tear). These patients may omit critical pieces of medical history, such as a diagnosis of diabetes or a recent auto accident. When consulting to an emergency department, keep in mind that the patient has not been under continuous medical scrutiny as would be implicit on a hospital ward.

Occasionally, some psychotic patients do arrive not needing any treatment. This usually happens when a patient stumbles into a new neighborhood, or a new clinician's office, or is visited by a new, temporary nurse. Such patients are at their chronically disturbed baseline. The challenge to consultants is to curb their therapeutic enthusiasm until they have contacted someone who really knows the patient.

5.3.10 Violence and Suicide

Violence is not treated per se (except in the movie *A Clockwork Orange*). However, consultants are frequently asked to evaluate patients for their potential to do violence: their risk to hurt themselves, or their risk to hurt others. If there is a significant, imminent risk, dangerous patients are usually admitted to a psychiatric unit.

This chapter does not explore the myriad aspects of suicide and homicide risk assessment. I favor looking at each patient's story; however, there has been much written on this subject, and this chapter aims only to review differences and similarities between hospital ward and emergency department consultation (American Psychiatric Association 2003; Paris 2006).

Emergency department consultations around potential violence are complicated by time pressures; patients have been observed for only a short period of time in an emergency department, and emergency staff would like patients discharged in a short period of time. Thus, a patient's angry, off-the-cuff, statement that "I wish I were dead" comes to be seen as the chief complaint, rather than an expression of irritation, uncomfortable examinations, and delayed treatment. A consultant's task is simplified by finding some collateral source of information about the patient's state of mind.

Many patients settle down if the consultant addresses the current problem in a matter-of-fact manner. For example: "Ever since Columbine, people get very worried whenever someone makes any kind of comment that smacks of suicide. Are you really out to kill yourself?" Assuming the answer is no, the consultant can follow-up: "I'm inclined to believe you. Is there anyone I can call to confirm your story?" Most patients do not want to be held in a psychiatric facility, so they will provide the number of a friend or family member to contact. Occasionally, there is a personal attorney available to provide information.

A similar approach to patients who make threats against others is appropriate to an emergency department setting. However, it is not uncommon to hear nonpsychiatric threats of violence from emergency department patients. It is not traditionally considered a psychiatric problem if a patient talks of killing his mother because she has called the police or changed the locks on door because he pawned her television set to buy drugs. However, it is assumed to be a psychiatric problem when a patient talks of killing his therapist because she is colluding with his mother to control his thoughts through TV broadcasts. Many psychiatric services will not admit the first patient, whose diagnoses are cocaine dependence and antisocial personality disorder. They will also balk at admitting someone for violent threats in the course of a domestic dispute or divorce.

Consultants should contact their lawyer or their facility's lawyer for directions in handling a nonpsychiatric risk of violence. These and other violence-related issues are better reviewed ahead of time, rather than at 2 a.m. in a busy emergency department. What are the local standards for risk or imminent risk? What are the local standards about confidentiality when the risk of life is involved? What are the local options for psychiatric and nonpsychiatric control of a patient?

5.4 Confidentiality

Traditional emphasis on protecting patient confidences must often be tempered in an emergency department. Consider a person who was dancing nude in the park at midday. Local police send him to your emergency department, and since it was a public act, there is no confidence to keep. Then there are acts that must be reported in many locales, for example, suspected child abuse or gunshot wounds. And certain threats are no longer to be kept secret, because of legal policy stemming from the Tarasoff case. Herbert and Young 2002 reference provides a very good review of the case. These limits on confidentiality may arise during consultation to general hospital wards, but arise more frequently in an emergency setting.

5.4.1 Realities

Public acts cannot be kept confidential. If the patient's parents called for an ambulance because the patient had cut his wrists, the consultant can call the family for further details about the patient's psychiatric problem without violating confidentiality because the family knows about it. On the other hand, a consultant would have little reason to make this event more public, say, by calling this patient's employer.

The spirit of keeping patient information confidential can be upheld. Suppose our nude dancer had simply overindulged. It would be appropriate to ask him whom to call for assistance and transportation. It is not necessary to immediately call his family. Not all local newspapers publish a complete police blotter, detailing every citizen's petty encounters with authorities. The patient may have a friend who is more understanding and discreet than his spouse or parents. Some events can be kept less public than others.

Private, voluntary patient contacts should be kept confidential. If patients come to the emergency department on their own for a problem that is not overtly dangerous (such as worsening anxiety) or for an understandable reason (for example, it is August and their psychiatrist is on vacation), and if they appear able to fend for themselves, then there is every reason to keep their visit confidential. Patients do not forfeit confidentiality just because they come to an emergency department rather than a private office or clinic.

It is the nature of a patient's acts and risks that determine the reality of confidential treatment. Information about private acts entailing no risk should be kept in confidence. This is true even if the patient has been openly sent to your emergency department for some other reason. However, if there is reason to believe a patient is at risk for harming himself or others, then the value of maintaining confidences has to be weighed against the apparent risks. The patient may be able to help minimize the loss of privacy by choosing which person is to be contacted, as discussed in the earlier subsection on violence.

5.4.2 Tarasoff Considerations

Most psychiatrists believe they have an obligation to warn their patient's potential victims. Tarasoff v. Reagents of the University of California is the case that most cite, though any such obligation stems from a number of related decisions. And, in truth, it has not been easy for the courts or society to balance the need for privileged communication against the need for personal safety. Practitioners should recognize there are many legal fine points and local variations in this matter (Herbert and Young 2002).

There is often a simpler approach to so-called Tarasoff cases, namely, to ask if someone likely to be hurt. If the answer is yes, then ask what we can do to prevent it. In other words, focus attention on preventing harm rather than on legal complexities concerning specific warnings. Admitting patients on the grounds that they are dangerous to others is one way to reduce risk. This approach may also simplify discussions with your own legal counsel. Are there grounds to force admission? If not, how compelling is the evidence that a warning is needed? (see earlier subsection on violence).

5.4.3 Child Abuse, Gunshot Wounds, and Local Rules

There is a long tradition of state statutes requiring doctors to report certain medical problems, such as gunshot wounds, active tuberculosis, and other infectious disease. In such matters, public safety is held to be more important than individual privacy. Unfortunately, there is much variation state to state. Physicians can expect to have to report suspected child abuse in all 50 states. Elder abuse reporting requirements are increasingly common. Whatever the locale, its emergency departments are a uniformly likely place for such problems to become evident. Consultants should be aware of their local requirements and their institution's mechanism for handling mandatory reports.

5.4.4 Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA privacy rules apply equally in emergency departments as on hospital wards. They have caused many procedural changes in an effort to ensure patient privacy. However, they were not meant to impede clinical care, to usurp state laws, or to shield physicians from mandatory reporting (as noted above). The HIPAA rules have little impact on the confidentiality issues that loom largest for clinicians, for example, whom to warn, when to contact family or friends for critical clinical information.

5.5 Special Problems in Emergency Departments

There are a few clinical problems that arise frequently in emergency departments, largely because emergency departments serve as a screening area for their hospitals and sometimes other local services. These issues must be resolved before a patient goes to a general ward, and thus are less commonly a subject of general hospital consultations. A request to evaluate a patient, for psychiatric admission, is the most obvious such consultation. Another frequent problem is to evaluate a suicidal patient brought from police lock-up, a situation in which secondary gain raises serious questions about veracity. Other problems may arise depending on local circumstances, e.g., evaluation of adolescents, children, and developmentally disabled of all ages can fall to adult psychiatric consultants if no specialized urgent care is available except for a general emergency department.

5.5.1 Adolescents, Children, and Developmentally Disabled

These populations have important common features. They are

- Often unable to provide an accurate account of themselves.
- Usually brought/sent by someone else.
- Not on their own, i.e., they often have responsible parents, guardians, other authorities.
- Unreliably responsive to medications and doses used for adult.

Adolescents and children are frequently sent from school, directly, or brought by parents who were told by school officials to bring their child to psychiatric attention. Few of such patients readily agree they are having trouble, and give a reasonable account of themselves. However, many do not describe a clear, definite problem. They may not recognize there is any problem at all. They may recognize there is a problem, but believe it lies elsewhere. They may recognize there is a problem but doubt they or anyone else available has any power to fix it (a view that cannot always be dismissed given the occasional newspaper horror story of failure in a department of child protective services). All these possibilities add to the consultants' efforts, even just to bring a chief complaint into focus.

For these groups of patients it is critical to determine who actually brought the patient to psychiatric attention and why, since odds are high that the patient will not give an accurate account. This has legal was well as clinical implications. A patient may arrive for evaluation

Tuesday morning not because there has been an acute onset or exacerbation of trouble, but rather, because Tuesday morning was the only time their parent could take time off work. Time course may be quite unrelated to actual presentation.

From a legal standpoint, who actually brought the patient may facilitate or impede treatment. If the officially designated parent/guardian brings a minor, they can usually provide consent for treatment, maybe even psychiatric admission. If a school or sheltered workshop sends a patient, there will have to be separate efforts to reach a designated, responsible party. And different states have different rules for commitment and treatment of minors or any individual adjudicated to be incompetent.

From a practical standpoint, these patients may not control their own domicile, i.e., even if they do not require emergent, formal psychiatric treatment, their parents may not be willing to take them back home. It may then require some clever social engineering to allow safe discharge from an emergency department. Beyond a traditional psychiatric evaluation of the designated patient, the consultant may have to make a judgement about the interaction between designated patient and designated guardian: will they come to blows? If fighting is likely, is there another place for the designated patient to stay? An aunt's home perhaps? And, if there is a reasonable place, does the designated guardian consent to this plan? Luckily, most families would prefer their members stay with friends and relatives than be left in an emergency department or asylum. Occasionally, a state agency must be called for a child that has essentially been abandoned.

Medication orders/prescriptions are complicated by the fact that most psychiatric drugs are only tested in adults and thus only approved for use with adults. That is not to say that these patients can not benefit from medication, only that careful attention is required. Paradoxical response to benzodiazepines is a classically reported problem with children (and elderly). Children, especially younger children, may be sedated more reliably with an antihistamine (Thomas and King 2007), e.g., diphenhydramine (not so for elderly patients). Likewise, some clinicians prefer chlorpromazine to haloperidol in younger children. Sedating phenothiazines are closer chemical relatives to the sedating antihistamines than are the butyrophenones, but whether that is clinically significant remains to be proven.

It is even harder to make predictions about medication response among the developmentally challenged. Matters are complicated by the admixture of problems that result in an emergency department visit. Some are quite depressed or psychotic and may respond to traditional treatment with antidepressants or antipsychotics: failure of normal development does not protect against "normal" psychiatric illness. On the other hand, some disabled folks simply have trouble with day to day variations in routine. If their parents are alerted, they may arrive separately, even tearful, demanding to intervene in evaluation/treatment of their disabled child. One mother declared "do what you have to do, I know they only brought him here 'cause their rules require it, but he doesn't need medication." Luckily, this patient had settled down, permitting time to explore his history and also confer with his day program staff. Yes, they were on an outing to a new swimming pool. Yes, the designated patient had refused to leave and fought with staff when pulled out. No, he was not otherwise threatening or bizarre. No, there was not any further trouble once police were called. Yes, the program had a rule requiring their charges be taken for evaluation if there was any new, disruptive behavior—only after evaluation could such a patient come back. Resolution: no new medication, just a piece of paper certifying that an evaluation had been completed.

Purely behavioral interventions may be the best course for some of this group of patients. That is hard to settle during an emergency department visit. A good behavioral analysis may require as much attention to the patient's family and environment as to the patient himself/herself. For the developmentally disabled, there may be a behavioralist already involved. If so, they can be more important than a traditional therapist or counselor. They may or may not be easily contacted. For children and adolescents, the most effective intervention may be to alert

an appropriate state agency to make a home evaluation.

Substance abuse is an increasingly common problem for adolescents and older children. State laws against liquor sales to minors and extra penalties for illicit substance sales around schools have an unintended consequence: nontraditional substance abuse is more common, e.g., *dexing* (dextromethorphan intoxication), taking dextromethorphan and an SSRI together, *bath salt* abuse, *K2*, Jimson Weed ingestion (anticholinergic), *huffing* (inhaling) solvents and spray propellants. Clinical evaluation would be easier if children would stick to the contents of their parents liquor or medicine cabinets. Psychiatric consultants will do well to confer with their pediatric counterparts and others to keep abreast of local proclivities.

Substance abuse by the developmentally disabled is not as common, but does occur. A deaf mute with congenital rubella racked up a number of complicated emergency department visits for suicidal gestures: he would literally make hand gestures as if hanging himself. He did not understand conventional ASL, American Sign Language, so his visits were prolonged by delays finding suitable interpreters. Eventually, careful review with his group home staff yielded a pattern. There was no history or family history of traditional psychiatric illness. And it seemed he was only suicidal every month or so, and then, only if caught using crack cocaine. Though his IQ was limited, he was unable to bargain with local dealers: he would let them use his disability benefits ATM card if they would give him crack. The emergency department visits ended when he was confronted (through an appropriate sign language translator). His substance abuse may have continued, but he no longer claimed he was suicidal. His group home redoubled efforts to enroll him in substance abuse treatment.

5.5.2 Admission Screening

Screening admissions is a multifaceted task: to ensure patients are directed toward appropriate treatment, to ensure there are beds available, and to ensure implicit and explicit criteria admission are met. Some patients have an obvious, easily verified need for inpatient psychiatric treatment. Others may need admission to a medical ward or a med-psych ward first; comorbidities like diabetes or emphysema may require treatment unavailable on some psychiatric wards. Psychiatric consultants to an emergency department are usually expected to make these clinical decisions. Checking bed availability would seem to be a clerical task, but it can devolve directly to consultants. Likewise, consultants may have to complete admission checklists (diagnosis, illness severity, risk of violence, medical needs, insurance status). Unfortunately, institutional politics may lead to a complicated collection of implicit admission criteria, requiring consultants to become negotiators or facilitators.

It is tempting to view admission screening simply as a nuisance, but this is to ignore fundamental organizational needs. Emergency departments buffer hospital inpatient units against the hour-by-hour variation in patient arrivals and case-by-case variation in clinical needs. If an emergency department does not serve this function, then the hospital has to commit other staff and resources to provide it. Unfortunately, from the patient's point of view, an emergency department can become a barrier to psychiatric inpatient treatment. Consultation requests for evaluation under these circumstances may be better understood as requests to help patients over this barrier.

5.5.3 Patients Brought from Jail

Patients brought from jail to an emergency department are problematic. There is the issue of secondary gain (a temporary reprieve from their jail cell). There may be a limited commitment to telling the truth. There is the sad fact that a number of our chronically mentally ill land in jail for lack of more suitable treatment settings. Consultants are nevertheless expected to evaluate and recommend treatment.

Examining a patient may or may not provide useful information under these very constrained

circumstances. Some patients are grossly unkempt or obviously psychotic, and even the prison authorities do not want them back in jail. A small number lack guile, or experience, and let it slip that they are fine, their real complaint is the wait over a long weekend until a judge will be available to set bond. That leaves a large fraction whose moods fall somewhere between unhappy and miserable, who may be disturbed, or who may simply be impulsive enough to harm themselves. For this large fraction, an interview leads to no direct conclusion.

One helpful tack is to obtain as much information as possible from authorities, lawyers, family, and old records. Local authorities should know what sentences have been passed, what charges are pending, and when court proceedings are scheduled. This provides a framework in which to consider a patient's behavior. Police may also have specifics about a patient's behavior when apprehended. A patient's lawyer, or prosecutor, can occasionally offer specific arrangements for a patient's care. Family may be able to describe a patient's behavior before his or her legal entanglement. Old medical/psychiatric records can provide any number of clues, including a history of similar behavior under similar circumstances. All of this information may be even more useful if it is available before interviewing the patient.

Depending on the circumstances of a case, it is worth asking a patient whether he or she wants to be admitted to a psychiatric ward, with an understanding that this would only delay, not reduce, jail time. If the answer is no, then there is an opening to discuss the patient's ability to keep from hurting himself or herself when returned to jail. If the answer is yes, then the implication is that this patient is unhappy enough to prefer more time in confinement. Unfortunately, the answer may be yes because some patients prefer any alternative to jail, and because some have discovered that any delay works to their advantage in the courts.

In some cases, all available information leads one to be concerned that a patient may try to hurt himself or herself on return to jail, but clinically does not lead one to believe that the patient requires admission to a hospital psychiatric service. It often helps to review such cases, keeping in mind the social matrix: Why has it expelled this patient? What rearrangements would allow it to accept this patient back? Perhaps extra precautions can be put in place in jail. Perhaps there is some way to expedite court action. Perhaps an inpatient psychiatric admission is not such an objectionable alternative. In very rare circumstances, perhaps the patient should remain in the emergency department under guard until a judge is available. Social engineering may yield a better solution than traditional psychiatric approaches.

5.5.4 Untruths

Trainees often ask how do you know what the patient says is true. The short answer is you don't. The longer answer is we don't need the truth, just a good story. Clinical practice yields unbelievable coincidental events that prove to have happened, and entirely plausible reports made of whole cloth. There is no easy way to be certain.

Questions about truth may arise more often in an emergency department for lack of an established doctor–patient relationship. Patients are probably no less reliable in this setting, just less well known. A known, compulsive liar is not a problem; his statements can be ignored in favor of objective signs and collateral reports. Patients from jail accentuate this issue: they are a mix of unsuccessful sociopaths who will say whatever is convenient, and otherwise upright citizens (only accused of misdemeanors) who would never mislead a physician.

Clinicians hell-bent on finding the truth should remind themselves that there is no reliable way to get the truth out of anyone. If there were a reliable technique, or drug, the Central Intelligence Agency and its less savory counterparts would use it. And any such approach would be used so frequently that details would inevitably become public. Public lore only maintains that anyone can be made to talk, but their statements may not reflect the actual state of our world.

The cultural context is critical for any discussion of truth and the value of truth-telling. Dominant social norms dictate that patients skip

over most toilet activities when answering the question, What happened today? Such omissions are considered good manners, not deliberate lies. However, social norms around exaggeration and discreet social lies may be in flux because of many widely reported incidents of politicians and other public figures being caught in telling lies. In this cultural context, how much truth can we expect from our patients?

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Interviewing in Consultation-Liaison Psychiatry

6

Jon Streltzer and Hoyle Leigh

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6.1 Vignette

After being paged by the CL service receptionist that there was a consultation request for evaluation of suicidality and psychosis for Melinda Smith in 3W Room 302, the psychiatric consultant rushed into the four-bed room. Around the third bed, the curtains were drawn, and there seemed to be a procedure being performed. Another patient was snoring. Another patient seemed to be in the middle of her lunch but looked at the consultant curiously. The fourth patient with a nasogastric tube was surrounded by several visitors. The consultant looked around the room, and asked in a loud voice, "Which one of you is Melinda Smith?" One of the visitors of the fourth patient pointed to the woman with the nasogastric tube. The consultant approached the bed, and said, "I am doctor Jones, the psychiatrist. Your doctor tells me that you have hallucinations and delusions and want to kill yourself. Is that correct?"

(What is wrong with this scene?)

6.2 Introduction

The psychiatric consultation interview that occurs in a medical setting often requires special techniques which distinguish it from interviews in other psychiatric settings. The referring physician, or sometimes a nurse, is more likely to recognize a psychiatric issue,

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and seek help, than the patient. As the consultation request comes from someone other than the patient, the consultant must first establish rapport with the patient, who might not have been aware of the need for psychiatric evaluation, then, assess the psychopathology if present in the context of the medical situation, and answer the particular referral question being asked or solve the underlying problem which may not be clearly stated or even recognized.

The psychiatric consultation interview generally consists of six phases: (1) Preparation Phase, (2) Introductory Phase, (3) History, (4) Mental Status Examination, (5) Discussion of findings and Recommendations, (6) Follow-up visits.

This chapter will focus primarily on phase 1, 2, 5, and 6, as well as the process rather than the content of phases 4, and 5, which are covered in detail in Chaps. 3 and 4.

6.3 Preparation Phase

It is a mistake to think that there is an advantage to interviewing the patient without any prior knowledge about the patient, ostensibly to avoid being biased. The consultation liaison psychiatrist needs to perform an assessment and make recommendations in a timely manner, keeping up with the fast pace of contemporary hospital care. In order to do this, the consultant must work as efficiently as possible, and this requires being well prepared going into the interview. Much of the work of the consultation, in fact, is done prior to seeing the patient.

The information that has been gathered from the referring physician, the nursing staff, the medical records, and sometimes from old records and family members or other interested parties should prepare the consultation liaison psychiatrist for what she/he is likely to encounter in the patient interview. The consultant should also plan the probable duration of the interview. The initial interview for the cognitively intact patient is usually allocated between 20 and 50 min. Before interviewing the patient, the consultant should obtain as much privacy as possible, such as drawing the curtains in a multi-bed room. The consultant should also plan for contingencies, such as what if the patient seems grossly confused or agitated? If there are visitors in the room, should the visitors be asked to leave? What if the patient is in the middle of a meal? What if the patient is asleep?

The rule of thumb for such contingencies to ask the question, "What would the primary responsible physician do under the circumstances?" When the consultant interrupts a meal or awakens the patient from sleep, he/she should apologize for doing so. "Ms. Jones, I am sorry to wake you up, but your doctor wanted me to speak with you in order to help in your care…" We discuss the visitor issue later in this chapter.

6.4 Introductory Phase

We will discuss the introductory phase separately for cognitively intact and cognitive impaired patients, and then discuss the issue of whether or not to include significant others in the interview.

6.4.1 Cognitively Intact Patient

The consultation liaison psychiatrist should introduce himself/herself with a brief statement regarding the reason for the consultation. It may also be useful to know whether the patient was expecting a consultation. For example, "Hello Mr. Jones, my name is Dr. Smith. I'm the psychiatric consultant that your doctor has called to see if I can be of help. Were you expecting me? "If the patient answers in the negative, the consultant might say, "Well, your primary doctor asked me to see you as he/she was concerned that you might be experiencing depression/anxiety/concerns." At this point most patients will not be offended or be upset about to visit. Ideally, they were informed ahead of time, and even if not, and they may realize that the consultation is appropriate. Only a small percent of patients become distressed or resist the consultation at this point. This most often occurs with patients who are paranoid, or who are drug abusers who are afraid that the psychiatrist may cut off the narcotic analgesics or tranquilizers that they are demanding.

Notice that in the example above the consultant mentioned depression or anxiety. If the patient is in fact concerned about depression or anxiety, or is self aware of having a psychological problem, rapport will be established as easily as in any other psychiatric setting. If the patient issues are of a different nature, however, say a personality disorder, a somatoform disorder, a behavioral problem on the ward, or a communication problem with the doctor or staff, rapport will be much more difficult to establish. In this case, the following approach will often allow rapport to develop quickly.

The brief introduction need only mention that you are a psychiatric consultant whom the primary doctor asked to assist. Then it is very useful to immediately begin talking to the patient, providing information, rather than asking questions. For example " Mr. Jones, I understand that you hurt your back more than 8 years ago and subsequently have had two operations on it. You are in the hospital now for diagnostic testing because the pain has been getting worse." By reviewing the patient's pertinent medical history and reason for being in the hospital, you have established that you are interested in the same things that the patient is interested in. The patient quickly realizes that you have done your homework, are part of the medical team, and there will be the opportunity to talk in detail about their specific problems. In contrast, an opening such as "what kind of problems are you having?" is occasionally irritating to the patient, particularly the more difficult patient who is more likely to have a psychiatric consultation requested.

At this point the consultant can pause in the interview, giving the patient a chance to expand on the problem, or to correct what the patient considers to be misinformation on the part of the consultant. Then the consultant does an expanded history of present illness. A patient commonly will describe his/her experience and include his/her beliefs, reactions, and contextual issues around the symptoms. Another medical specialist may try to focus down the history to delineate the symptoms that are important to sort out the differential diagnosis. In contrast, for the psychiatric consultant, the goal is not so much the differential medical diagnosis, but to understand the patient's experience of what is going on in the patient's life and how this influences the presentation of symptoms, the experience of illness, the response to medical care, and the doctor–patient relationship. We not only allow this expanded history, but we encourage it. Often the patient appreciates this chance to tell the story, without too much interruption, and without being diverted from what she/he wants to say. If, as the patient tells the story, the consultant is attentive, empathetic, and facilitating, a positive rapport is likely, crucial in a short interview. Diagnostically important information is more likely to come out, and the interview is often therapeutic in and of itself.

6.4.2 Cognitively Impaired Patient

When the information obtained about the patient prior to the interview suggests that the patient may be confused, disoriented, or has an altered mental status, one must consider the probability that the patient might be delirious or otherwise cognitively impaired. Sometimes delirium or dementia has already been diagnosed, but in perhaps half the cases where this is ultimately found, this will not have been done. In such an instance, the stated reason for referral may be, for example, depression or agitation. Even in these cases, the nurses' notes often reveal that the patient is confused, at least at times. One must be careful not to uncritically accept the nurses' notation "A&Ox4" as being indicative of no cognitive dysfunction, however. This is sometimes seen in patients who are clearly delirious.

If a cognitive disturbance is suspected, the interview proceeds differently than if it is not. A delirious or seriously demented individual cannot give a reliable history. Attempting to obtain history from such a patient may stress the patient beyond his/her capabilities and may be a waste of time. Asking questions that are beyond the patient's capabilities of comprehending may result in a *catastrophic reaction*, in which the patient becomes anxious, agitated, defensive, and may even refuse to communicate. The interviewer may be in doubt as to whether the patient

is just being non-cooperative as opposed to having a cognitive disturbance.

A good way to start the interview when significant cognitive impairment seems to be present is by indirectly testing orientation. Instead of introducing oneself immediately, one might say, "Hello Mr. Jones, have we met before?" If that patient is disoriented to person he/she will not know that you are a doctor seeing him in the hospital. The patient may say something like, "Yes, I think I've seen you down the hall." A follow-up question might be, "How long have you been here now?" This question is testing for orientation to time but it does so subtly, in a manner that is not likely to antagonize the patient with a mild or no cognitive deficit. If the patient says "3 years" and she/he has only been in the hospital 3 days, one can conclude that there is disorientation to time. On the other hand if a patient in the intensive care unit has been comatose or under sedation for an extended period of time, they may well not know where they are or how long they have been there. Then the patient can be told, "Actually, you are in the Memorial Hospital, and you have been here for 6 weeks following a motor vehicle accident." Perhaps 2 min later the patient can be asked if he or she remembers the name of this place and how long he or she has been here. If the patient cannot remember this, he or she should be oriented again and asked once more only 1 min later. If the patient answers correctly, they could be asked again, say 5 min later. In this way memory span can be tested without having to bother giving three words to remember.

If the memory span is less than 30 s it is unlikely the patient will be able to learn and remember anything that the nurses say. The nurses can be informed, so they don't accuse the patient of being uncooperative when they fail to follow their instructions. If the memory span is a minute or longer, the patient should be capable of learning and remembering after multiple repetitions. If the memory span approaches 5 min, they are likely to have minimal cognitive impairment.

Thus, the interview for the suspected cognitively impaired patient consists primarily of a mental status examination that can confirm the diagnosis of delirium or dementia within a few short minutes. Of course if the cognitive abilities appear intact, the rest of the interview would go on as usual.

6.4.3 Visitors: The Presence of Family Members or Significant Others

When the consultant enters the patient's room, there may be visitors present, since visiting hours ordinarily have few restrictions in contemporary hospitals, and since the patient is likely to be seen at the consultant's convenience, not by appointment

What if a patient's spouse is present in the room? If the consultant ignores the spouse, and just begins to interview the patient, it will be awkward, let alone being impolite, and makes it harder to establish rapport with the patient. It is prudent not to identify yourself as a psychiatrist in the presence of visitors initially as some patients feel embarrassed about seeing one. For psychiatric interview to be conducted, the consultant must have the patient's permission for others, even the spouse, to be present. The consultant should introduce himself/herself to the patient, "Hello, Ms. Smith, I am Dr. Jones", then ask the visitor what the relationship of the visitor is to the patient. At this point, the interview can proceed in two ways, depending on the context of the situation and the inclination of the consultant. If the consultant suspects, based on his/her prior knowledge of the clinical issues, that it will be necessary or helpful for the patient to talk privately without the presence of significant others, he or she might say, "I am going to talk to your husband/wife for a while. Would you excuse us for a few minutes?" When the visitor has left the room, the consultant should introduce him/her self as a psychiatrist and might ask, "Would you mind my speaking with your wife/husband/relative/friend after we finish?"

At times, however, the consultant may judge that the presence of a significant other may be of great advantage. If the consultant is confident in his or her ability to interview couples (and

families), he or she may directly ask, "Ms. Smith would you prefer Mr. Smith to be present while we talk, or would you like to talk with me alone? Most of the time, a patient will feel more comfortable in the presence of a loved one, unless there is something to hide.

The presence of a significant other is particularly helpful if the patient has dementia, severe psychosis, chronic illness, or drug abuse problems. The spouse/significant other can often revise or corroborate the patient's story. The history that is then obtained is often much richer and more complete. In addition, the consultant can assess the relationship for the degree of support that exists within it and how well a couple communicates with each other.

In order to bring the spouse/significant other into the conversation, the consultant may turn to him/her and say something like "I can see how difficult this illness has been for Mr. Jones—how has it affected you?" Another way to bring the spouse into the conversation, particularly with elderly couples who may be more reticent to talk, is to ask, "How long have you two been married?" When the answer comes back something like "45 years," the next question can be "That's wonderful. What is the secret of your success?" A couple that gets along well often responds with laughter, and the husband may say something like, "She's the boss and I do what she says". The couple usually enjoys this banter and this enhances rapport with the consultant. The consultant now knows that the marital relationship is one that provides significant support.

If there are significant problems of the relationship they are likely to come out at this juncture and the consultant can assess how much the marital conflict interferes with the medical care or the response to illness.

In general, interviewing the patient with a significant other involved in the interview is much more likely to give the consultant a good sense of what the patient is like as a person. On the other hand, some patients may be reluctant to reveal conflicts with the significant other if he or she is present. The consultant should make a judicious decision concerning whether to interview the patient with significant others. Sometimes it may be appropriate to ask the patient to invite the significant other to be there for a particular time when the consultant can interview them together.

6.5 Discussion of Findings and Recommendations

After the history has been obtained and the mental status examination performed, the consultant should share with the patient and significant other, if present, relevant findings and recommendations. This should be done in lay terms and with recognition of patient's and family's sensitivities. It is often useful to simply recognize the symptoms and signs that the patient has already told the consultant, e.g., "As you said, Ms. Jones, you have been feeling blue and depressed, and you have trouble falling asleep and sleeping through the night. You also lost considerable weight in the last several months. For these symptoms, I will recommend to your doctor an antidepressant medication called mirtazapine that you take at night. This medication is likely to help you sleep better, and increase your appetite, too. Do you have any questions?"

It is always a good idea to allow the patient to ask questions, and discuss any concerns or misgivings about psychiatric diagnosis and/or treatment.

For patients whose psychiatric condition is intimately related to the medical condition or its treatment, leaving the interview on a positive note is often very helpful and comforting to the patient. For example, the consultant might say, "I know it has been rough, but your blood tests show definite improvement. Your job right now is to be as patient as you can while your treatment (specify) continues. I expect that you will be feeling better soon." The more the psychiatric consultant has learned about the patient, the more they will be able to conclude in a meaningful, supportive manner. Patients are very sensitive to the words and nuances of their doctor's communications when they are sick. Many patients take great comfort in anything positive the doctor says.

6.6 Follow-Up Interviews

At least one follow-up interview is desirable for all consultations (if the patient remains in the hospital). As the initial consultation interview was a cross-sectional slice of the patient's state and behavior, it is necessary to observe them at another point in time. Quite often, the difference is astounding, especially when a patient is emerging from delirium. A visit from a family or friend sometimes dramatically changes a suicidal patient's mood.

As with the initial interview, the consultant needs to be prepared for the follow-up interview. The consultant needs to know how the medical treatment is proceeding, and what is being planned. The consultant should also know the patient's responses and behaviors since last interview. When the patient realizes that the consultant is knowledgeable and up-to-date about the medical course, further trust is engendered and misunderstandings or miscommunications, all too frequent, can be clarified and corrected.

6.7 Psychotherapeutic Aspects of Consultation Interviews

The purpose of the initial consultation interview is primarily evaluative, but any interview conducted by a psychiatrist has inherent psychotherapeutic aspects. By deliberately making the effort to form a rapport with the patients, the patients feel respected and valued, which is, unfortunately, not always what they experience in the hospital setting. In the course of history taking, the psychiatrist elicits information about the patient's emotions and emotional responses to important events that allows the patient to share and express pent-up feelings. By sharing with the patient, in a language that the patient can understand, the assessment and recommendations, the patient feels reassured that the consultant now has a handle on the emotional problem that was difficult to describe or express. Through follow-up visits, the patient feels that the consultant continues to be interested.

Basic Foundations of Diagnosis, Psychiatric Diagnosis, and Final Common Pathway Syndromes

7

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7.1 Diagnosis: The Basics

The word *diagnosis* derives from the Greek prefix *dia*, meaning *across*, *apart,* or *through*, and the Greek word *gnosis*, meaning *knowing*. Diagnosis, a thorough (through and through) knowing of the patient's illness, including knowing it apart from other possibilities (differential diagnosis), is the essential first step in all medical intervention including psychiatric consultation.

When a psychiatric consultation is requested from our non-psychiatric colleagues, one or more medical diagnoses are probably at least suspected or being evaluated. The psychiatric consultant is then expected to consider possible psychiatric diagnoses and to integrate an understanding of the patient from the psychiatric, medical, and psychosocial dimensions in making a recommendation.

7.1.1 DSM—Historical

The standard reference in making a psychiatric diagnosis is the Diagnostic and Statistical Manual (DSM) of Mental Disorders, published by the American Psychiatric Association (APA), now in its fifth edition (APA 2013). The APA published a predecessor to a DSM in 1844, which was a statistical classification of institutionalized mental patients. The first official DSM, published in 1952, was based on Adolf Meyer's psychobiology, a model that prominently posited the interaction between constitution, personality, and environment (Meyer and Winters 1950). Psychiatric disorders were considered to be "reactions" of the personality while adapting to environmental demands.

Both DSM I and DSM II (published in 1968) were based on the then prevailing etiologic theory—psychodynamics. DSM III, published in 1980, was a frank admission of the inadequacy of the psychodynamic model as it attempted to redefine psychiatric diagnoses as research questions rather than coherent entities. By adopting an "atheoretical" model, it dropped the psychodynamic view of etiology and the notion of neurosis, that there is a continuum of psychiatric problems or conflicts between the normal and the psychiatrically ill. It adopted, to a large measure, the "research criteria for psychiatric diagnosis" that was designed to choose "pure cultures" of major psychiatric disorders for genetic research (Feighner et al. 1972). DSM III and its direct successor, DSM IV (1994), classified major psychiatric syndromes into mutually exclusive categories (e.g., schizophrenia vs. schizoaffective disorder), presumably based on the notion of different genetic underpinnings. Though it claimed to be atheoretical, it thus implicitly adopted a biological/genetic model of psychiatric syndromes. Another outstanding feature of DSM III and IV was the multiaxial system of diagnosis—Axis I: Major Psychiatric Syndromes, Axis II: Personality Disorders and Developmental Disorders, Axis III: Medical Diseases, Axis IV: Stressors, Axis V: Global level of functioning (scale of 0–100). This system explicitly made the important declaration that psychiatric syndromes and medical diseases coexist in a patient, and made important contributions in avoiding the "either physical or all in the head" notion of a symptom.

DSM III and IV have helped foster psychiatric research by defining reliable populations for study. This fortuitously coincided with the rapid development in molecular biology and genetics, psychopharmacology, neuroimaging, and the completion of the Human Genome Project. If we can define a "pure culture" of a genetic syndrome, we were now in a position to understand its genetic underpinnings.

The multiaxial system of DSM III and IV, in addition to recognizing the coexistence of medical and psychiatric conditions, had also pioneered the notion that diagnosis is more than the listing of diseases and includes the personality aspect of the patient, as well as the role of stress and the level of functioning. It was an attempt to diagnose the *patient*, not merely the disease.

On the negative side, the problems included: confusion concerning the categories and criteria for diagnosis, confusion concerning the distinction between Axis I and Axis II, and confusion concerning the nature and function of multiaxial diagnosis (Leigh 2009).

As DSM III/IV were based on research diagnostic criteria (Feighner et al. 1972) and was designed to obtain a "pure culture" for biologic research, the diagnoses were categorical and mutually exclusive, even though many psychiatric syndromes represent extremes of gradations of symptoms, many of which overlap and coexist. This overlap is not surprising, as the same susceptibility genes may have different phenotypic expressions depending on early experience and stress (See Final Common Pathways, below). Furthermore, there is a continuum of experiences and moods from normality to repeated distress, not quite reaching the criteria for the disorders of frank major psychiatric syndromes. Especially in consultation-liaison settings, patients often experience anxiety and depression associated with both medical conditions and the stress of hospitalization. The term *disorder*, adopted since DSM-III, is also problematic as it is a vague and pejorative term not commonly used in medicine. "Syndrome" is a better designation widely used in medicine, which term may be substituted for "disorder."

7.1.2 DSM-5

DSM-5, published in 2013, attempts to address some of the problems in DSM III/IV. DSM-5 dropped the multiaxial system of DSM III/IV, so that psychiatric diagnoses (both major syndromes and personality disorders) may be listed side by side, together with relevant medical diagnosis/conditions. Stressors (formerly Axis IV) and global level of functioning (formerly Axis V) are no longer part of the diagnosis but may be specified using non-DSM classifications such as certain codes and scales such as ICD and WHO Disability Assessment Schedule. DSM-5 adopts a dimensional approach to psychiatric diagnosis (i.e., gradations between health and disorder), and psychiatric diagnoses are not mutually exclusive. Thus, a patient may develop a mild depressive episode, then develop at a later time a psychotic disorder, and may also have a diagnosis of borderline personality disorder.

DSM-5 adopts a developmental and life span approach, as well as an internalizing/externalizing distinction in the ordering of chapters as follows:

Neurodevelopmental disorders
Schizophrenia spectrum and other psychotic disorders
Bipolar and related disorders
Depressive disorders
Anxiety disorders
Obsessive-compulsive and related disorders
Trauma and stressor-related disorders
Dissociative disorders
Somatic symptom and related disorders
Feeding and eating disorders
Elimination disorders
Sleep–wake disorders
Sexual dysfunctions
Gender dysphoria
Disruptive, impulse-control, and conduct disorders
Substance-related and addictive disorders
Neurocognitive disorders (in which there is delirium and major and minor neurocognitive disorders due to Alzheimer's disease, etc.)
Personality disorders
Paraphilic disorders
Other mental disorders
Medication-induced movement disorders and other adverse effects of medication
Other conditions that may be a focus of clinical attention

The adoption of the Arabian numerals instead of the Roman numerals indicates the readiness for revisions to DSM-5 without having to wait 20 years for a new edition, e.g., DSM-5.1, DSM-5.2.

In our CL Service, we do a formal differential diagnosis for any salient symptom or behavior, such as depression or overdose. For example, for depression, the large differential diagnostic categories are:

Secondary Contributing factors:
  Medical Disease (e.g., hypothyroidism)
  Substances
    Prescribed (e.g., steroids)
    Recreational (e.g., cocaine)

Primary Psychiatric Disorder
- Depressive disorders
- Bipolar and related disorders
- Schizophrenia spectrum and other psychotic disorders
- Trauma and stress-related disorders (including PTSD and Adjustment disorder)
- Neurocognitive disorders (delirium and dementias)
- Others (e.g., gender dysphoria)

Once psychiatric diagnoses are made, we also indicate certain important considerations as example below:

Psychiatric Diagnoses: Major depressive disorder, moderate, with anxious distress, contributed by methamphetamine use; Schizophrenia by history, Borderline personality disorder by history, methamphetamine withdrawal

Relevant Medical Diagnoses: anemia, diabetes mellitus

Stresses: childhood abuse, recent divorce

Assets: boyfriend, brother

Formulation: Patient with genetic predisposition for depression and substance use (both parents had both), early childhood physical abuse and ensuing depression was self-treated with methamphetamine causing further mood instability and was unable to develop sufficient coping skills as she dropped out of school in 11th grade. Recent stress of divorce caused heavy use of methamphetamine which caused both depression and neglect of adequate nutrition, which, in turn, may have caused anemia, further contributing to pt's current fatigue and depression.

7.1.3 Levels of Diagnosis

Thorough knowledge of a patient's illness involves knowing (1) the patient as a person, who has a personal history that determined his or her way of perceiving the self and the outer world, and habitual ways of coping; (2) the illness, which is a result of the interaction between the patient and the effects of disease, for example, pain, discomfort, anxiety, and its treatment, including drugs, procedures, and laboratory tests; and (3) the patient in interaction with the social and physical environment, including the health care personnel, family, and the hospital setting.

Thus one has to also consider, in addition to the patient's illness, who the patient is, what the support systems are, and the nature of the biologic problems that may affect the patient's physical and psychological condition.

Historically, medical diagnosis evolved from the naming of symptoms (e.g., fever), to a syndromic diagnosis based on a cluster of symptoms and signs that might indicate a common pathology (e.g., grippe: influenza; dropsy: glomerulonephritis, and congestive heart failure, a term still in use), to the current etiologic diagnosis that relies heavily on laboratory findings. Etiologic diagnosis is based on the biologic abnormality that is a necessary condition for the development of the syndrome.

Psychiatric diagnosis, on the other hand, has not yet evolved beyond the syndromic stage, and with a few exceptions, is based on clusters of symptoms and signs.

7.2 Psychiatric Syndromes

7.2.1 Characteristics of Psychiatric Syndromes: Extremes of Adaptive Normal Traits

Most major psychiatric illnesses are chronic conditions and tend to run in families. This seems to indicate that heredity plays an important role. Yet most psychiatric syndromes consist of symptoms that represent extremes of normal human experiences, such as anxiety, depression, and euphoria. These emotions clearly have evolutionarily adaptive value. Imagine a person who congenitally lacks anxiety, sadness, or pleasure. Survival itself from early childhood, let alone socialization and procreation (and therefore empathy), would be seriously in doubt for such a person!

Many psychiatric conditions are precipitated or exacerbated by stressful events. Once a psychiatric syndrome develops, it often has a course of its own, and is not easily reversible without psychiatric intervention. Taken together, these

characteristics indicate that (1) many of the genes that confer susceptibility for psychiatric syndromes probably also subserve normal emotional and cognitive functions, and (2) psychological stress and early environment are important in the eventual precipitation of the illness.

A genetic model that might explain this is the *cliff-edged fitness* model (Nesse 2004), in which fitness increases as a trait (or its alleles) increases, and then at a certain point it crashes. An example might be one's ability to be sensitive to others' feelings in social interactions, until it reaches the point of sensing the least amounts of rejection or hostility, leading to anxiety and depression. Some individuals with a very low anxiety threshold might have the equivalent of a highly sensitive smoke-detector alarm that would be a nuisance in normal neighborhoods but might be lifesaving in a fire-prone environment. Some individuals may have inherited such sensitivity genes, which at one time had a great evolutionary advantage. Another example might be the ability to think about and understand others' needs and motivations, until it reaches the level where every word or act of another person attains great significance and ulterior motives—that is, paranoia. There is a continuum of emotional and cognitive experiences from normality to abnormality, with repeated abnormal experiences not quite reaching the diagnostic criteria for major syndromes. The subsyndromal personality traits, such as neuroticism (Eysenck 1990), may predispose an individual to a major syndrome under stress (see below—Sect. 7.2.5).

Many putative genes that code for vulnerability for psychiatric syndromes are evolutionarily conserved and serve adaptive functions. This explains why schizophrenia, which is associated with low fertility rates in the afflicted, has not become extinct.

Certain genes that endow vulnerability to anxiety, e.g., the short allele of the serotonin transporter promoter gene, may confer sensitivity to the "smoke detector" of anxiety activation (Nesse 2001) and have been evolutionarily adaptive when humans dwelled in caves in fear of predatory animals. In the modern world, however, such sensitivity to anxiety would be dysfunctional for the individual, and thus be considered a psychiatric syndrome.

7.2.2 Brain Areas and Circuits in Normal Emotions and Cognition

There are important brain structures and circuits involved in emotions and cognition, the dysfunctions of which may underlie psychiatric symptoms and syndromes. The Web site http://www.thebrain.mcgill.ca/flash/index_i.html has excellent diagrams to use in following the descriptions below.

7.2.2.1 Mood, Emotions, Pleasure, and Sadness

How do we experience mood and emotions? Activations of certain areas of the brain seem to be associated with the subjective experience of emotions and are responsible for the patterns of behavioral/muscular activations we call emotional expression, and for the autonomic and endocrine arousal that accompany emotions (Figs. 7.1 and 7.2). The emotion of pleasure and reward seems associated with the dopaminergic activation of a circuitous pathway, first involving a descending medial forebrain bundle component and then involving the ascending mesolimbic ventral tegmental pathway (Bozarth 1987; Wise and Bozarth 1984), eventually activating the dopaminergic nucleus accumbens. The septum, the amygdala, the ventromedial prefrontal cortex, and certain parts of the thalamus also participate in the circuit.

The ventromedial prefrontal cortex, with its extensive connections with the limbic system, may link the conscious to the unconscious and ascribe meaning to perceptions by associating them with a meaningful whole. The ventral tegmental pathway can also be activated by various substances including alcohol, amphetamines, exogenous and endogenous opiates, barbiturates, caffeine, marijuana, and nicotine.

All of these pleasure centers are interconnected and innervate the hypothalamus, particularly the lateral and ventromedial nuclei. The hypothalamus then activates the ventral tegmental area, as well as the autonomic and endocrine functions through the pituitary gland.

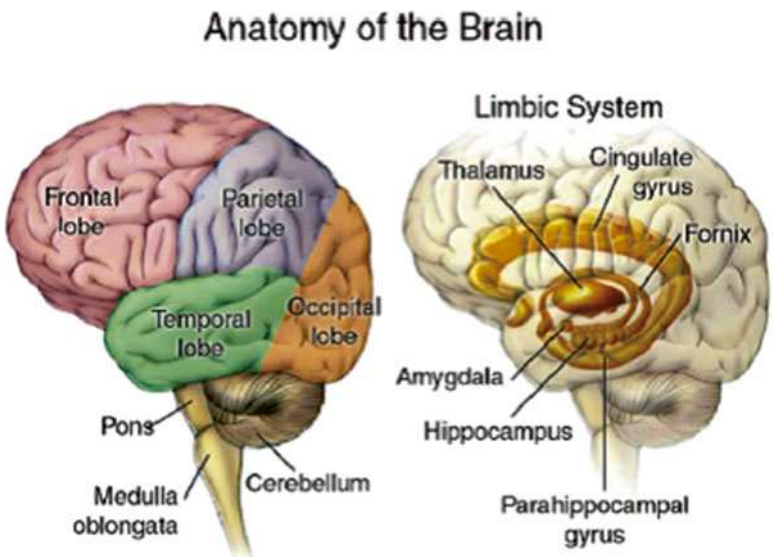

Fig. 7.1 Anatomy of the brain (From http://www.stanford.edu/group/hopes/basics/braintut/ab5.html, with permission from The Huntington's Disease Outreach Project for Education at Stanford.)

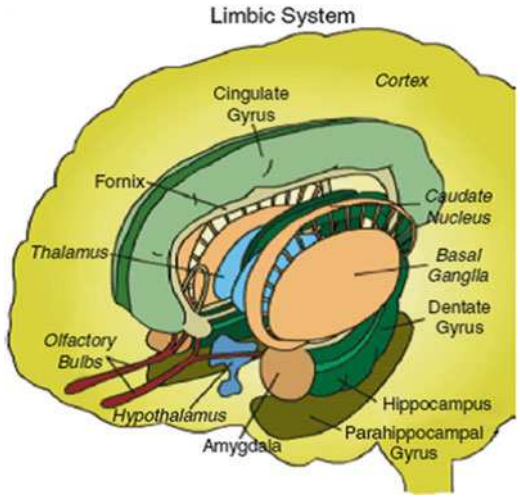

Fig. 7.2 Limbic system. (From http://www.stanford.edu/group/hopes/basics/braintut/ab5.html, with permission from HOPES.)

Aversive stimuli that provoke fight or flight responses activate the brain's punishment circuit [the periventricular system (PVS)] to cope with unpleasant situations. This circuit includes the hypothalamus, the thalamus, and the central gray substance surrounding the aqueduct of Sylvius. Some secondary centers of this circuit are found in the amygdala and the hippocampus. The cholinergic punishment circuit stimulates the secretion of adrenocorticotropic hormone (ACTH) as well as the adrenal medulla and sympathetic outflow; ACTH in turn stimulates the adrenal cortex to release adrenocortical hormones. Stimulation of the punishment circuit can inhibit the pleasure circuit; thus fear and punishment can drive out pleasure.

The behavioral inhibition system (BIS), associated with the septohippocampal system, the amygdala, and the basal nuclei, receives inputs from the prefrontal cortex and transmits its outputs via the noradrenergic neurons of the locus ceruleus and the serotonergic fibers of the medial raphe nuclei. Serotonin may also play a major role in this system. The BIS is activated when both fight and flight seem impossible and the only remaining behavioral option is to submit passively.

When a sensory stimulus is perceived by the cortex to indicate a danger, it is routed first to the thalamus. From there, the information is sent out over two parallel pathways: the thalamo-amygdala pathway (the "short route") and the thalamo-cortico-amygdala pathway (the "long route"). The short route quickly activates the central nucleus of the amygdala. Then the information that has been processed by the cortex through the long route reaches the amygdala and modifies

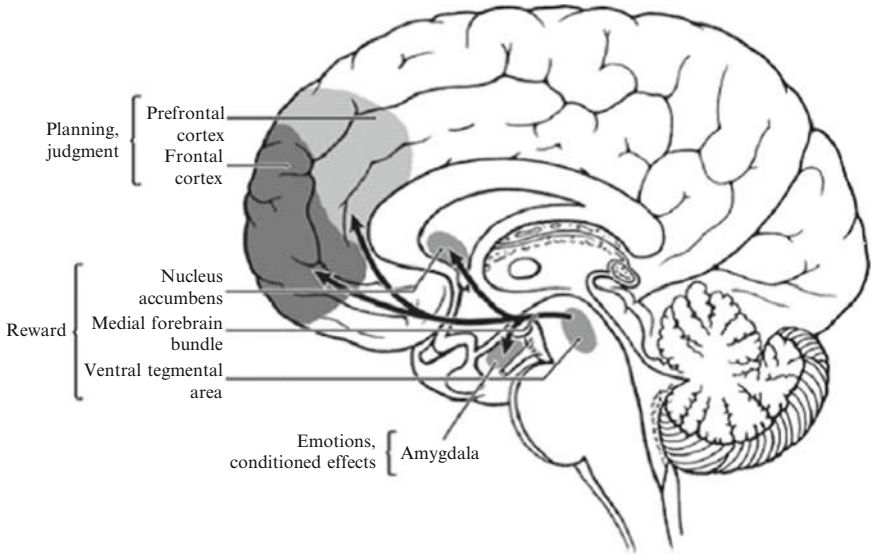

Fig. 7.3 Schematic diagram of the human brain that highlights some of the main brain areas and neurotransmitter pathways implicated in reward processes. ("Addiction and the brain: the role of neurotransmitters in the cause and treatment of drug dependence"—Reprinted from, *CMAJ* 20-Mar-01;164(6), Page(s) 817–821 by permission of the publisher. ©2001 Canadian Medical Association.)

its response dependent on the cortical evaluation of the threat. This cortical evaluation involves the following steps: (1) The various modalities of the perceived object are processed by the primary sensory cortex. Then the unimodal associative cortex provides the amygdala with a representation of the object. (2) The polymodal associative cortex conceptualizes the object and transmits the information to the amygdala. (3) This elaborated representation of the object is then compared with the contents of explicit memory available through the hippocampus, which also communicates closely with the amygdala.

The hippocampus is also involved in the encoding of the context associated with a fearful experience, i.e., memory. The amygdala conveys the gratifying or aversive nature of the experience through connections to the nucleus accumbens, the ventral striatum, the septum, the hypothalamus, the nuclei of the brainstem, and the orbitofrontal, cingulate, piriform, and other parts of the cortex. The combination of stimuli from the amygdala with working memory in the dorsolateral prefrontal cortex may constitute the experience of emotion. The basal ganglia have close connections with the amygdala and are involved with the voluntary expression of emotions. The amygdala has outputs to the nuclei of the sympathetic nervous system in the brainstem and the hypothalamus, controlling the pituitary gland and the endocrine system.

The anterior cingulate gyrus of the frontal lobe seems to be important in emotions and cognition. The subgenual anterior cingulate, together with the rostral cingulate, is considered to be the emotional sector of the anterior cingulate gyrus and it subserves autonomic arousal, reward mechanisms, and emotions, particularly anxiety and sadness in close coupling with the amygdala (Grady and Keightley 2002; Pezawas et al. 2005).

The dorsal portion of the anterior cingulate, called the cognitive cingulate, is involved with error monitoring and selecting among competing responses. Orbitofrontal cortex plays an important role in decision making in the context of emotional situations. Ventrolateral prefrontal cortex, together with the subgenual cingulate, plays a role in responding to reward contingencies (Fig. 7.3).

7.2.2.2 Memory and Cognition

The dorsolateral prefrontal cortex seems to play an important role in reasoning. It stores the memories

needed for doing tasks (working memory). The concept of working memory posits that a limited-capacity system temporarily stores information and thereby supports human thought processes. One prevalent model of working memory consists of three components: a central executive, a verbal storage system ("phonological loop"), and a visual storage system ("visuospatial sketchpad") (Baddeley 2003). It has been proposed that the phonological loop evolved to facilitate the acquisition of language. Visuospatial working memory predicts success in fields such as architecture and engineering. The phonological loop is associated with the left temporoparietal region and activates the Wernicke's and Broca's areas. The visuospatial working memory is an associated analogous area in the right hemisphere and the visual cortex. The central executive, including the reasoning and decision-making function, is probably associated with the frontal lobes.

Declarative memory, that is, the memory of facts and events, seems to be a function of the hippocampus and its connections with the cortex. The hippocampus seems to connect various memory traces in the sensory and association cortices into discrete "episodes" that also include emotion-associated inputs from the limbic system. The hippocampus seems to enable us to "play a scene back" by reactivating this particular activity pattern in the various regions of the cortex. The hippocampus plays an essential role in the consolidation of short-term memory into long-term memory, which may represent various cortical regions activated during an event becoming so strongly linked with one another that they would no longer need the hippocampus to act as their link. Thus, information that has been encoded in long-term memory no longer requires the intervention of the hippocampus. This is the case in particular for general knowledge (semantic memory), which is associated with the activation of the frontal and temporal cortices. The activity in the temporal lobe may correspond to the activation of the fact in question, while the activity in the frontal cortex may correspond to its reaching consciousness. Spatial memory, unlike semantic or episodic memory, appears to be confined to the right hippocampus. Procedural memory, such as how to walk or ride a bike, seems to be stored in motor areas, cerebellum, amygdala, and the basal ganglia, particularly the striatum (Barnes et al. 2005).

7.2.3 Neurotransmitters and Brain-Derived Neurotrophic Factor (BDNF)

7.2.3.1 Neurotransmitters

Nerve transmission occurs when neurotransmitters bind to specific receptors in the postsynaptic neuron. In addition to potentially causing an action potential, neurotransmitters play a modulating role in the excitability of the neuron depending on specific receptor activation. Many chemicals serve the role of neurotransmitters, including acetylcholine, biogenic amines (dopamine, norepinephrine, serotonin, and histamine), amino acids [γ-aminobutyric acid (GABA), glycine, glutamate, aspartate], and neuropeptides (corticotropin-releasing hormone, corticotropin, ACTH, endorphins, substance P, somatostatin, bradykinin, vasopressin, angiotensin II).

There are two types of neurotransmitter receptors: ligand-gated receptors and G-protein-linked receptors. Stimulation of a ligand-gated receptor enables a channel in the receptor to open and permits the influx of chloride and potassium ions into the cell. The positive or negative charges that enter the cell either excite or inhibit the neuron. Ligands for these receptors include excitatory neurotransmitters, such as glutamate and aspartate. Binding of these ligands to the receptor produces an excitatory postsynaptic potential (EPSP). Binding of inhibitory neurotransmitter ligands, such as GABA and glycine, produces an inhibitory postsynaptic potential (IPSP). These ligand-gated receptors are also known as ionotropic or fast receptors.

G-protein-linked receptors are indirectly linked to ion channels through a second messenger system involving G proteins and adenylate cyclase. These receptors modulate the actions of the excitatory and inhibitory neurotransmitters such as glutamate and glycine. G-protein—linked receptors are known as metabotropic or slow receptors and examples

include GABA-B, glutamate, dopamine (D_1 and D_2), and the 5-hydroxytryptamine (5-HT) receptors 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, and 5-HT_{2C}.

Several different neurotransmitters can be released from a single nerve terminal, including neuropeptides and biogenic amines. Neuropeptides can act as co-transmitters or primary neurotransmitters. As co-transmitters, they bind to specific presynaptic or postsynaptic receptors to alter the responsiveness of the neuronal membrane to the action of other neurotransmitters, such as norepinephrine and serotonin.

Glutamate is a pivotal amino acid in the brain. It is derived from α-ketoglutarate, which is one of the intermediates in the Krebs cycle. Glutamatergic neurons are extensively distributed in the brain, comprising more than 50 % of the neurons. Glutamate is an excitatory neurotransmitter. There are four types of glutamate receptors: the NMDA (*N*-methyl-D-aspartate) receptor, the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor, the kainate receptor, and the metabotropic receptor. The NMDA receptor is regulated by at least five binding sites, that is, those for (1) glutamate, (2) glycine, (3) magnesium, and (4) zinc, and a site that binds to (5) phencyclidine (PCP). The NMDA receptors have a capacity for long-term potentiation (LTP), an activity-dependent increase in synaptic efficiency that is crucial for learning and memory. The NMDA receptors are most densely concentrated in the cerebral cortex, especially the hippocampus, the frontal lobes, the amygdala, and the basal ganglia.

Excess glutamate has been shown to be neurotoxic, and an inability to remove glutamate by glial cells, thus eventually resulting in a hypofunction of the glutamatergic neurons, may underlie the cognitive deficits in schizophrenia as well as in certain dementias.

Nitric oxide may be synthesized and released when the NMDA receptor is stimulated by glutamate, enhancing neurotransmitter release from adjacent synapses and playing a role in LTP. Granule cells of the dentate gyrus of the hippocampus are rich in nitric oxide synthetase.

γ-Aminobutyric acid (GABA) is derived from glutamate and is distributed extensively throughout the brain, playing an inhibitory role. Following its release, GABA can be taken up by the neurons or by astrocytes. There are two basic GABA receptors, GABA-A and GABA-B. Stimulation of the GABA-A receptor increases the permeability to chloride ion, resulting in a hyperpolarization of the neuron or inhibition. The GABA-A receptor has three basic binding sites: for GABA, for benzodiazepine, and for barbiturates. The GABA-B receptor is a G-protein-related receptor that increases the efflux of K^+ from the cell, causing hyperpolarization. The principal effect of GABA-B agonism is muscle relaxation.

Dopaminergic neurons are widely distributed throughout the brain in three pathways: the nigrostriatal, the mesocorticolimbic, and the tuberohypophysial. There are two primary dopamine receptor types, D_1 and D_2, both of which act through G proteins. D_2 receptors often function as autoreceptors, providing negative feedback.

The mesolimbic and mesocortical dopaminergic systems play an important role in motivation, by attaching cognition of incentive to stimuli. Cocaine increases dopaminergic activity in the mesolimbic areas by inhibiting dopamine reuptake in the ventral tegmental area and the nucleus accumbens. Amphetamine seems more generalized in its action, not only by inhibiting reuptake but also by releasing dopamine from most brain regions. Both cocaine and amphetamine produce feelings of psychological energy and arousal, and cause diminished appetite and sleep. Both cocaine and amphetamine can cause visual and tactile hallucinations and paranoia.

Perception of time intervals may be mediated by dopaminergic spiny neurons located in the striatum of the basal ganglia. Marijuana slows subjective time by lowering the amount of dopamine available, whereas cocaine and methamphetamine accelerates the sense of time by increasing dopamine availability.

Dopaminergic neurons are important in pleasure and reward systems as well as in regulation of movement. They are also important in sustaining attention and concentration.

Overstimulation of D_2 receptors in the mesolimbic and mesocortical systems may result in psychotic symptoms, as D_2 agonists such as

amphetamines can cause them and antagonists like haloperidol can reverse them. An overstimulation of striatal D_2 receptors and an understimulation of cortical D_1 receptors have been postulated for schizophrenia.

There is a significant relationship between dopamine and GABA neurons. In general, GABA acts to reduce the firing of the dopaminergic neurons in the tegmentum and substantia nigra. It forms the basis for benzodiazepine augmentation in the treatment of psychosis. In addition, benzodiazepines may be helpful in cases where there is an overactivity of dopamine in the motor striatum such as Huntington's chorea or tardive dyskinesia. The feedback inhibition from the GABA neurons of the globus pallidus and putamen to the dopaminergic neurons of the substantia nigra is an important modulating force on the activity of the dopamine neurons.

The natural brain amine phenylethylamine (PEA), which is also found in chocolate, has been associated with sexual attraction and emotional infatuation. Phenylethylamine concentrations are high in the nucleus accumbens and the frontal and cingulate cortices. Levels spike during orgasm and ovulation. Phenylethylamine is very similar to amphetamine in chemical structure and likewise may act by causing dopamine release, but endorphin release may also be a significant effect.

Histamine is synthesized in the tuberomammillary nucleus of the posterior hypothalamus. These neurons project diffusely to most cerebral areas including the suprachiasmatic nucleus (SCN) and have been implicated in regulating circadian rhythms, ACTH secretion, cardiovascular control, thermoregulation, food intake, and memory formation. Outside of the central nervous system (CNS), histamine is stored in mast cells, whose release causes the allergic reaction. There are three types of histamine receptors: H_1 receptors, which are widely distributed in the body; H_2 receptors, which are distributed in the stomach and the heart; and H_3 CNS autoreceptors. There is close interaction between histamine and serotonin, as both are concerned with circadian rhythms and feeding behavior, and in the CNS there is a stimulatory effect of endogenous serotonin on histamine release.

Serotonin is synthesized from the amino acid, L-tryptophan, which readily crosses the blood–brain barrier unlike serotonin itself. Most L-tryptophan that crosses the blood–brain barrier becomes serotonin. Meals high in branch-chained amino acids and L-tryptophan or in carbohydrates increase insulin secretion, which facilitates the transport of the branch-chained amino acids into muscle cells, thereby reducing the competition for L-tryptophan for the large neutral amino acid transporter that will transport it across the blood–brain barrier. This increase in serotonin often results in drowsiness. The pineal body has the richest concentration of serotonin in the brain, but the pineal serotonin is used for synthesis of melatonin rather than as a neurotransmitter. Serotonin neurotransmitter neurons are located in the raphe nuclei. The caudal nucleus projects largely to the medulla and spinal cord for the regulation of pain perception. The rostral nucleus projects extensively to the limbic system and the cerebral cortex. In the limbic system, the serotonergic receptors are co-localized with norepinephrine receptors, and serotonin and norepinephrine may work in conjunction in the regulation of arousal. At least 15 subtypes of serotonin receptors have been identified.

The suprachiasmatic nucleus (SCN) of the hypothalamus regulates the mammalian circadian clock. It is richly innervated by serotonergic input from the dorsal raphe nucleus. When light is present, the release of melatonin by the SCN is inhibited. Serotonin also seems to inhibit the responsiveness of the SCN to light.

Serotonin plays an important role in sleep, satiety, and mood. Serotonergic hypofunction in certain areas may underlie depression, aggression, and impulsive behavior.

About 95 % of serotonin in the body is outside of the CNS, mainly in the intestines. There are seven families of serotonin receptors, among which 5-HT_1 and 5-HT_2 receptors are mostly in the brain, and 5-HT_3 and 5-HT_4 receptors are mostly in the gut.

When stretch receptors on the gut wall are stimulated, serotonin, which enhances peristalsis, is released. Vagus nerve stimulates serotonin release in the gut. Current antidepressants that

block reuptake of serotonin at synapses (SSRIs) often have gastrointestinal side effects.

Serotonin syndrome is a potentially life-threatening adverse reaction to drugs that increase serotonin levels in CNS and the body. Signs of excess serotonin range from tremor and diarrhea in mild cases to akathisia, clonus, delirium, neuromuscular rigidity, and hyperthermia in life-threatening cases. Patients usually manifest mydriasis, hyperactive bowel sounds, and diaphoresis, and show flushing or normal skin color. Creatine phosphokinase (CPK) is usually normal. Serotonin syndrome usually develops rapidly following the ingestion of drug, often in an overdose or drug interaction (e.g., a serotonin reuptake blocker with a monoamine oxidase inhibitor). Management of the syndrome involves the removal of the precipitating drugs, supportive care, control of agitation, prescribing serotonin antagonists (e.g., cyproheptadine), the control of autonomic instability, and the control of hyperthermia. Benzodiazepines are helpful for muscular rigidity and agitation. Olanzapine and chlorpromazine parenterally may also be helpful (Boyer and Shannon 2005; also go to http://www.benbest.com/science/anatmind/anatmd10.html).

Norepinephrine (noradrenaline)-containing neurons arise mainly from the locus ceruleus in the pons. They project extensively to the cortex, hippocampus, thalamus, and midbrain. Norepinephrine tends to increase the level of excitatory activity within the brain, and seems to be particularly involved in attention, arousal, and anxiety. Norepinephrine is the neurotransmitter of the sympathetic nervous system, and its activation, as in anxiety, has major effects on heart rate and blood pressure. There are benzodiazepine receptors in the locus ceruleus, as well as opiate receptors and α_2-autoreceptors, that all reduce its firing. The beta-blocker propranolol also has been used to treat anxiety. By blocking the adrenergic inputs to the amygdala, beta-blockers may inhibit the formation of traumatic memories. Cortisol stimulation of the locus ceruleus due to chronic stress exacerbates norepinephrine stimulation of the amygdala.

Acetylcholine is abundant in the interpeduncular nucleus located near the substantia nigra, and all the interneurons in the striatum and the nucleus accumbens are cholinergic. The septum provides cholinergic fibers to the septal hippocampal tract. The primary cholinergic input to the cerebral cortex comes from the basal nucleus of Meynert, which also innervates the basolateral amygdala, the basal ganglia, and the reticular nucleus of the thalamus. Cholinergic transmission is important in cognition and sleep, and is the main neurotransmitter in the parasympathetic nervous system as well as in muscles. There are two types of cholinergic receptors: fast-acting nicotinic receptors and slow-acting muscarinic receptors. The presynaptic parasympathetic fibers and fibers innervating the voluntary muscular system are nicotinic, which are antagonized by curare. Atropine, which blocks the muscarinic receptors, can cause memory loss, and there seems to be a deficiency of muscarinic cholinergic transmission in patients with Alzheimer's disease. Postganglionic parasympathetic fibers are also muscarinic.

Oxytocin is a nonapeptide released from the paraventricular nucleus of the hypothalamus through the posterior pituitary. It is a central mediator of pro-social behavior. Oxytocin is also released during stress and is an important modulator of anxiety and fear response (McCarthy et al. 1996).

7.2.3.2 Significance of Neurotransmitters in Psychiatry

Functional changes in neurotransmitters have been implicated in many psychiatric syndromes. Most antidepressant drugs enhance the functional availability of biogenic amines (dopamine, serotonin, norepinephrine) in the synapse either through reuptake blockade, blocking degradation, or direct agonistic action. Most antipsychotic drugs, particularly the first generation antipsychotics block the dopamine D2 receptors in the brain. Benzodiazepines, the principal anti-anxiety drugs, are GABA agonists.

7.2.3.3 Brain Derived Neurotrophic Factor (BDNF)

BDNF is a protein secreted in many cells by the endoplastic reticulum. It is encoded in BDNF

gene, and it acts on neurons of the CNS and the peripheral nervous system, helping to support the survival of existing neurons and enhancing neurogenesis and the growth and differentiation of new neurons and synapses (Acheson et al. 1995; Huang and Reichardt 2001). BDNF is widely distributed—in the kidneys, retina, and motor neurons as well as in the brain. In the brain, it is particularly active in the hippocampus, cortex, and basal forebrain—areas vital to learning, memory, and higher thinking. BDNF plays an essential role in long-term potentiation (LTP) and the formation of long-term memory (Bekinschtein et al. 2007, 2008a, b, 2013, 2014; Yamada and Nabeshima 2003).

BDNF binds to at least two receptors, TrkB (pronounced "Track B") and the LNGFR (for *low-affinity nerve growth factor receptor*, also known as p75) (Patapoutian and Reichardt 2001; Reichardt 2006). It may also modulate the activity of various neurotransmitter receptors, including the Alpha-7 nicotinic receptor (Fernandes et al. 2008).

There is evidence that BDNF expression is decreased in patients with depression or schizophrenia and that BDNF levels may predict the outcome of antidepressant treatment (Tadic et al. 2011; Thompson Ray et al. 2011).

In fact, most antidepressant drugs and electroconvulsive therapy eventually increase BDNF levels (Haghighi et al. 2013; Okamoto et al. 2008; Ryan et al. 2013; Sen et al. 2008). Exercise and caffeine also increase BDNF levels (Adlard et al. 2005; Costa et al. 2008a, b; Cotman and Berchtold 2002).

Traditional antidepressants require many weeks before therapeutic effects occur.

Ketamine intravenous administration in subanesthetic doses has been shown to result in rapid antidepressant response in a matter of hours in treatment resistant depressed patients. Ketamine is an NMDA receptor antagonist and participates in the regulation of glutamatergic transmission. There is robust evidence that the glial cells, astrocyte and satellite oligodendrocyte populations are reduced in prefrontal cortex and other cortical regions in postmortem tissue from individuals who had suffered from major depression and bipolar disorder and ketamine has been shown to be effective in both types of depression.

The glial loss in depression may reflect the convergence of many features of stress response in animal models, including immunologic attack on glial integrity due to elevated brain cytokine and cortisol levels, increased oxidative stress, and reduced levels of free radical scavengers including glutathione, and stress-induced glutamate release. Glial loss has a number of downstream consequences that may lead to the pathophysiology of major depression. Glial loss, produced by specific glial toxins, produces biochemical and behavioral signs of depression in animal models (Banasr et al. 2010; Sanacora and Banasr 2013). Because glia are centrally involved in glutamate inactivation, glial loss may elevate glutamate levels in both synaptic and extrasynaptic spaces. Overstimulation of presynaptic receptors has been shown to depress glutamate neurotransmission and compromise synaptic connectivity, consistent with the association of elevated anterior cingulate glutamate levels and reduced cingulate functional connectivity in major depression (Horn et al. 2010). A consequence of elevated extrasynaptic glutamate levels is overstimulation of extrasynaptic NMDA receptors. Overstimulation of these receptors has a number of downstream consequences including a reduction in BDNF levels, culminating in dendritic regression and activation of apoptosis. Thus, glial deficits in depression may contribute to abnormalities in cortical functional connectivity by compromising structural connectivity and dysregulating glutamate synaptic transmission. (Horn et al. 2010; Kavalali and Monteggia 2012; Krystal et al. 2013; Liu et al. 2013, 2012).

Thus, ketamine and other glutamatergic drugs might target rapid BDNF enhancement, which may result in rapid antidepressant action as well as cognitive enhancement (Krystal et al. 2013; Salvadore and Singh 2013).

There is a recent intriguing report indicating an increase in the methylation status (i.e., inactivation) of the BDNF gene in borderline personality disorder patients who had childhood abuse history, and that responders to dialectical behavioral therapy showed an eventual decrease in the

BDNF methylation, while non-responders showed an increase in methylation (Perroud et al. 2013). Thus, the epigenetic changes of the BDNF gene through the experience of childhood abuse may be reversed through psychotherapy in adulthood.

7.2.4 The Brain in Psychiatric Syndromes

7.2.4.1 Prefrontal Cortex

In the prefrontal cortex, the ventromedial cortex seems affected by both depression and mania. It is located on either side of the center line separating the two hemispheres and is closely involved with the pleasure circuit. It also seems to be involved in switching from one kind of affect to another. The ventromedial cortex has extensive connections with the limbic system (Fellows and Farah 2003). The volume of the ventromedial cortex is decreased in chronic depressives, mostly owing to a decrease in the number of glial cells.

There seems to be a hyperactivity of the rostral and subgenual cingulate (Area 25) in depression, and hyperactivity of the rostral cingulate may be a predictor of the response to antidepressant therapy. Recently, a number of studies indicate that there is impairment of the connectivity and function of subcallosal anterior cingulate in major depression, PTSD, as well as anorexia nervosa, and deep brain stimulation of the area may be effective in a variety of conditions. (Davey et al. 2012; Grady and Keightley 2002; Holtzheimer et al. 2012; Lane et al. 2013; Lipsman et al. 2013; Pizzagalli et al. 2001; Siegle et al. 2012; Tripp et al. 2012). Anterior cingulate and amygdalar activation has been shown to predict the response to cognitive behavioural therapy in PTSD (Bryant et al. 2008), and CBT for depression has been shown to change the activity of anterior cingulate and medial prefrontal cortex (Yoshimura et al. 2014).

The dorsolateral prefrontal cortex (DLPFC) is involved in executive functions and working memory, which are particularly disturbed in schizophrenia. In schizophrenia, there is cortical thinning within the cingulate, occipital, and frontopolar cortices, and a reduction in overall brain volume. Functional imaging studies show a reduction in neuronal density and activity in the prefrontal cortex and hippocampus in schizophrenia (Jann, 2004).

7.2.4.2 Locus Ceruleus

The locus ceruleus, which supplies a majority of noradrenergic neurons in the brain, plays an important role in anxiety and in activating physiologic and behavioral arousal.

7.2.4.3 Basal Ganglia

The basal ganglia, including the caudate and substantia nigra and thalamus, show hyperactivity in obsessive-compulsive disorder (OCD), and dopaminergic corticostriato-thalamic circuit dysfunction has been postulated for this disorder (Graybiel et al. 2000). Provocation of OCD symptoms is associated with an increase in cerebral blood flow in the orbitofrontal cortex, anterior cingulate cortex, striatum, and thalamus (Lagemann et al. 2012; McGuire et al. 1994; Rauch et al. 1994). Hypofunction of serotonergic neurons arising from the rostral raphe nucleus may result in a lack of inhibitory effect on the putative OCD pathway. Successful treatment with pharmacotherapy or cognitive-behavioral therapy has resulted in reversal of some of the brain activation (Carey et al. 2004; Figee et al. 2013; Schwartz et al. 1996).

7.2.4.4 The Limbic System and the Amygdala

Intimately involved in all things emotional, the limbic system, and particularly the amygdala, is dysregulated in psychiatric syndromes. Functional imaging studies show an increase in activation of the limbic structures, including the amygdala, hippocampus, and adjacent temporal cortex, in anxiety states including phobia. As described below, a dysfunction of the circuit that connects the amygdala to the anterior cingulate gyrus may underlie anxiety and depressive syndromes.

7.2.5 Final Common Pathways: Genes, Memes (Memory), Stress, Brain Function, and Psychiatric Syndromes

The net result of activations of various parts of the brain manifests itself in the efferent pathways of behavior (motoric), in the hypothalamic–pituitary–adrenal axis (autonomic and endocrine), and in intracranial subjective cognitive and emotional experiences. When these manifestations are dysfunctional or disordered, a psychiatric syndrome results.

We are at the threshold of understanding the genetic mechanisms of emotions and psychosis, and of understanding how some of the genes might be turned on or off by experiential, environmental, and developmental factors(i.e., epigenetics) and how such experiential factors affect brain structures and function, resulting in normal emotions/behavior or a psychiatric syndrome.

As far as psychiatric diagnosis goes, the current state of affairs concerning genes can be summarized as follows: for each diagnostic category, there are many susceptibility genes, and a single gene or a few genes may code for the susceptibility for many different disorders.

7.2.5.1 Serotonin Transporter Gene, Depression, Anxiety, and Neuroticism

An example of a single gene that codes for the vulnerability to multiple psychiatric (and medical) conditions is the serotonin transporter gene *(SERT)* and its promoter region polymorphism (5-HTTLPR). *SERT* is highly evolutionarily conserved, and regulates the entire serotoninergic system and its receptors. DNA screenings of patients with autism, attention-deficit hyperactivity disorder, bipolar disorder, and Tourette's syndrome have detected signals in the chromosome 17q region where *SERT* is located (Murphy et al. 2004a) .

The 5-HTTLPR polymorphism consists of short (s) and long (l) alleles, and the presence of the short allele tends to reduce the effectiveness and efficiency of *SERT* .

A variable number of tandem repeats in the serotonin (5-HT) transporter gene linked polymorphic region (5-HTTLPR), located at the SLC6A4 locus on chromosome 17 (17q11.1–17q12) influences the transcriptional activity and subsequent availability of serotonin [see National Center for Biotechnology Information (NCBI) map Web site for 5HTTLPR gene at http://www.ncbi.nlm.nih.gov/mapview/maps.cgi?taxid=9606&chr=17&MAPS=morbid,genec,ugHs,genes,pheno%5B24579425.12:27953447.37%5D-r&query=uid(7812322,5968)&QSTR=SLC6A4.] The 5-HTTLPR short allele "s" has reduced transcriptional efficiency compared with the long allele, and individuals carrying the "s" allele tend to show increased anxiety responses and seem to show an increased risk of depression (Lotrich and Pollock, 2004). The short-allele carriers show reduced gray matter in limbic regions critical for processing of negative emotion, particularly the perigenual cingulate and amygdala.

Functional magnetic resonance imaging (MRI) studies of fearful stimuli show a tightly coupled feedback circuit between the amygdala and the cingulate, implicated in the extinction of negative affect. Short-allele carriers showed relative uncoupling of this circuit, and the magnitude of coupling inversely predicted almost 30 % of variation in temperamental anxiety (Pezawas et al. 2005). Pezawas et al. (2005) showed that the short-allele carriers show reduced gray matter in limbic regions critical for the processing of negative emotions, particularly the subgenual cingulate and amygdala. They also show increased amygdala activation to fearful stimuli (Beevers et al. 2011; Bertolino et al. 2005; Hariri et al. 2002) . Thus, this gene seems to increase the sensitivity of the affected individual's brain to negative affect and anxiety (Caspi et al. 2010; Sugden et al. 2010; Uher et al. 2011)

The short-allele carriers have also been reported to have an increased risk for irritable bowel syndrome (Yeo et al. 2004) and migraine (Gonda et al. 2007). 5-HTTLPR short-allele carriers with neuroticism have been found to be more likely to smoke, especially to reduce negative mood and to feel stimulated, and have the most difficulty in quitting smoking (Hu et al. 2000; Lerman et al. 2000). On the other hand, the long allele has been reported to be associated

with increased cardiovascular disease and reactivity (Brummett et al. 2011).

A dietary deficiency in the serotonin precursor, tryptophan, has been shown to induce depression in healthy women with the 5-HTTLPR s/s, regardless of their family history of depression, while those with l/l were resistant to depression regardless of family history of depression (Neumeister 2003; Neumeister et al. 2006)

Caspi et al. have shown, in an elegant longitudinal study, that stress during the previous 2 years in adulthood and maltreatment in childhood interacted with the 5-HTTLPR status. Individuals with 2 copies of the short allele who also had the stressors had greatest amount of depressive symptoms and suicidality than heterozygous individuals, and those with only the long alleles had the least amount of depression(Caspi et al. 2002; Caspi et al. 2003; Enoch 2006; Machado et al. 2006; Stein et al. 2008).

Thus, the 5-HTTLPR short allele, in conjunction with childhood stress, may confer an individual with a trait of responding to later stress with increased anxiety, neuroticism, and subclinical depression (Gonda et al. 2005), which, in turn, may predispose the individual for later major depression, suicidality, bulimia (Ribases et al. 2008) and psychophysiologic disorders.

Studies in monkeys have shown that the anxiety-enhancing effect of the short allele is mitigated with good mothering in infancy (Barr et al. 2004; Suomi 2003, 2005).

5-HTTLPR may also determine the response to drugs. Depressed individuals with the short allele were found to respond better to antidepressants that are both serotonergic and noradrenergic (i.e., mirtazapine), rather than serotonin specific reuptake blockers. On the other hand, individuals with the long allele may have more side effects with exactly those drugs that are more effective for those with the short allele (Murphy et al. 2004b) . This is an elegant example of genetic polymorphism and resulting brain structural variations interacting with stress and producing susceptibility to anxiety and depression, and influencing the treatment choice.

There is evidence that 5HTTLPR polymorphisms may have differential effects on ethnicity, gender, and age. For example, females with the short allele may be more susceptible to depression (Beaver et al. 2012), and Caucasians with the short allele may be more susceptible to depression (van Ijzendoorn et al. 2012). The short allele interacted with environmental factors in the self esteem of adolescents (Jonassaint et al. 2012).

Why does a single gene code for so many traits, both adaptive and maladaptive, and vulnerabilities? One simple answer may be that the gene codes for one or more basic evolutionarily adaptive predispositions that, in combination with other factors, may determine the development and severity of a psychiatric syndrome. There is also the effect of other genes that may interact with the gene in question (epistasis) (Goenjian et al. 2012; Thaler et al. 2013).

When we look at the list of conditions affected by 5HTTLPR polymorphism, it seems clear that there is a continuum, from anxiety to adaptive/maladaptive behavior to phobia to major depression, and/or to physical symptoms (Fig. 7.4).

7.2.5.2 Monoamine Oxidase Gene

Similar interactions have also been reported with functional polymorphism in the gene encoding the monoamine oxidase A *(MAOA),* located on the X chromosome Xp11.4-11.3 (for maps of genes, go to http://www.ncbi.nlm.nih.gov/projects/mapview/). It encodes the MAOA enzyme, which metabolizes neurotransmitters such as norepinephrine (NE), serotonin (5-HT), and dopamine (DA), and renders them inactive. Genetic deficiencies in MAOA activity have been associated with aggression in mice and humans. Maltreated males with the low-MAOA activity genotype were more likely than non-maltreated males with this genotype to develop conduct disorder in adolescence and be convicted of violent crimes in adulthood. In contrast, among males with high MAOA activity, maltreatment did not confer significant risk for either conduct disorder or violent conviction (Caspi et al. 2002).

7.2.5.3 Stress and the Aging Process

Stress affects the aging process directly at the cellular level. Perceived stress and chronicity of stress was significantly associated with higher oxidative stress, lower telomerase activity, and shorter telomere length—known determinants of

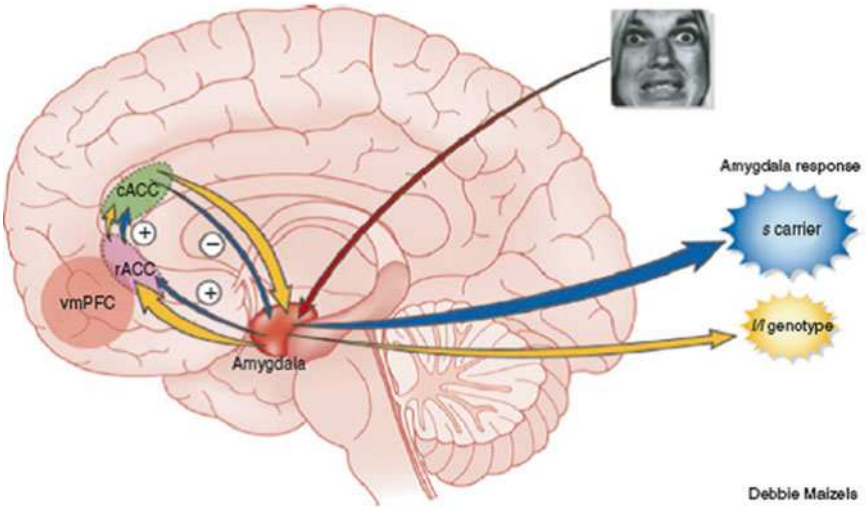

Fig. 7.4 Serotonin transporter promoter polymorphism (5-HTTLPR s/s) and emotional hypersensitivity to negative stimuli. Differences in processing of emotional stimuli between *s* allele carriers (*darker arrows*) and homozygous *l* allele carriers (*light arrows*). Negative emotional stimuli are evaluated by the amygdala (*arrow* from eyes) after preliminary analysis in the ventral visual pathway (not shown). Carriers of the *s* allele have markedly reduced positive functional coupling between the rostral anterior cingulate (rACC; lower oval) and the amygdala, which results in a net decrease in inhibitory feedback from the caudal anterior cingulate (cACC; *upper oval*), via connections between rACC and cACC (*short upward arrows*). Brain volume was also substantially reduced in *s* allele carriers in the rACC and, to a lesser extent, the cACC and amygdala. The consequence of these genotype-based alterations is an emotional hyperresponsivity to negative affective stimuli in *s* allele carriers (*large dark cloud*) compared with individuals lacking this allele (*small lighter cloud*), which may be related to an increased risk of developing depression. As found in a previous study, functional coupling between the vmPFC (*light circle*) and the amygdala was also increased in *s* allele carriers. (From Hamann, 2005. Reprinted by permission from Macmillan Publishers, Ltd: Nat Neurosci, copyright 2005.)

cell senescence and longevity. Telomeres are DNA–protein complexes that cap chromosomal ends, promoting chromosomal stability. When cells divide, the telomere is not completely replicated, leading to telomere shortening with every replication. In one study, women who had highest levels of perceived stress had telomeres that were, on the average, at least a decade older than women with lowest stress levels (Epel et al. 2004).

7.3 Final Common Pathway Model

7.3.1 The Role of Memory and Memes

Since the elegant demonstration by Caspi and colleagues of gene–environment interaction (Caspi et al. 2002, 2003; Risch et al. 2009), other studies including a meta-analysis (Risch et al. 2009) failed to support the interaction. There is, however, abundant evidence that early experiences affect gene expression in the brain, affecting both morphology and physiology (Caspi et al. 2010; Eley et al. 2004; Sugden et al. 2010; Uher et al. 2011). These data suggest that external environment does not directly interact with genes, but rather an individual's experience of the environment, i.e., memories of past experience interact with perception, forming new information that interact with genes in the brain. Such information resides in the brain as reinforced neural clusters, and their activity causes epigenetic changes of vulnerability genes.

In the course of evolution, the brain evolved as a specialized organ dedicated to processing memory, both learned and intrinsic (DNA), which in turn facilitated learning, survival, reproduction, and further enlargement of the brain. Learning through trial and error created memories that facilitated individual and species

survival, and resulted in building bigger brains, but the memories themselves died with the organism until the brain developed imitation as a learning tool. With imitation, which is robustly in evidence in primates and in songbirds, learned behavior (memory) could be transferred from one brain to other brains in the form of memes. "Meme" is a term coined by the evolutionary biologist Richard Dawkins in his book, *The Selfish Gene,* (Dawkins 1976, 2006), which I use here to denote any portable memory, i.e., information (Leigh 2010, 2012a, b). Chimpanzees could observe a bright chimpanzee cracking a nut with a stone, and this information could spread, but only to a limited degree. First, they had to be in visual contact with the bright chimpanzee, and second, the bright chimpanzee must engage in the behavior for the meme (how to crack a nut) to spread, and this presupposes that there are nuts and stones around. If chimpanzees had language, one who observed the behavior could describe it even when there were no nuts and stones, and such a meme could spread much faster and wider. Such was the case with humans.

With the development of written word, memes found an abode outside of brains. Now they could reside in patterns of indentations in clay or stone, or ink on paper, and eventually as electronic signals in magnetic tapes and optical media. Now, more memes reside outside of human brains than inside them, in printed form in libraries and homes, in electronic media, and in digital form in computers, CDs and DVDs, and in the cloud. The acquisition of language by *Homo sapiens* was instrumental in memes' attaining dominance over genes for the first time on planet earth. In fact, memes in the form of moral codes have suppressed gene-derived sexual drive in many cultures, and memes in the form of scientific knowledge provides humans with the ability to control gene propagation.

7.3.2 Neural Memes and Evolution of Memes in the Brain

How exactly does a meme reside in the brain? Kandel described a sequence of events in long-term memory formation in Aplysia. With repeated stimulus of a neuron, a sequence of chemical reactions causes gene activation in the nucleus of the neuron, resulting in release of messenger RNA in a dormant form. Further stimulation of the neuron causes a prion-like protein, CPEB (Cytoplasmic Polyadenylation Element-Binding Protein), which is present in all synapses, to become activated (to an infectious form), which in turn activates dormant messenger RNA, which in turn makes protein to form a new synapse. The prion-like infectious form of CPEB infects adjacent CPEB, and thus perpetuates itself and the protein synthesis, maintaining and reenforcing the new synaptic connection (Kandel 2006).

In higher organisms, the stimulus that reaches a neuron resulting in this series of events is itself modified in several interneurons which have their own connections, i.e., stimulus (perception) is modified by existing memory (memes). Furthermore, neurons are capable of generating impulses without external stimulus, which may stimulate and reinforce connected neural clusters. Memories thus formed and residing in reinforced neural connections are the basis of memes. A reinforced neural cluster may be represented as a binary neural code (Lin et al. 2006; Yang et al. 2007). In this sense, memory in the brain may be similar to memory encoded in the hard drive of a computer. How does memory become portable and thus a meme?

Originally, Dawkins pointed out that through imitation, memes are replicated in the brains of the imitators. As the replications are not always exact, memes undergo Darwinian natural selection and evolution by being copied inexactly by different brains. How about the memes within an individual's brain?

Edelman described Darwinian natural selection of certain clusters of reinforced neurons in the brain in somatic time (Edelman 1987). Neuronal groups may be reinforced by signals from other similarly firing neuronal groups (forming memes) and thus gain survival advantage.

This may be particularly important during adolescence, when neuronal pruning occurs. We are born with approximately 100 billion neurons

which are whittled down by about 50 % before adulthood (Pfefferbaum et al. 1994). Neurons with stronger synaptic connections survive while those with weaker connections are pruned (Chechik et al. 1999; Low and Cheng 2006; Osan et al. 2011). One might say that neurons thrive on memes.

When a competing meme becomes dominant, neural clusters underlying it are enhanced, i.e., better fed, with more synapses. Such enhanced connections may be of nurturance or stress memes as in childhood abuse (Cisler et al. 2013). Thus, some memes will become dominant with repeated exposure and rehearsal and proliferate, i.e., recruit other neuronal groups; others will become dormant, not forming new connections or recruiting others. The process resulting in new parallel connections may be seen to be a process of replication of the meme, a prion-like replication by contact through synaptic and/or dendritic connection. This is not to imply that one neuron serves only one meme. In fact, a neuron has many connections and may be a component of a number of different memes and mimetic connections.

Meme replication in the brain, therefore, does not involve reproducing new neurons, but rather occurs through recombination of component memes in existing neuronal groups. Such replication may occur through meme-processing mechanisms such as cognition, often stimulated by the entry of new memes into the brain.

The brain, in my view, is more like the Internet than a computer, with redundant storage and constantly changing connections and storage, in which memes are constantly created, propagated, combined, disintegrated, mutated, and evolved. Like the Internet, there are many interconnected processing centers that execute these functions. Some of these functions may involve a threshold number of processing units and reach consciousness, others functions occur without reaching consciousness. Just like information on the internet, some memes stay dormant and others become activated and spread.

Cognition is the brain's activity of processing memes. This may involve comparing new memes with existing ones, juggling existing memes to make way for new memes, rearranging memes by combining or breaking down memes and reassembling them. When memes combine to form memeplexes, i.e., neural clusters forming a meme develop strong connections to another, these memes may become synergistic and powerful.

Most of our memes are unconscious, and have migrated into our brains through auditory (verbal and sound), visual (books, images), and other senses. In fact, the unconscious may be likened to a meme pool where memes generated from our genes, as well as memes that have invaded our brains, percolate vying to surface.

Many of our memes are mutually supportive and coherent; others are in conflict with each other. Some may be frankly toxic, e.g., "Die for me (the meme may be a god, a cause, a clan); Kill for me."

Some memes, such as clichés, jingles, rhythms, and melodies propagate particularly well because they are adaptive memeplexes, i.e., the rhythm or melody is coupled with words that by themselves may not be as catchy. Earworms, melodies that keep on recurring in the head to the annoyance of the individual, are an example.

Gene-based life has evolved over some 3.7 billion years to the present splendor and diversity. The rapid increase in memes parallels the rapid increase in brain size that began in earnest some 2.5 million years ago when *homo habilis ("handyman")* began to use stone tools (Blackmore 1999). *Homo sapiens* emerged some 200,000 years ago, and in this eye-blink of geologic time, memes have built cultures, language, ethics, religions, ideologies, art, and science that have all evolved in a Darwinian fashion.

7.3.3 Memeplexes, Development, and Psychopathology

Why are our brains full of thoughts? According to Blackmore, the answer lies in the fact that memes are replicators, and the thoughts we have are expert replicators that survived Darwinian selection (Blackmore 1999). While most of the memes in our brains come from outside of the brains, some memes are created or cobbled

together in new combinations within our brains in the form of new memeplexes. Our brain is full of memes and memeplexes that we have acquired over time.

Some examples of memeplexes include: "I am intelligent," "good," "evil," "health," "God," "Devil," "socialism," "psychiatry," etc. Memeplexes may be complexes of ideas, sounds, and other perceptual memories, e.g., songs, scenes, posters, jingles.

A person is the net result of gene x meme x environment interaction that we call development. Except in rare cases where the environment interacts directly with genes as with environmental toxins and climate, genes interact with memes in the brain, which may have been absorbed directly from the environment as information, or may have been induced through experiential learning. Some newly introduced memes may conflict with existing memes in the brain, and may either die or become dormant (unconscious). Others may combine with existing dormant memes and activate them.

While the aggregate of these memes and memeplexes constitute our personalities, some such acquired memes are pathogens, and in interaction with genes and other "host factors" may cause mental illness. Treating such an infection may require the equivalents of either a pathogen-specific antibody or a broad-spectrum antibiotic therapy.

Prevention may also be possible through appropriate immunization.

7.3.4 Gene x Meme x Environment Interaction in the Pathogenesis of Mental Illness

Genes may create an environment in the brain that is more hospitable to certain types of memes than others. For example, in the presence of the short allele of the serotonin transporter promoter gene (5HTTLPR), the amygdala tends to be more sensitive to threatening stimuli (memes) (Caspi et al. 2010; Sugden et al. 2010). In spite of the gene, if the child experiences abundant nurturance, the gene may be turned off. On the other hand, if the child is mistreated, the brain will respond with increased fear, anxiety, and helplessness, generating corresponding memes, which are likely to epigenetically activate the vulnerability gene. Such a brain would be more susceptible to infection by depressive memes and memeplexes coming from social interactions, learning, and even the media. A stressful event in adulthood may then infuse the brain with a massive dose of depressive memes. Thus, a brain that is already inhabited with a large number of depressive memes (most of which may be unconscious) may be overwhelmed by addition of new infection resulting in a depressive syndrome, a state of total control by the depressive memes (Figs. 7.5 and 7.6).

In drug-induced depression, the drug attenuates the brain's ability to suppress already resident depressive memes which then multiply as well as making the brain to be more accepting of new depressive memes.

Similar models may be constructed for bipolar disorder, paranoia and delusions, obsessive-compulsive disorder, anxiety disorder, PTSD, etc. (Leigh 2012a).

Figure 7.4 may thus be reset, according to this model, as Fig. 7.7.

7.3.5 Psychiatric Syndromes as Final Common Pathway Phenomena

The final common pathway model of psychiatric syndromes may be described as follows: Genes adapted to serve various normal emotional and cognitive functions have natural variations. Some such genes may confer susceptibility to exaggerated reactions to stress, particularly if coupled with childhood stress. The final common pathway leading to pathology would be a functional cliff-edge change in the functional status of brain regions, such as a decoupled feedback loop.

Final common pathway syndromes are phenomenologic diagnoses with potentially multiple etiologies and contributing factors. Once having made the syndromic or phenomenologic diagnosis, it is important to elucidate the potential

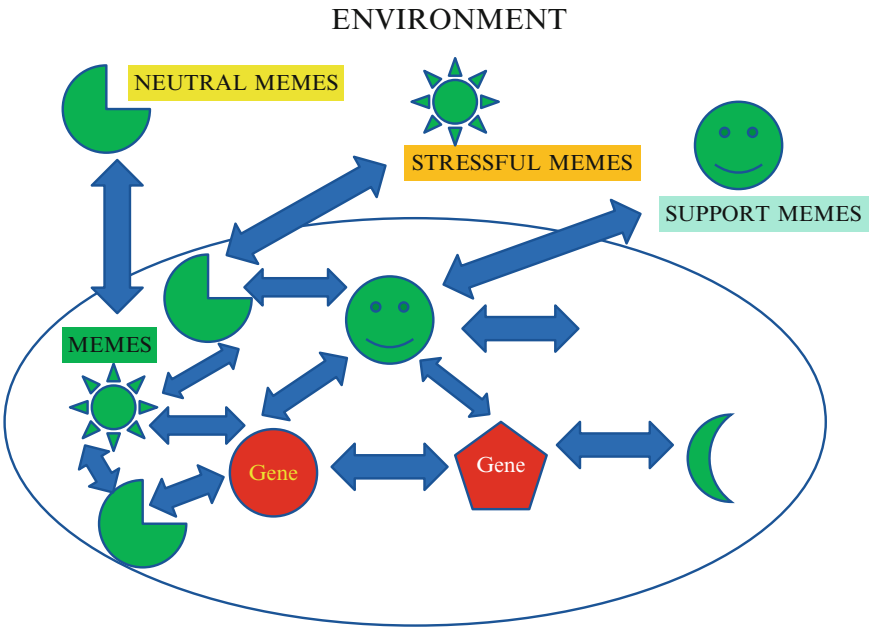

Fig. 7.5 Memes, genes, and environment

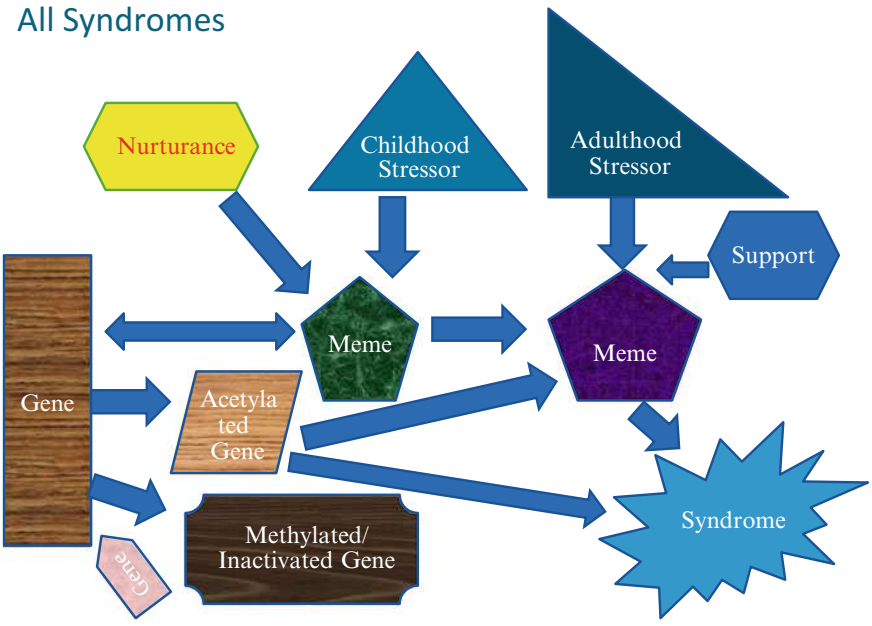

Fig. 7.6 Gene–meme–environment interaction in all syndromes

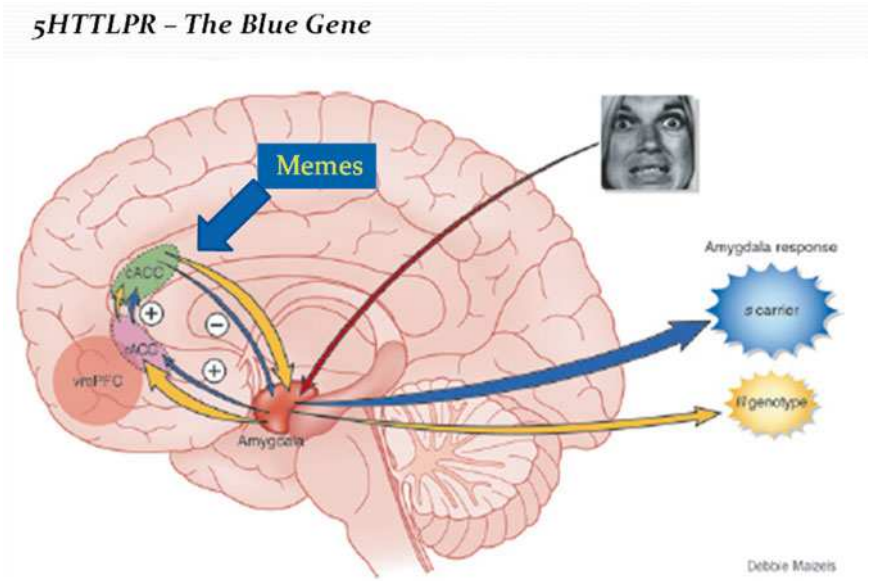

Fig. 7.7 Gene x Meme Interaction. Memes, consisting of memories and learned information including coping mechanisms and trauma-induced threat sensitivity, affect the processing of perception, modulating amygdalar response.

etiologic and contributing factors as well as the protective and mitigating factors such as social support and coping skills (Figs. 7.8 and 7.9).

7.3.6 Evaluation of Final Common Pathway Psychiatric Syndromes

As most psychiatric syndromes represent a final common pathway change in the specific areas of brain function, it is crucial to evaluate the various paths that may contribute to the syndrome. In general, the following factors should be considered in a systematic evaluation:

1. Susceptibility genes: As a direct assessment of the susceptibility genes is not yet a practical diagnostic tool in psychiatry, taking a careful family history for psychiatric syndromes/symptoms is helpful. If family members responded to a particular medication, that medication should be seriously considered for the patient.
2. Onset: A careful inquiry concerning onset of the psychiatric symptom helps differentiate between an ongoing chronic psychiatric illness (that might also be exacerbated by the stress of a nonpsychiatric illness or hospitalization) and a psychiatric condition directly secondary to a medical illness, medications, or medical disability.
3. Secondary psychiatric syndromes: This step entails recognition of, or ruling out, a medical illness, a prescribed medication, or a

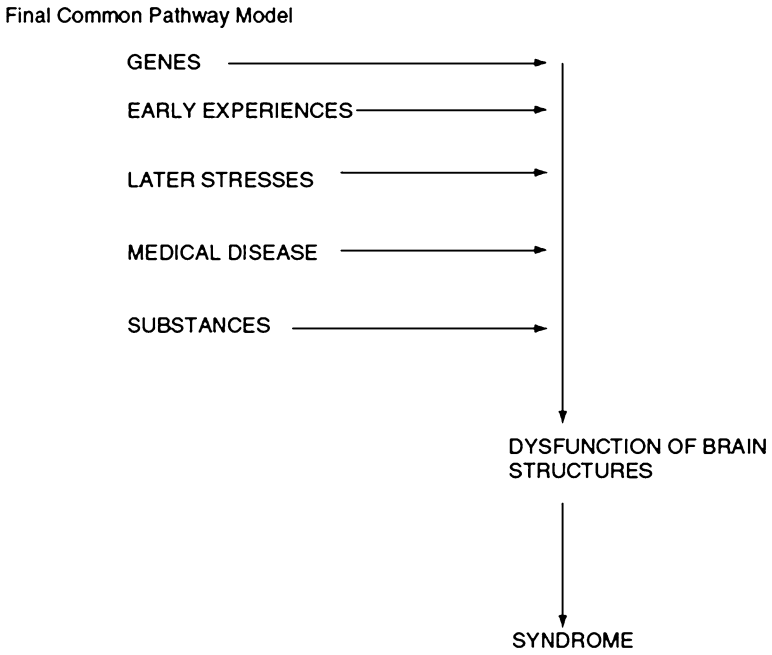

Fig. 7.8 Final common pathway model

recreational drug contributing significantly to the psychiatric symptoms. Many medical illnesses and conditions cause psychiatric syndromes directly, particularly endocrine/metabolic disorders, infections, neoplasms, CNS diseases, and cardiovascular diseases. The mechanism by which nonpsychiatric illnesses cause psychiatric syndromes varies, from direct endocrine effect, paraneoplastic syndrome, to direct tissue destruction in a CNS disease. Prescribed medications and recreational drugs often cause psychiatric complications that range from delirium, to anxiety, to depression, to psychosis (Table 7.1).

4. Primary psychiatric syndrome: Consideration of the above three parameters will enable the consultant to decide whether the psychiatric syndrome is predominantly secondary or primary. Primary psychiatric syndromes are the final common pathway syndromes resulting from interactions of genetics, early experience, environment, and stress rather than due to an identifiable nonpsychiatric illness, a prescribed medication, or a recreational drug. An example of secondary psychiatric syndrome would be major depression secondary to pancreatic cancer. The consultant may also diagnose a combination of both primary and secondary psychiatric syndrome, for example, schizophrenia, with visual hallucinations and confusion secondary to delirium caused by morphine.

   In making a primary psychiatric disorder diagnosis, the clinician should refer to the DSM, published by the American Psychiatric Press, for diagnostic criteria and coding. Alternatively, the International Classification of Diseases (ICD-10), published by the World Health Organization (http://www3.who.int/icd/vol1htm2003/fr-icd.htm), may be used.
5. Role of stress: Stress has impact on the pathogenesis of psychiatric final common pathway syndromes in several ways—by increasing the individual's susceptibility, by precipitating the onset of the syndrome, and by precipitating a recurrence or contributing to exacerbation of the syndromes.

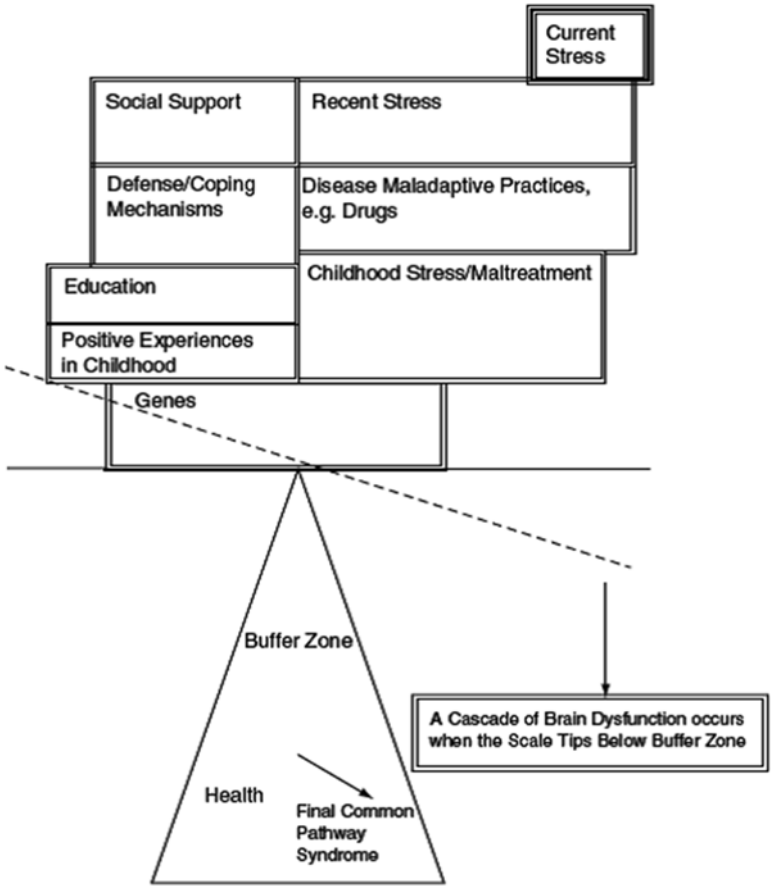

Fig. 7.9 A model of the final common pathway syndrome. An imbalance between salutary and pathogenic factors results in a cliff-edge cascade of brain dysfunction

7.3.7 Management of Final Common Pathway Syndromes: How to Change the Brain with Psychotherapy and Pharmacotherapy

Multiple interacting paths, some sequential, others parallel, may lead to a final common pathway syndrome. The treatment and management of such a syndrome may also follow multiple interacting sequential or parallel paths. For example, the depressive syndrome may be treated with a selective serotonin reuptake inhibitor (SSRI), such as fluoxetine; a serotonin and norepinephrine reuptake inhibitor (SNRI), such as duloxetine; or electroconvulsive therapy, in conjunction with either cognitive-behavioral therapy (CBT) or interpersonal therapy (IPT). All of these treatments may be done after an environmental change (admission to a psychiatric unit). The susceptibility for depression in some individuals with 5-HTLPR short allele may be attenuated if maltreatment in childhood was prevented, protective memes are introduced through education and coping skills training, and eventually, by genetic engineering to modify the pathogenic aspects of the genome.

Judicious use of treatment modalities in biologic, psychological, and social/environmental dimensions is indicated in managing final common pathway syndromes. Protecting an acutely suicidal patient through hospitalization may be the first priority, followed by psychoeducation (both of patient and family) and antidepressant

Table 7.1 Identifiable factors causing secondary psychiatric syndromes/symptoms

A. Medical disease/condition
1. Endocrine/metabolic disturbances
a. Pituitary gland: Sheehan's syndrome, pituitary adenoma
b. Thyroid gland: thyrotoxicosis, Hashimoto's disease, hypothyroidism, cretinism
c. Adrenal cortex: Cushing's disease/syndrome, Addison's disease
d. Parathyroid gland and hypercalcemia/hypocalcemia
e. Insulin and hypoglycemia, diabetes mellitus
f. Gonadal hormones: Turner's syndrome, Klinefelter's syndrome, polycystic ovaries (Stein–Leventhal)
g. Electrolyte imbalance
h. Wilson's disease
2. Deficiency diseases
a. Malnutrition/iron deficiency
b. Vitamin deficiencies
Thiamine: Wernicke–Korsakoff syndrome
Niacin: pellagra
B_{12}: macrocytic anemia, combined degeneration
Folate: macrocytic anemia
3. Infections
a. HIV/AIDS: encephalitis, delirium, dementia
b. Syphilis: general paralysis
c. Viral encephalitis/post-viral syndromes
d. Other infections, e.g., coccidioidomycosis, tuberculosis
4. Immunologic
a. Systemic lupus erythematosus
b. Iatrogenic immune suppression (e.g., in transplant)
B. Substances
1. Prescribed medicines: most prescription drugs can cause mood changes and psychosis; steroids and opiates are particularly common causes
2. Recreational drugs: narcotics, stimulants (amphetamines, cocaine, etc.), phencyclidine (PCP), d-lysergic acid (LSD), peyote, etc
C. Environmental
Sensory deprivation and/or overload (as in intensive care units), extremes of temperatures, altitude, carbon monoxide, environmental toxins

drug therapy as well as psychotherapy. Brain function imaging studies show that both drug therapy and psychotherapy affect the functional status of the brain when successful.

In depression, with successful treatment with CBT or IPT, patients exhibited decreased activity in dorsal frontal regions and increased activity in ventral frontal and subcortical regions (notably including limbic and paralimbic structures). Of note is that the brain changes seen with psychotherapy of depression, unlike those in OCD or phobias, are different from those seen with successful treatment with medications, which results in an increase in prefrontal cortex metabolism and a decrease in the activity in the posterior cingulate and in the subgenual cingulate, and may represent different mechanisms of recovery from depression (Goldapple et al. 2004; Roffman et al. 2005).

Long-term psychotherapy has been shown to reduce the increased activation of left anterior hippocampus/amygdala, subgenual cingulate, and medial prefrontal cortex. This reduction was associated with improvement in depressiveness specifically, and in the medial prefrontal cortex with symptom improvement more generally (Buchheim et al. 2012). Deep brain stimulation of the subgenual anterior cingulate (Area 25) has been used successfully in treatment refractory depression (Holtzheimer et al. 2012; Lozano et al. 2012).

In OCD, behavioral therapy reduces the metabolism in the caudate nucleus. Both fluoxetine and psychotherapy seem to uncouple dysfunctional corticostriato-thalamic circuitry. Deep brain stimulation for nucleus accumbens has been used successfully in treatment refractory OCD patients as they exhibit excessive connectivity between nucleus accumbens and prefrontal cortex (Figee et al. 2013; Ooms et al. 2013).

In phobias, patients have significant activation in the parahippocampal gyrus and right dorsolateral prefrontal cortex as compared to normals. With successful CBT utilizing exposure therapy, patients demonstrated significantly less activation in both the parahippocampal gyrus and right dorsolateral prefrontal cortex (DLPFC), and

increased activation in the right ventral prefrontal cortex (PFC) (Paquette et al. 2003). The abatement of the parahippocampal gyrus response may be due to a dampening of contextual memory believed to be mediated by this structure. A shift of activity to the ventral PFC could prompt downregulation of limbic activity, dampening the fear reaction.

In social phobia, CBT that targeted the anxiety associated with public speaking demonstrated a significant reduction of activity in the limbic system including the amygdala. Psychotherapy and pharmacotherapy seem to have differential effects in phobia. Citalopram, an SSRI, reduced the activity of ventral prefrontal cortex in phobics, while CBT caused no change. Patients receiving CBT showed decreased CBF in the periaqueductal gray area, which has been associated with defense behaviors. Citalopram reduced the blood flow to the thalamus, potentially reflecting reductions in sensory input to the amygdala (Charney and Deutch 1996).

In schizophrenia, the functional hypofrontality has been partially reduced with second-generation antipsychotic drugs (see Chap. 19), and the limbic overactivation of D2 neurons are reduced with antipsychotics in general.

In considering psychotherapies, broad-spectrum meme directed therapies should be considered. These therapies are geared to generalized reduction in meme proliferation that is often seen in psychiatric syndromes. Such broad spectrum meme-directed therapies would include mindfulness training, general relaxation therapy, music and dance therapy, etc. (Leigh 2010)

In the final common pathway model, the therapeutic intervention may be directed at any and all of the specific pathways leading to the syndrome, including genetic, epigenetic, memetic, and environmental factors.

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Psychopharmacology in Medically Ill Patients

8

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Contents

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8.1 Introduction

Appropriate use of psychopharmacology in the medically ill patients requires careful consideration of the risks and benefits of using these medications. This would involve careful assessment of the underlying medical condition, interaction of psychotropic medications with other medications used to treat medical problems, potential alterations to pharmacokinetics from the medical condition, and increased vulnerability to side effects from medications because of impaired hepatic, renal, cardiac, and gastrointestinal functioning.

This chapter focuses on:

- Understanding the principles of psychopharmacology
- Understanding the pharmacokinetic and pharmacodynamic drug–drug interactions
- Understanding the use of psychotropic medications in various medical conditions and organ failure
- Diagnosis and management of medical emergencies from the side effects of psychotropic medications including serotonin syndrome and neuroleptic malignant syndrome

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8.2 Principles of Psychopharmacology in the CL Setting

1. Review patient's medical problems, laboratory findings, and imaging studies if available.
2. Review all inpatient and outpatient medications: psychotropics and non-psychotropics, over-the-counter medications, herbal medications and supplements, and determine whether these medications were actually taken.
3. Check for medications that could be contributing to patient's altered mental state like anticholinergic agents, opioids, and benzodiazepines.
4. Avoid polypharmacy: Consider lowering the dosage or discontinuing medications rather than adding new medications.
5. Use the minimum dose of medication necessary to obtain the desired response.
6. Determine past response to psychotropic medications.
7. Avoid prescribing medications to be given as needed (PRN). If as needed medications are required, monitor dosage and frequency of use.
8. Add or discontinue one drug at a time: simultaneous changes can make it difficult to determine efficacy and adverse drug reaction.
9. Use drug serum level if possible to check for toxicity and compliance.
10. Understand patients' psychosocial and financial background which could affect patient's compliance to medication.

8.3 Pharmacokinetics and Pharmacodynamics in the Medically Ill

Impaired hepatic, renal, cardiac, and gastrointestinal functioning can alter the absorption, metabolism, distribution, and excretion of the psychotropic medications.

8.3.1 Absorption

Absorption of a drug is influenced by the characteristics of the absorption site including surface area, pH, mucosal integrity and function, local blood flow and the chemical properties of the drug. The absorption of orally administered drugs can be altered by food, pH, chelating agents, gut flora changes, diseases, or other drugs affecting gastric or small bowel function. Absorption of intramuscular injections is dependent on muscle mass and tissue perfusion.

8.3.2 Distribution

Distribution of a drug is influenced by serum pH, blood flow, protein binding, lipid solubility, and the degree of ionization. This could be altered in cardiac, hepatic, and renal impairments.

8.3.3 Elimination

The majority of psychotropic drugs are eliminated by hepatic metabolism and a few by renal clearance. The hepatic clearance of drugs can be affected in liver disease. In conditions like cirrhosis there is decreased hepatic blood flow that will affect the rate of delivery of the drug to the liver. There is also decrease in the intrinsic metabolic capacity of enzymes which will result in impaired metabolism and clearance of the drug. Renal clearance of drugs can be affected in kidney failure. Dose adjustment by starting low and slowly titrating up is required in these situations.

8.3.4 Metabolism

Drug metabolism in the liver is divided into two phases: *Phase I* reaction involves oxidation, reduction, and hydrolysis. These processes tend to increase water solubility of the drug and can generate metabolites that are chemically active and potentially toxic. Cytochrome P450 enzymes are the major enzymes involved in the Phase I

metabolism. They consist of a closely related family of 50 isoforms; six of them metabolize 90 % of drugs with the two most significant enzymes being CYP3A4 and CYP2D6 (Lynch and Price 2007). *Phase II* reaction involves glucuronidation, acetylation, and sulfation (conjugation pathway). UGTs (uridine glucuronosyltransferases) are the important enzymes, mainly 2B7. Chemically active Phase I products are rendered relatively inert and suitable for elimination by Phase II.

8.3.5 Drug–Drug Interactions (DDI)

Understanding the use of psychotropic medication in the medically ill patients requires understanding of drug–drug interactions at pharmacokinetic and pharmacodynamic levels. Most interactions go unreported because they are mild or unrecognized. DDI can have significant clinical implications when using medications with a narrow therapeutic index, when there is a serious adverse drug reaction, and when treatment is ineffective. It can result in considerable patient morbidity and mortality (Sandson et al. 2005).

8.3.5.1 Pharmacokinetic DDI

Pharmacokinetic DDI through alteration in metabolism can result in either induction of metabolism, which will result in decrease in the drug level, or inhibition of metabolism, which will increase the drug level. The third way is through the polymorphic nature of enzymes which results in fast metabolizers or slow metabolizers.

Examples of potent inhibitors of P450 are fluoxetine (2D6, 2C9), paroxetine (2D6, 2B6), fluvoxamine (1A2, 2C19), sertraline (dose dependent 2D6, potent inhibitor of UGT 1A4), nafazodone (3A4), bupropion (2D6), duloxetine (2D6), haloperidol (2D6), cimetidine (all-cyp450), ciprofloxacin (1A2), fluconazole (2C9), ketoconazole (3A4), erythromycin (3A4), isoniazid (2C19), diltiazem (3A4), grape fruit juice (1A2, 3A4), omeprazole (2C19), most protease inhibitors (3A4), quinidine (2D6), diphenhydramine (2D6), valproic acid (2C9), ritonavir (2C9, 2C19, 2D6, 3A4) (Lynch and Price 2007; Sandson et al. 2005).

Examples of potent inducers of P450 are rifampin, carbamazepine, phenobarbital, phenytoin, St. John's Wort, chronic smoking.

Examples of pharmacokinetic DDI include:

Carbamazepine (3A4 inducer) and ethinyl estradiol containing contraceptive: this can reduce estradiol level and lead to failure of contraception (Crawford et al. 1990).

Fluoxetine, paroxetine (2D6 inhibitor) and Risperidone: this can increase risperidone level and increase the risk for adverse extrapyramidal effects (Spina et al. 2002).

8.3.5.1.1 Pharmacodynamic DDI

Pharmacodynamic DDI involves interaction of drugs at the intended site of action. This may be additive, synergistic, or antagonistic. Classic examples of pharmacodynamic interactions include that between a monoamine oxidase inhibitor and a serotonin reuptake inhibitor, resulting in serotonin syndrome, and that between a tricyclic antidepressant and an anticholinergic agent like benztropine, causing anticholinergic toxicity. Pharmacodynamic DDI is easier to anticipate, recognize and avoid.

8.4 Pharmacogenomics

Drug efficacy and toxicity vary substantially across individuals. Clinical consequences may include a prolonged time to optimal therapy and in some cases, serious adverse events.

Various factors may influence the variability of drug effects, including age, liver function, concomitant diseases, nutrition, smoking, and drug–drug interactions and inherited polymorphisms in genes coding for drug metabolizing enzymes, drug receptors, drug transporters and molecules involved in signal transduction. Genetics may account for 20–95 % of variability in drug disposition and effects (Evans and McLeod 2003).

It may be possible to predict therapeutic failures or severe adverse drug reactions in

individual patients by testing for important DNA polymorphisms (genotyping) in genes related to the metabolic pathway (pharmacokinetics) and in genes related to signal transduction pathway (pharmacodynamics) (Phillips et al. 2001).

There is pronounced ethnic variability in the population distribution of metabolizer types for a given CYP enzyme. For example: less than 1 % of Asians, 2–5 % of African-Americans, and 6–10 % of Caucasians are poor metabolizers of CYP2D6 (Bradford 2002). The presence of the HLA-B*1502 allele is associated with carbamazepine-induced Stevens-Johnson syndrome (SJS) and/or toxic epidermal necrolysis (TEN) (Chung et al. 2004).

8.5 Alternate Routes of Administration

In medically complicated patients who are either agitated and refusing to take oral medication or are intolerant of oral dosing of psychiatric medication because of nausea, vomiting, nothing by mouth restrictions, aspiration risk, difficulty swallowing, post oro-maxillary surgery, or physiologically incapable of intestinal absorption (because of gastric or bowel dysfunction or resection), there is clinical dilemma. These situations require alternate routes to administer psychotropic medications (Thompson and DiMartini 1999). Using alternate routes like intravenous (IV), intramuscular (IM), sublingual (SL), and rectal route bypasses the effect of first-pass metabolism and can cause a significant increase in bioavailability of the drug. The parenteral route (IM/IV) is used to sedate highly anxious or agitated patients. For patients with severe muscle atrophy and poor tissue perfusion, such as in cardiac insufficiency, IM injections should be avoided. Poor venous access, infiltration and infection can complicate IV use. Some antipsychotics like chlorpromazine, haloperidol, droperidol, ziprasidone, olanzapine, aripripazole and benzodiazepines like lorazepam are available in IM forms. Haloperidol can be used IV with 40 % improved bioavailability compared to oral administration (Chang et al. 1992) and with less extrapyramidal side effects (Menza et al. 1987) but patients should be on a cardiac monitor because of the increased risk of QTc prolongation and torsade de pointes if high doses are used. Similarly lorazepam can be used IV in severely agitated and anxious patients but the patient should be monitored for respiratory depression. The only mood stabilizer available in parenteral form (IV) is valproate sodium.

Depot antipsychotics are administered intramuscularly. Their rate limiting step is the release of the medication from the depot solution which is dependent on the amount of subcutaneous fat. Sublingual form may be an effective route, especially for nonionized, highly lipid-soluble medications. Haloperidol, chlorpromazine, clomipramine, diazepam, nitrazepam, promethazine, and trihexyphenidyl are examples of nonionized, highly lipophilic drugs that may diffuse across the mucosal membranes at physiologic pH (pH 7.4) Mirtazapine, olanzapine, and asenapine are available in sublingual forms. For patients with severe nausea any oral stimulation is intolerable and may not benefit from this form. In addition, many medications have a bitter taste, causing further nausea (Thompson and DiMartini 1999). Selegiline is available in a transdermal patch as an antidepressant. Selected benzodiazepines like lorazepam can be given in IM/IV/Sublingual, intranasal, intrathecal, and rectal routes.

8.6 The Elderly

Elderly patients have slower absorption, metabolism and elimination of drugs. The distribution of the drugs can be affected by impaired hepatic, renal, and cardiac functioning. The elderly will be more sensitive and susceptible to side effects of medications. It is very important to start psychotropic medications at a lower dose and titrate the dose slowly monitoring for side effects. Also drugs with anticholinergic properties like tricyclic antidepressants and benzodiazapines should be avoided to reduce the risk of fall.

8.7 Psychopharmacology in Organ Diseases

8.7.1 Hepatic Disease

Liver disease is highly prevalent in patients with psychiatric illness and comorbid substance use disorder. The liver is responsible for a number of physiological processes including synthesis of proteins and clotting factors and the metabolism of drugs and other substances. Abnormal liver function can cause physical and psychiatric symptoms including abnormal blood clotting, ascites, variceal bleeding, muscle wasting, fatigue, personality changes, psychomotor dysfunction, affective symptoms, cognitive impairment including impaired memory, concentration, and reaction time, and in severe cases, coma. In patients with end stage liver disease psychiatric symptoms emerge not only from the underlying organ failure but also from the stress of dealing with a terminal illness (Crone et al. 2006).

Liver disease can affect medication pharmacokinetics from absorption to metabolism, to distribution and elimination. This can affect the drug level, duration of action and increase the risk for adverse effects. In cirrhosis, synthesis of plasma protein is altered. This can affect the protein binding of drugs resulting in higher levels of free pharmacologically active drugs. There is impaired metabolism and elimination of drugs because of reduced synthesis of liver enzymes and decreased blood flow to the liver. Most psychotropics are lipid soluble and undergo extensive phase I hepatic metabolism. Only a few psychotropics are dependent on renal clearance including lithium, gabapentin, and topiramate. Phase I enzymes (cytochrome P450 isoenzyme families), which are centrally located in the portal triad, are mainly affected in cirrhosis, whereas Phase II metabolism (mainly glucuronidation) is preserved in cirrhosis (Pacifici et al. 1990). Choosing a psychotropic drug that mainly uses the phase II pathway for metabolism (lorazepam, temazepam, and oxazepam) may be useful in patients with cirrhosis (Crone et al. 2006). Sedatives should be used with caution in liver failure because they can precipitate hepatic encephalopathy (Häussinger 2010).

When using psychotropic drugs in patients with liver disease the severity of the disease and therapeutic index of the drug should be carefully considered to avoid drug toxicity and side effects.

Hepatotoxicity is a known rare side effect of some psychotropics including nafazodone, duloxetine, valproic acid, and carbamazepine. They are either relatively contraindicated in patients with preexisting liver disease or should be used with extreme caution. Minor elevations in transaminases are common and usually benign. Elevation of AST or ALT levels of 2–3 times the baseline is significant. Low platelets from liver failure can increase the risk of bleeding when using drugs like valproic acid that can cause thrombocytopenia.

Drugs like tricyclic antidepressants and low potency antipsychotics that have significant anticholinergic effects may exacerbate hepatic encephalopathy in cirrhotics secondary to intestinal stasis and central effects (Levenson 2005).

Prophylactic administration of SSRIs to patients with hepatitis C has been found to significantly lower the incidence of interferon-induced major depression when compared with placebo in a meta-analysis, and the SSRIs were well tolerated (Jiang et al. 2014).

Lithium is renally excreted but its level could fluctuate in patients with end stage liver disease with ascites because of the fluctuating fluid balance.

Haloperidol in low dose remains the most commonly chosen antipsychotic for psychosis and agitation associated with hepatic encephalopathy (Prabhakar and Bhatia 2003).

The rule of thumb is to reduce the initial dose of medication and titrate the dose slowly for drugs primarily metabolized by the liver. Choose drugs with wide therapeutic index and monitor for side effects.

8.7.2 Renal Disease

Subsyndromal depression is seen in about 25 % of individuals with end stage renal disease (ESRD) and major depression in 5–22 % of this

population (Cohen et al. 2004). Anxiety, substance use disorders, delirium, and dementia are also common psychiatric conditions in this population.

Most psychotropic medications are well tolerated and efficacious in the treatment of patients with ESRD and renal insufficiency. End stage renal disease may affect the pharmacokinetics of the drugs. The Physician's Desk Reference generally recommends that patient with ESRD be administered *two-thirds the usual or maximum dose of most psychotropic drugs.*

In ESRD, excess urea may affect the absorption of medications by gastric alkalinizing and by changes in gastrin levels. A cachetic person has less fluid and less body mass and a decreased volume of distribution resulting in higher concentration of medication. The patient with ascites and edema has a higher volume of distribution and may require higher initial doses of medication. Patients with renal failure often have decreased amount of albumin. Also, retention of urea and other substances that compete for plasma protein binding sites will result in a higher free fraction of plasma protein bound drug like valproic acid. The greater the protein binding of a medication, the lower the dose required in renal failure. Drug metabolites that are pharmacologically active may be retained in patients with renal insufficiency and may cause adverse effects.

In a review of psychotropic medication use in renal disease (Cohen et al. 2004), SSRIs are beneficial in ESRD. Excretion of fluoxetine and sertraline is unchanged in ESRD, plasma concentration of paroxetine is increased in renal impairment and a starting dose of 10 mg is recommended. Venlafaxine and Mirtazapine have active metabolites and their clearance is reduced by 50 % in renal disease. Bupropion has active metabolites that are completely excreted through the kidney. The metabolites may accumulate in dialysis patients and predispose these patients to seizures. Less than 1 % of haloperidol is excreted in the urine and it appears to be a safe medication to use in ESRD. With risperidone, wide variation in clearance is noted between poor and extensive metabolizers. Clearance of the sum of risperidone and its metabolite 9-hydroxy risperidone is reduced by 60 % in renal failure (Heykants et al. 1994). Antipsychotics that prolong QTc like thioridazine and ziprasidone are best avoided in ESRD because of risk of life threatening arrhythmias with electrolyte shifts. Benzodiazepines are metabolized in the liver and dose reduction is generally not necessary. The half-life of lorazepam may be prolonged in ESRD (Wagner and O'Hara 1997). Lithium is contraindicated in acute renal failure but not in chronic renal failure patients on dialysis. Lithium is completely dialyzed and can be given as a single dose post hemodialysis.

8.7.3 GI Diseases

Psychotropic drugs with anticholinergic properties should be avoided in patients with gastroparesis and constipation. Antidepressants, when used to treat concomitant mood disorders in inflammatory bowel disease, have been shown to reduce relapse rates, use of steroids, and endoscopies (Goodhand et al. 2012). TCAs have been found to be effective in controlling symptoms in irritable bowel syndrome (Rahimi et al. 2009).

Gastrointestinal side effects are common with initiation of SSRIs and may be undesirable in patients with increased gastric motility or diarrhea. There are reports of prolonged bleeding time, ecchymosis, purpura, epistaxis, gastrointestinal, genitourinary, postoperative, and intracranial bleeding in patients receiving SSRIs. Serotonin plays a role in hemostasis. Platelets release serotonin in response to vascular injury. Serotonin binds to receptors on adjacent platelets and contributes to platelet aggregation. SSRIs inhibit about 90 % of the activity of serotonin transporter in platelets. Decreased serotonin in platelets may increase the risk of abnormal bleeding (Bismuth-Evenzal et al. 2012; de Abajo et al. 2006).

There are multiple studies relating the use of SSRIs with upper gastrointestinal bleeding (Dalton et al. 2003; Andrade et al. 2010). Older age, a history of gastrointestinal problems, and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) are identified as risk factors. Increased gastric acidity and gastric

erosion in conjunction with an SSRI could also contribute to increased risk for bleeding. For patients with a previous history of upper-gastrointestinal bleeding or peptic ulcer, and for those who take NSAIDs, oral anticoagulants, antiplatelet drugs, or corticosteroids, the addition of an acid-suppressing agent to SSRI may reduce the risk of bleeding (de Abajo and García-Rodríguez 2008). The risk of abnormal bleeding is associated with the degree of serotonin reuptake inhibition by antidepressants. Antidepressants with a higher degree of inhibition of serotonin reuptake have 2.6 times the risk of bleeding compared with antidepressants with a low degree of serotonin reuptake inhibition (Meijer et al 2004).

8.7.4 Cardiovascular Disease

Depression is highly prevalent in patients with cardiovascular disease and is independently associated with poor prognosis (Joynt et al. 2003). Among individuals with established ischemic heart disease, depression has been found to be associated with an approximately threefold to fourfold increase in the risk of subsequent cardiovascular morbidity and mortality (Zellweger et al. 2004)

Depressed patients are more likely to eventually develop cardiovascular disease and also have a higher mortality rate than the general population. There is a graded relationship: the more severe the depression, the higher the subsequent risk of mortality and other cardiovascular events (Hare et al. 2013). Between 31–45 % of patients with coronary artery disease (CAD) suffer from clinically significant depressive symptoms (Celano and Huffman 2011). Fifteen to twenty percent of patients with coronary artery disease meet criteria for MDD at any given time (Carney and Freedland 2008).

Depression is associated with changes in an individual's health status which may influence the development and course of cardiovascular disease, including noncompliance with medical treatment, increased presence of cardiovascular risk factors like smoking and hypertension, physiological changes including nervous system activation, cardiac rhythm disturbances, systemic and localized inflammation, and hypercoagulability (Joynt et al. 2003).

Sertraline is considered safe and effective in patients with recurrent depression post MI. It has been found to reduce the incidence of severe cardiac events (death, myocardial infarction, congestive heart failure, stroke, and recurrent angina ("SADHART" study, Glassman et al. 2002).

Psychotropic medications can cause adverse cardiovascular effects including tachycardia, orthostatic hypotension, conduction disturbances, and arrhythmias. TCAs and low potency antipsychotics block alpha1 receptors which can cause postural hypotension resulting in syncope and fall.

Tricyclic antidepressants are contraindicated after myocardial infarction because of their cardiotoxic side effects including QTc prolongation, postural hypotension, anticholinergic effects, and conduction delays (Bilgi and Campbell 1979). Venlafaxine can cause hypertension in higher doses (Mbaya et al. 2007).

Studies on the cardiac effects of lithium indicate high frequency of electrocardiographic T wave morphology changes especially nonspecific T-wave flattening. Therapeutic and toxic levels of lithium have infrequently been associated with sinus node dysfunction or sinoatrial block, atrioventricular conduction disturbances and the appearance or aggravation of ventricular irritability and premature ventricular contractions (Mitchell and Mackenzie 1982; Mohandas and Rajmohan 2007). The effects are more profound during lithium intoxication. The incidence of cardiac complications may increase with age. Higher lithium concentration has been correlated with prolonged QTc (Mamiya et al. 2005). Lithium should be used with caution in patients with congestive heart failure because of salt restriction and diuretic therapy.

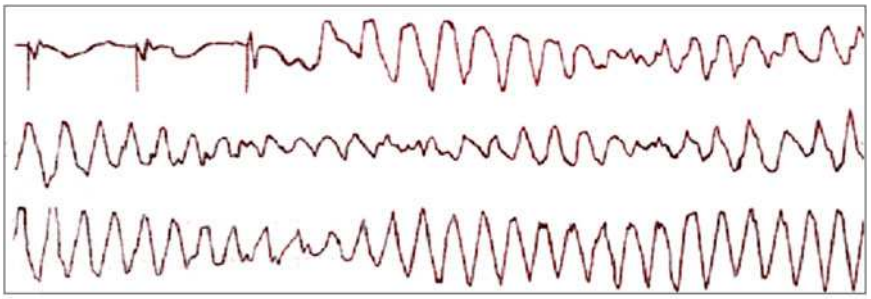
Methylphenidate is well tolerated in the medically ill, the terminally ill, and older adults. Most studies indicate about 5 and 30 % patients develop some adverse effects on methylphenidate. These are usually mild and resolve with discontinuation of medication (Hardy 2009). The most common side effects reported are agitation or restlessness, sinus tachycardia or palpitations, delirium or

confusion, and insomnia. Both hypertension and hypotension have been reported in older adults on methylphenidate, which are relatively infrequent. One serious uncommon adverse effect is arrhythmia, which is reversible with discontinuation of the medication. In 2007, the FDA required new warnings in psychostimulant labeling regarding reports of serious cardiovascular events, including sudden death, stroke, and myocardial infarction in children and adults using stimulants for attention deficit hyperactivity disorder.

Both typical and atypical antipsychotics have a similar, dose-related increased risk of sudden cardiac death (Ray et al. 2009).

8.7.4.1 Psychotropics and QTc

Psychotropic drugs can delay cardiac repolarization and prolong the rate-corrected QT interval (QTc). A prolonged QTc can be followed, in rare cases, by the life-threatening polymorphic ventricular tachyarrhythmia called torsade de pointes (TdP)



Torsade de pointes

There are individual and environmental risk factors for QTc prolongation including age over 65 years, female sex (longer QTc interval than men and twice the risk of drug-induced TdP), preexisting cardiovascular disease, congenital long QT syndrome (Jervell and Lange-Nielsen syndrome), bradycardia (sinus bradycardia, second and third -degree atrioventricular block) and electrolyte disturbances (hypokalemia, hypomagnesemia). High plasma concentrations of the offending drug from overdose, rapid infusion of the drug, inhibition of drug metabolism by concomitantly administered drugs, and/or reduced drug clearance due to renal or hepatic insufficiency can also increase the risk for QTc prolongation (Wenzel-Seifert et al. 2011).

TdP typically presents as dizziness, seizures, and syncope. It can lead to ventricular fibrillation and sudden cardiac death. Prolonged QTc interval at baseline has been shown to be a risk factor for drug induced QT prolongation and life threatening arrhythmia (Shouten et al. 1991). Drugs that prolong the QT interval bind to cardiac potassium channels (I_{Kr}, also known as HERG channels). The resulting blockade of potassium efflux from cardiomyocytes prolongs the repolarization phase. In the congenital long-QT syndrome a mutation of the I_{Kr} gene causes prolongation of the QT interval.

There is considerable intra-individual variability of QTc. In a given individual QTc can vary from 76 to 102 millisecond (ms) over the course of 24 h (Wenzel-Seifert et al. 2011). In normal persons, the mean QTc length is roughly 400 ms. The upper limit of normal is defined as 460 ms for women, and 450 ms for men. A QTc interval >500 ms is considered to be a major risk factor for the development of TdP.

Among psychotropic medications thioridazine and ziprasidone have the highest risk of QTc prolongation (Wenzel-Seifert et al. 2011; Beach et al. 2013). Clinically significant risk is associated with haloperidol given intravenously in high doses. QTc prolongation has been reported with newer antipsychotic drugs (mainly quetiapine, risperidone, olanzapine, clozapine), most of the tricyclic and tetracyclic antidepressants, selective monoamine reuptake inhibitors—citalopram, fluoxetine, paroxetine, venlafaxine, and lithium. The risk of pathological QTc prolongation

increases with the dose. Thioridazine, pimozide, sertindole, droperidol, and IV haloperidol have been documented to cause torsade de pointes and sudden death. There is no documented association with olanzapine, quetiapine, or risperidone and sudden death (Glassman and Bigger 2001). There are case reports of ziprasidone causing Tdp especially in overdose (Heinrich et al. 2006; Manini et al. 2007).

Individual risk in each patient should be carefully considered. Factors that can help to reduce the risk includes checking EKG for QTc before treatment in high risk patients, slow dose escalation in cases of altered elimination or inhibited metabolism, regular EKG monitoring of patients at high risk and those taking additional medications that can prolong the QTc interval, monitoring serum potassium and potential electrolyte loss in patients with vomiting, diarrhea, diuretic therapy, and eating disorders, and administration of magnesium sulfate if the QTc is markedly prolonged (Wenzel-Seifert et al. 2011). Discontinue psychotropic medication if the QTc is longer than 500 ms, Use alternate medication for agitation like benzodiazepines or anticonvulsants until QTc returns to normal.

8.7.5 Neurological Conditions

8.7.5.1 Cerebrovascular Disease

Patients with cerebrovascular disease are sensitive to the CNS side effects of psychotropic medications. Psychotropic drugs causing postural hypotension like TCAs and low potency typical antipsychotics should be avoided in patients with syncopal episodes. SSRIs are preferred in post-stroke depression. Studies on use of SSRIs on post stroke patients have shown improvement in global cognitive functioning, specifically in verbal and visual memory functions (Jorge et al 2010) and decrease in dependence, disability, neurological impairment, anxiety, and depression (Mead et al. 2012).

SSRI exposure is associated with an increased risk of intracerebral and intracranial hemorrhage especially in combination with anticoagulants (Hackam and Mrkobrada 2012).

All antipsychotics—typical and atypical—are associated with an increased risk of stroke when used in elderly demented patients (Gill et al. 2005; Douglas and Smeeth 2008).

8.7.5.2 Epilepsy

The prevalence of depression in patients with epilepsy ranges from 20 to 30 % in community samples to 50 to 55 % in epilepsy clinics (Jackson and Turkington 2005) with a 4–5 times increased risk of suicide in this population (Matthews and Barabas 1981).

All antidepressants and antipsychotics are known to lower seizure threshold. Seizure incidence rate ranges from approximately 0.1–1.5 % in patients treated with a therapeutic dose of these medications compared to the general population rate of 0.07–0.09 %. In overdose, the seizure risk increases to 4–30 % (Pisani et al. 2002). It is a dose-dependent adverse effect.

Risk factors for seizures include individual factors like inherited seizure threshold, history of seizures, brain injury, older age, and reduced drug clearance. Medication risk factors include higher dose, rate of upward titration of medication and sudden drug withdrawal. To reduce risk for seizures it is important to evaluate for these factors and start medication at a low dose with a slow escalation avoiding complex drug combinations (Pisani et al. 2002).

Psychotropic drugs with the highest seizure risk include bupropion, maprotiline, and clomipramine among antidepressants, and chlorpromazine and clozapine among antipsychotics. Antidepressants with lower seizure risk include phenelzine, tranylcypromine, fluoxetine, paroxetine, sertraline, trazadone, and venlafaxine. Fluphenazine, haloperidol, pimozide, and risperidone are among antipsychotics with the lowest seizure risk (Pisani et al. 2002).

8.7.5.3 Parkinson's Disease (PD)

Neuropsychiatric symptoms are common in PD including depression, anxiety, apathy, fatigue, and cognitive impairment. Medications used for the treatment of PD can cause psychiatric symptoms including delusions, hallucinations, manic symptoms, impulsive behaviors, and agitation.

These symptoms can affect the quality of life and daily functioning and place the patient at increased risk for nursing home placement. Depressive symptoms are present in 30–40 % of PD patients and 40 % of patients have anxiety symptoms (Aarsland et al. 2009).

Most antidepressants have been reported to be effective and well tolerated when used to treat depression and anxiety symptoms in PD. SSRIs can potentially have interaction with monoamine oxidase inhibitors used to treat PD like selegiline, with increased risk for serotonin syndrome. Benzodiazepines should be used with caution as they can increase the risk for falls and worsen cognitive, autonomic, and sleep related problems (Aarsland et al. 2009).

Apathy and fatigue are common symptoms in patients with Parkinson's disease and can contribute significantly to disability. Apathy is seen in 17–70 % of patients with PD. Prevalence of fatigue is about 32–58 % which may predate the onset of motor symptoms and increase over time. Medications used to treat these symptoms have limited evidence of efficacy, including dopamine agonists, psychostimulants, and modafinil (Aarsland et al. 2009).

Psychotic symptoms occur frequently in patients with PD and may be accompanied by affective and behavioral symptoms. Conventional antipsychotics are not recommended for use in patients with PD, as they have been reported to significantly worsen the motor symptoms of PD. Clozapine has been shown to be effective for the treatment of psychosis in PD without aggravation of parkinsonian symptoms (Eng and Welty 2010). Even a low dose of clozapine, 50 mg or less, can significantly improve drug induced psychosis without worsening parkinsonism (The Parkinson study group 1999). Quetiapine has been frequently used to treat psychosis in PD and has shown some efficacy in open label trials, even though placebo controlled studies have shown conflicting results. One comparative study with clozapine showed no statistically significant difference in effectiveness compared to quetiapine (Shotbolt et al. 2010). Olanzapine has worsened parkinsonian symptoms in three trials (Weintraub and Hurtig 2007).

8.7.6 Diabetes Mellitus

Serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine) provide benefit both for depression and diabetic neuropathic pain (Goldstein et al. 2005; Sindrup et al. 2005; Zin et al. 2008). TCAs can also help with the neuropathic pain but patients may be more vulnerable to the anticholinergic side effects, postural hypotension, and sexual dysfunction.

Use of atypical antipsychotics in diabetes should be weighed against the risk of metabolic syndrome with these drugs including weight gain, glucose intolerance, new onset type 2 diabetes mellitus, diabetic ketoacidosis, and hyperlipidemia. Clozapine and olanzapine have the highest risk and should be avoided in diabetics (Jin et al. 2004).

8.7.7 Psychotropics and the Syndrome of Inappropriate Release of Antidiuretic Hormone (SIADH)

Antidiuretic hormone (ADH) induces water retention in the distal tubule and collecting duct of the nephron. SIADH involves sustained release of ADH from the posterior pituitary or enhanced action of ADH on the kidneys. Increased ADH activity impairs kidney's ability to dilute urine resulting in decreased excretion of ingested water and concentrated urine. If fluid intake is not reduced serum hypotonicity and hyponatremia will occur. Patient will present with normal volume status (euvolemia) because the excess water distributes evenly throughout the body's fluid compartments. Common symptoms of SIADH include weakness, lethargy, headache, anorexia, and weight gain. Severe cases present with confusion, convulsions, coma, and death. The early symptoms are vague and nonspecific, and may mimic symptoms of psychiatric disorder (Spigset and Hedenmalm 1995).

SIADH is reported with all class of psychotropics except lithium, which was used in the past to treat SIADH. Risk factors for SIADH and

hyponatremia with psychotropics include concomitant use of thiazide diuretics, female gender, older age, low BMI, first few weeks of treatment, polypharmacy, CYP3A4 interactions, basal low levels of sodium (hyponatremia), and hyperkalemia (Wilkinson et al. 1999; Madhusoodanan et al. 2002; Spigset and Hedenmalm 1997). There are a large number of reports of SIADH and hyponatremia associated with SSRI use, with the incidence varying from 0.5 to 32 % (Jacob and Spinler 2006). In a review of reported cases of hyponatremia and SIADH associated with SSRIs, fluoxetine was involved in about 75 % of the cases, paroxetine in about 12 %, sertraline and fluvoxamine in about 11 % of the cases. The median time to onset of hyponatremia was 13 days (range 3 to 120 days). Most (83 %) of the published cases involved patients 65 years of age or more (Liu et al. 1996). Elderly patients should be monitored closely in the first 4 weeks of SSRI therapy for clinical signs suggestive of hyponatremia.

Treatment of SIADH includes discontinuation of the offending drug, restriction of fluid intake, and in severe cases may require infusion of sodium chloride. If continued treatment with an antidepressant or antipsychotic is indicated, a drug with a different pharmacological profile should be chosen, and the serum sodium levels should be monitored closely. If treatment with the drug that caused SIADH must be continued, concomitant treatment with demeclocycline may reduce the tendency to hyponatremia.

8.7.8 Respiratory Illness

The prevalence of clinical anxiety ranges from 10 to 55 % among patients with COPD (Willgoss and Yohannes 2013). Prevalence of depressive symptoms is 2.5 times greater for patients with severe COPD than controls (van Manen et al. 2002).

Antidepressants (SSRIs and SNRIs) are indicated as first line agents for treating depression and anxiety in COPD patients. Benzodiazepines can significantly reduce the ventilatory response to hypoxia. This may precipitate respiratory failure in a patient with marginal respiratory reserve. Patients with severe bronchitis ("blue bloaters"), severe restrictive lung disease, and sleep apnea are most vulnerable to the adverse effects of benzodiazepines. Antipsychotics in small doses are safer alternatives to benzodiazepines for treating acute anxiety in COPD but their potential neurological and cardiovascular side effects should be considered before use in medically ill patients. Non-pharmacological interventions like cognitive behavior therapy, pulmonary rehabilitation, relaxation therapy, and palliative care have shown to reduce depression and anxiety and improve quality of life in patients with COPD (Cafarella et al. 2012; Mikkelsen et al. 2004).

8.8 Psychotropic Drug Induced Medical Emergencies

8.8.1 Neuroleptic Malignant Syndrome (NMS)

NMS is a rare, idiosyncratic, life threatening complication of treatment with antipsychotic drugs. It is characterized by fever, severe muscle rigidity, autonomic dysfunction, and mental status changes. Recent data suggest an incidence of 0.01–0.02 % (Stubner et al. 2004). NMS remains a significant source of morbidity and mortality (10 %) in patients on antipsychotics if unrecognized and untreated.

Risk factors associated with increased incidence of NMS include agitation, dehydration, restraint, preexisting brain pathology, malnutrition, and iron deficiency (Rosebush et al. 1991). In 15–20 % of cases a prior episode of NMS is described (Caroff and Mann 1993). Pharmacologic variables that increase the risk include exposure to drugs that block dopamine D2 receptors. NMS has been reported in non-psychiatric patients treated with dopamine antagonists like prochlorperazine and metoclopramide. Withdrawal of dopaminergic agents like L-dopa can precipitate NMS like reaction. High potency conventional antipsychotics are associated with the greatest risk compared to low potency and atypical antipsychotics. Higher dosage and rapid dose escalation, depot neuroleptics, and more

than one antipsychotic (33 % increased risk) are other factors found to increase the risk for NMS (Keck et al. 1989).

8.8.1.1 Clinical Features

The signs and symptoms useful to make the diagnosis of NMS include recent exposure to dopamine antagonists, or dopamine agonist withdrawal; hyperthermia >100.4 °F or >38.0 °C on at least two occasions; rigidity; mental status alteration; creatine kinase elevation at least four times the upper limit of normal; sympathetic nervous system lability; tachycardia plus tachypnea; and a negative workup for other causes (Gurrera et al. 2011).

Clinical Course: Onset is related to the initiation of neuroleptic treatment. Progression of symptoms is usually insidious over days. There are occasional cases of fulminant onset within hours of drug administration. Alteration in mental status and other neurological signs precede systemic signs in more than 80 % of cases of NMS (Velamoor et al. 1994).

Laboratory investigations are essential to rule out other disorders or complications. Abnormal laboratory findings seen in NMS, although not specific for the diagnosis, include elevated creatine phosphokinase (CPK), leukocytosis, elevated transaminases, and low serum iron.

Complications include metabolic acidosis, respiratory failure, irreversible brain damage, pulmonary embolus, electrolyte disturbances, coagulopathy, rhabdomyolysis, and renal failure.

Once NMS is diagnosed and oral antipsychotic drugs are discontinued, it is self-limited in most cases. The mean recovery time after drug discontinuation is about 7–10 days. The duration of NMS episode may be prolonged when long acting depot antipsychotics are implicated.

Risk factors for increased mortality include older age, higher temperatures, depot neuroleptics, preexisting brain pathology, and development of renal failure.

8.8.1.2 Management of NMS

Early diagnosis and discontinuation of the offending agent including antipsychotics, lithium, and all dopamine blocking agents including antiemetics, and initiating supportive medical therapy is the mainstay in the management of NMS. Supportive measures include serial monitoring of CPK and electrolytes, aggressive volume resuscitation, physical cooling measures for extreme hyperthermia, and antihypertensives or pressors for autonomic instability. Intensive medical care should include careful monitoring for complications including cardiorespiratory failure, renal failure, aspiration pneumonia, and coagulopathies. Benzodiazepines do not have a preventive effect but they may ameliorate symptoms and hasten recovery in milder cases. In patients with more severe symptoms not responding to supportive measures, dantrolene (1–10 mg/kg/day in divided doses), bromocriptine (2.5–15 mg tid), or amantadine (200–400 mg/day) have been reported to reduce time to recovery and decrease mortality. ECT may be effective if symptoms are refractory to supportive care and pharmacotherapy, even late in the course of NMS, and in patients with severe rigidity and catatonia (Strawn et al 2007)

8.8.1.2.1 Guidelines for Treatment (Strawn et al. 2007)

Mild or early NMS: Discontinue antipsychotics, use supportive measures and benzodiazepines

Moderate NMS (rigidity and temperatures 38–40 °C, HR 100–120 bpm): Discontinue antipsychotics, use supportive measures, and use benzodiazepines or amantadine or bromocriptine.

Severe NMS: (severe rigidity, catatonia, temp >40, HR > 120 bpm) Discontinue antipsychotics, use supportive measures and use dantrolene or bromocriptine or amantadine. Consider ECT.

8.8.1.2.2 Guidelines for Rechallenge

There is a 30 % risk of recurrence following subsequent rechallenge with antipsychotics (Pope et al. 1991). At least 2 weeks after recovery from NMS should be allowed before rechallenge with antipsychotics. Reduce potential risk factors and consider alternate medications. Low doses of low potency typical antipsychotics or atypical

antipsychotics should be titrated gradually after a test dose. Patients should be carefully monitored for early signs of NMS. Ideally, rechallenge should occur in a hospital.

8.8.2 Serotonin Syndrome (SS)

Serotonin syndrome is a potentially life threatening adverse reaction resulting from therapeutic drug use, intentional or accidental overdose of drug or from interactions between drugs that result in excess of serotonergic agonism of the central and peripheral serotonergic receptors. The serotonin syndrome can range from mild to moderate to lethal. Differentiating serotonin syndrome from neuroleptic malignant syndrome can be difficult in a patient receiving both serotonergic and antipsychotic medications.

Overstimulation of serotonin receptors can be caused by precursors of serotonin or by serotonin agonists like buspirone, L-dopa, lithium, LSD, L-tryptophan, and trazodone, from decreased serotonin metabolism from MAOIs, from increased serotonin release from amphetamines, cocaine, MDMA ("ecstasy"), fenfluramine, or from inhibition of serotonin reuptake from antidepressants, meperidine, and tramadol.

8.8.2.1 Clinical Features

The symptoms and signs of serotonin syndrome include (Boyer and Shannon 2005):

1. Neuromuscular symptoms: Delirium, agitation, anxiety, irritability, affective instability, restlessness, ataxia/incoordination, muscle rigidity, myoclonus, tremor, hypereflexia, clonus, trismus, teeth chattering, seizures.
2. Gastrointestinal symptoms: Nausea, vomiting, diarrhea, incontinence.
3. Autonomic symptoms: Hypertension, hypotension, tachycardia, diaphoresis, shivering, sialorrhea, mydriasis, tachypnea.
4. Hyperthermia.

Differential diagnosis for serotonin syndrome includes infections, toxic-metabolic delirium, alcohol withdrawal delirium, extrapyramidal side-effects, adrenergic or anticholinergic toxicity, neuroleptic malignant syndrome, malignant hyperthermia, pheochromocytoma, and carcinoid tumor.

Clinical course and outcome: Symptom onset is rapid, usually developing within 6 h of an increase or addition of a serotonergic agent and typically resolves within 24 h (Iqbal et al. 2012). Patients with mild SS may present with chronic or subacute symptoms. Serotonin syndrome is usually self-limited, with an uneventful resolution, once the offending agent has been discontinued.

Nonspecific laboratory findings may include elevated total white blood cell count, CPK levels, transaminases, and decreased serum bicarbonate level. Severe cases can result in complications like disseminated intravascular coagulation, rhabdomyolysis, metabolic acidosis, renal failure, myoglobinuria, and adult respiratory distress syndrome.

8.8.2.2 Management of SS

Discontinuation of serotonergic agents, supportive measures including intravenous fluids, cooling blankets, treating autonomic dysfunction usually reverses the symptoms in mild cases. Benzodiazepines can be used to treat tremors and agitation. In more severe cases, serotonin antagonists—cyproheptadine and chlorpromazine, have shown to reverse the symptoms (Gillman 1999; Graudins et al. 1998). Cyproheptadine, 4–8 mg orally or through the nasogastric tube, repeated every 6 h up to a maximum of 32 mg/day has produced rapid resolution of symptoms. Antipsychotic agents with 5-HT2A antagonist activity such as chlorpromazine may reverse the symptoms in severe cases of SS. Chlorpromazine should not be routinely used to manage SS, especially if the patient is hypotensive and/or NMS cannot be excluded (Iqbal et al 2012).

Drug rechallenge: Switch to non-serotonergic antidepressant if possible. Consider 6 weeks serotonin drug free period before restarting a serotonergic agent.

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Integrated Care: A Population-Based Approach to Consultation-Liaison Psychiatry

9

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9.1 An Illustrative Case in an Integrated Care Setting

Ms. F is a 44-year-old Caucasian woman who was seen in an academic internal medicine clinic for treatment of uncontrolled type 2 diabetes mellitus. The integrated mental health team had noticed from their database that Ms. F's PHQ-9 depression screening scored above 20 on her last two visits, signaling that perhaps she was experiencing moderate to severe depressive symptoms. However, the team saw that she was not receiving any evidence-based treatment for depression, neither medication nor brief therapy. The behavioral health care manager assigned to the internal medicine clinic contacted internal medicine resident Dr. C to offer assistance. Dr. C had already received extensive training from the consulting psychiatrist and care managers about diagnosing and treating depression, had confidence in prescribing and managing antidepressant medications, and knew how to access brief evidence based-psychotherapies that were being provided in primary care and in the community. Dr. C indicated that he had already diagnosed Ms. F as suffering from a major depressive episode when she had a PHQ-9 score of 21 at a previous visit. He remembered that she was very tearful when he had warned her about the high likelihood of diabetic complications if she did not adhere to the recommended diet, exercise, and medications. However, he stated that Ms. F had minimized her depressive symptoms and had blamed her

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tearfulness on the clinic staff who she claimed "just want to run my life." Ms. F also refused both treatment with an SSRI and a referral to brief individual therapy.

The care manager placed the patient on his caseload and made several attempts to reach her by phone for a consultation. Although unsuccessful in his initial attempts to contact her, he continued to follow the case in the electronic medical record. At a subsequent meeting he informed the other behavioral health care managers and the team psychiatrist that Ms. F had an appointment in the internal medicine clinic the following day. At the beginning of the clinic, the internal medicine team also had a "team huddle." The care manager attended this meeting, and was asked to provide suggestions on several of the patients who were discussed, including Ms. F.

When it came time to discuss Ms. F, Dr. C was given an opportunity to express his frustration with trying to treat Ms. F's diabetes in the setting of significant non-adherence to recommended medications and dietary restrictions. Her last hemoglobin A1c value was 11.4. Her body mass index was 42, and she seemed to still be gaining weight, despite repeated "dire" warnings about impending complications of her uncontrolled diabetes. The care manager normalized the frustration Dr. C was feeling, and presented a brief description of motivational interviewing as a possible alternative approach with this patient. He then described how motivational interviewing not only has strong outcomes in many cases, but how this type of approach also helps to "liberate" the provider from at least some of the frustration that invariably comes with treating patients who are non-adherent.

With the support of the care manager, Dr. C was able to see Ms. F and show her empathy and compassion. This prompted Ms. F to then apologize for her past behavior, including all the obstacles that she faced in coming to the clinic. This then allowed Dr. C to point out that he notices that Ms. F is trying very hard to make her appointments and that he was curious about what motivates her to come in at all. Ms. F then explained how she values being strong and independent, and that she wanted to make it to appointments to prove that she was capable of doing so. She stated that she often feels lonely and doesn't have many friends, but that she liked coming to the clinic and wanted to feel accepted by clinic staff, including by her doctor. Dr. C thanked Ms. F for sharing this with him and offered to partner with her in meeting her goals. He expressed understanding of how difficult it must be for Ms. F to feel judged by clinic staff and of her desire to connect with people who accept her. Dr. C then told Ms. F about the "healthy choices" group, and that he thought that this might be a place where Ms. F could come to connect with other people with health struggles like hers, without being judged. Ms. F was interested, and Dr. C then called in the care manager, who told Ms. F more about the group and connected with Ms. F on a personal level.

Ms. F attended the "healthy choices" group later that week. She was able to commit to a seemingly small dietary change, eating only one dessert with dinner instead of her usual two to three, which she expressed a high degree of confidence that she could attain. She was very proud to report to the group the following week that she had been successful. The group encouraged her and she began to feel close to several members. She began to reveal more details about her obstacles to change, including being a victim of sexual assault. After attending the "healthy choices" group for several weeks in a row, Ms. F agreed to participate in a support group for people with posttraumatic stress disorder at the community mental health center that was also co-led by one of the care managers.

At her 3-month follow-up appointment with Dr. C, Ms. F's BMI had dropped to 39 and her hemoglobin A1c had dropped to 10.2. However, she continued to have significant depressive symptoms, with a PHQ-9 score of 18, and hypertension, with blood pressure of 154/91. At that point, Ms. F agreed to initiate sertraline to assist in the treatment of her depression. She also agreed to take lisinopril and metformin, which she previously had resisted. The integrated mental health team maintained close contact with Ms. F during the initiation of sertraline, inquiring about any side effects or any other obstacles to adherence. Ms. F tolerated 50mg of sertraline with very few side effects, but her level

of depressive symptoms was still quite high. At the recommendation of the consulting psychiatrist, passed on via the care manager, Dr. C increased the sertraline dose to 100mg. Ms. F saw a partial response, with a PHQ-9 score of 12 after 1 month at this dose. Dr. C then increased the sertraline dose to 150mg. By the next 3 month follow-up visit, Ms. F had a PHQ-9 score of 7. More remarkably, she had a hemoglobin A1c of 8.4, a BMI of 36, and BP of 133/86.

9.2 Why Is a Population-Based Approach to Consultation-Liaison Psychiatry Needed?

Our population is growing rapidly, and with a geriatric population outpacing all other demographics we will see nearly one in five US residents aged 65 and older by 2030. Between 2010 and 2050, the US population is projected to grow from 310 million to 439 million, an increase of 42 %. The nation will also continue to become more racially and ethnically diverse, with the minority population projected to become the majority by 2042. (US Department of Commerce Economics and Statistics Administration 2010). With this growth comes an expanding need for care with a diminishing set of resources including financing, providers, and infrastructure. The largest component of this growing burden stems from chronic diseases such as diabetes and heart disease which are worsened by health characteristics like obesity and hypertension, and can be directly linked to ongoing health behaviors such as unhealthy diet, lack of exercise, poor sleep habits, and nicotine and alcohol use.

Mental illnesses and substance use disorders are very prevalent and are responsible for a significant amount of disability and mortality, either directly, or indirectly through poor medical health and decision making. In the population there is a 5–10 % prevalence of major depression, with up to three times that percentage having significant subsyndromal symptoms. In hospitalized patients this number is as high as 25 % (Barkin et al. 2000). Patients who have chronic medical illnesses have even higher risks of mental illnesses (such as major depressive disorder) and their complications (such as suicidal ideation) (Wells et al. 1988; Druss and Pincus 2000). In addition, mental illnesses, substance use disorders, and psychosocial factors can significantly complicate other medical illnesses. Mental illnesses, such as major depressive disorder, are associated with increased disability, reduced adherence to medical treatments, and worsened medical outcomes (Katon 1996). Early identification and effective treatment of mental disorders and other psychological factors affecting medical illness can dramatically reduce the costs, disability, and suffering associated with medical illnesses.

However, many people who suffer from mental illnesses and substance use disorders are not properly diagnosed, and those who are diagnosed often do not receive effective treatment. There are many factors that contribute to this unfortunate reality, including lack of awareness of mental illness and the availability of effective treatments, ineffective screening programs for mental illnesses, inadequate access to mental health treatment (due to shortages of trained mental health providers and limited insurance coverage of mental health services), isolation of mental health systems from other systems of care, and the stigma against mental illness which often makes people reluctant to discuss their mental health concerns or seek treatment. While mental health treatments for individual patients have advanced considerably in the last several decades, relatively little attention has been paid to translating these advances into advances for the mental health of large populations, until more recently. And unfortunately, the USA is currently ranked last in the quality of care outcomes in nearly every category of mental health and medical treatment in the developed world despite care being ranked as one of the most expensive health care systems globally (Kane 2013).

9.3 What Changes Are Being Seen?

As health systems adapt to more effectively and efficiently serve the health needs of entire populations, there is a growing recognition of the importance of more systematic approaches to the

identification and treatment of mental illnesses and substance use disorders at the population level. The patient-centered medical home (PCMH) and the Accountable Care Organization (ACO) are examples of health care delivery models designed to provide high-quality, cost-effective care to entire populations. These models effectively link a primary care "hub" to acute care and specialty care supports and provide incentives for prevention, early intervention, and proactive management of chronic illnesses at the most cost-effective level of care possible. Managing chronic illness at the most cost-effective level of care usually means avoiding unnecessary hospitalizations and specialty referrals and implementing standardized disease screening[1] and management protocols to increase the likelihood of efficient delivery of quality care. In these models, common, uncomplicated illnesses must be managed by primary care providers (not by specialists and not in acute care settings) whenever possible. This frees up the much fewer specialist physicians, psychiatrists in particular, to treat the more serious and emergent cases while the primary care doctors treat the simpler and more routine symptoms. This is particularly timely as experts and officials predict that the nation's psychiatric workforce will be short more than 22,500 physicians by 2015 (Iorfino 2013).

While outpatient psychiatric consultation-liaison services in the USA and the UK have been available since the first half of the twentieth century (Dolinar 1993), the vast majority of consultation-liaison psychiatry services have historically been oriented toward the highest levels of medical care (Mayou 1989), such as tertiary care inpatient medical/surgical hospitals and less commonly subspecialty outpatient consultation clinics (e.g., HIV psychiatry, perinatal psychiatry, and psycho-oncology clinics). This new model focuses on the general outpatient setting where the majority of patients are seen for more routine care and maintenance of the chronic conditions that will often lead to the need for treatment in this higher level of care. This provides a primary (prevention) or secondary (early treatment) level of preventive care rather than tertiary (minimizing consequences) at best (Centers for Disease Control and Prevention 2013).

Indeed, there have been a number of significant barriers to integration, including the following: inability of general medical patients to identify the psychiatric nature of some symptoms; reluctance of patients to seek or health care providers to recommend mental health care due to stigma; limited training of medical providers in mental health; lack of time to address mental health concerns (in addition to other general medical concerns) in the relatively brief general medical clinical encounter; and restrictions on insurance coverage for mental health services, particularly those provided in general medical settings and/or by general medical providers (Unutzer et al. 2006). However, the increased interest in integrated care (IC) and population health with PCMHs and ACOs, has sparked a renewed interest in the integration of mental health into overall health care, and particularly integration into primary care and other outpatient medical clinics. Integrated care answers each of these barriers in turn with specifically designed and targeted solutions. It is also constructed to change and adapt to apply to the diverse and the rapidly changing medical delivery environment.

9.4 What Is Integrated Care?

The concept of a health care system caring for the "whole person," including mental health needs, is not a new one. In fact, the delivery of care was historically far more all-encompassing, and in much of the world remains that way for reasons of culture, economy, or necessity. Treatment in many developing countries as well as much more rural areas in the industrial world have physicians that provide care from medical, to mental, to dental and surgical. Many deeply held cultural and spiritual beliefs specifically focus on the

[1] Editors' Note: There is some controversy concerning screening in general, including for depression (Force 2009; Thombs and Ziegelstein 2013, Deneke et al. 2014). The general consensus seems to be that this is effective only if reliable systems of care are in place to ensure accurate diagnosis and appropriate treatment by clinicians.

mind–body connections and can be seen to dominate the fields of traditional medicine practices that many people will turn to long before seeking care from more "western" approaches even in large US cities. These include: homeopathy, ayurveda, acupuncture, spinal manipulation, hypnosis, and traditional Chinese medicine (Turner 2013). When medical care involves these "eastern" techniques in practice, this is often labelled as "alternative, complementary, or integrative (not to be confused with integrated)."

There is a broad lexicon in the medical literature that expresses this general concept of combined care. This lexicon includes phrases such as "medical-mental health integration" or "collaborative care," "shared care," "co-located care," "primary care behavioral health," "integrated primary care," and even "behavioral medicine." In some ways, this divergent lexicon was beginning to become an obstacle to advancing research into and effective implementation of integration of behavioral health services into systems of general medical care due to the misclassification of different levels of integration in the research literature. In addition, because of the growing enthusiasm for integrated care, there was a temptation for programs to simply declare themselves "integrated," without performing the work necessary to achieve this distinction. In short, intervention was needed to prevent the integrated behavioral health landscape from becoming one in which "anything goes" (Peek 2013).

As a result, the Agency for Healthcare Research and Quality (AHRQ) convened an expert consensus panel to help provide a common integrated care lexicon. While many different models of integration are available and useful, the consensus panel defined the core concept of behavioral health and primary care integration as:

> "The care that results from a practice team of primary care and behavioral health clinicians, working together with patients and families, using a systematic and cost-effective approach to provide patient-centered care for a defined population. This care may address mental health and substance abuse conditions, health behaviors (including their contribution to chronic medical illnesses), life stressors and crises, stress-related physical symptoms, and ineffective patterns of health care utilization" (Peek 2013).

This restates what is known as the Alma-Ata Declaration from the International Conference for Primary Health Care in September 1978. The Declaration of Alma-Ata begins by stating that health:

> which is a state of complete physical, mental and social wellbeing, and not merely the absence of disease or infirmity, is a fundamental human right and that the attainment of the highest possible level of health is a most important world-wide social goal …

It goes on to call for all governments, regardless of politics and conflicts, to work together toward global health. Those who ratified the Declaration of Alma-Ata hoped that it would be the first step toward achieving health for all by the year 2000. In 2008, the World Health Organization (WHO) revisited the topic and released a 200 page report on the application of integrated care in vastly different populations across the globe and detailed the planning, implementation, and the successes and failures of many of these different strategies. These were largely successful and increased the number of patients successfully treated by orders of magnitude (2008).

The AHRQ consensus panel went on to define the key functions of integrated behavioral health care.

The key functions included:

1. A practice team tailored to the needs of each patient and situation
   Goal: To create a patient-centered care experience and a broad range of outcomes (clinical, functional, quality of life, and fiscal), patient-by-patient, that no one provider and patient are likely to achieve on their own.
   (a) *With a suitable range of behavioral health and primary care expertise and role functions available to draw from*—so team can be defined at the level of each patient, and in general for targeted populations. Patients and families are considered part of the team with specific roles.
   (b) *With shared operations, workflows, and practice culture* that support behavioral health and medical clinicians and staff in providing patient-centered care.
   (c) *Having had formal or on-the-job training* for the clinical roles and relationships of

integrated behavioral health care, including culture and team-building (for both medical and behavioral clinicians).
2. With a shared population and mission
3. Using a systematic clinical approach (and system that enables it to function)
   (a) *Employing methods to identify those members of a population who need or may benefit* from integrated behavioral/medical care, and at what level of severity or priority.
   (b) *Engaging patients and families in identifying their needs for care,* the kinds of services or clinicians to provide it, and a specific group of health care professionals that will work together to deliver those services.
   (c) *Involving both patients and clinicians in decision-making* to create an integrated care plan appropriate to patient needs, values, and preferences.
   (d) *Caring for patients using an explicit, unified, and shared care plan* that contains assessments and plans for biological/physical, psychological, cultural, social, and organization of care aspects of the patient's health and health care. Scope includes prevention, acute, and chronic/complex care.

Finally, the AHRQ consensus panel defined the supports necessary for these functions to become sustainable on a meaningful scale. These supports included:

1. A community, population, or individuals expecting that behavioral health and primary care will be integrated as a standard of care so that clinicians, staff, and their patients achieve patient-centered, effective care.
2. Supported by office practice, leadership alignment, and a business model
   (a) *Clinic operational systems, office processes, and office management* that consistently and reliably support communication, collaboration, tracking of an identified population, a shared care plan, making joint follow-up appointments or other collaborative care functions.
   (b) *Alignment of purposes, incentives, leadership, and program supervision* within the practice.
   (c) *A sustainable business model* that supports the consistent delivery of collaborative, coordinated behavioral and medical services in a single setting or practice relationship.
3. And continuous quality improvement and measurement of effectiveness
   (a) *Routinely collecting and using measured practice-based data* to improve patient outcomes—to change what the practice is doing and quickly learn from experience. Include clinical, operational, demographic, and financial/cost data.
   (b) *Periodically examining and internally reporting outcomes*—at the provider and program level—for care, patient experience, and affordability (The "Triple Aim") and engaging the practice in making program design changes accordingly (Peek 2013).

9.5 What Is the Continuum of Care Integration?

While the AHRQ consensus panel provided much-needed consensus as to the functions and supports necessary for "true integration," the reality is that attempts at integrated behavioral health care fall short of this ideal. In fact, most attempts at integration start as something less than full integration, and only achieve ideal integration with considerable time and effort. In a 1996 article, Doherty, McDaniel, and Baird proposed five levels of integration of mental health services into primary care (Doherty et al. 1996). However, since that seminal article, there have been many different adaptations that seemed to conflict with each other to some extent. Heath, Wise Romero, and Reynolds recently proposed a standard framework for levels of integrated health care. These levels are helpful, as they realistically describe different levels of integration on a continuum, recognizing the merits of each

level, and challenging health systems to aspire to higher levels of integration, whenever possible. The continuum of integration is as follows:

9.5.1 Coordinated Care

This is the system historically, and currently, present in most private medical and psychiatric offices.

Level 1—Minimal Collaboration:

Behavioral health and primary care providers work at separate facilities, have separate systems, and rarely communicate. When attempts at communication do occur, they are usually based on a particular provider's need for specific information about a mutual patient. Many referrals between practices are unsuccessful.

Level 2—Basic Collaboration at a Distance:

Behavioral health and primary care providers maintain separate facilities and systems, but view each other as resources and communicate periodically about shared patients. Behavioral health is viewed as "specialty care." Referrals between practices may or may not be routinely successful.

9.5.2 Co-located Care

This system is in place in some large organizations like Kaiser Permanente, the Veteran's Administration, and many teaching hospitals. Movement is steady towards this level of coordination.

Level 3—Basic Collaboration Onsite:

Behavioral health and primary care providers are co-located in the same facility, but may or may not share the same practice space. Providers still use separate systems, but communication becomes more regular due to close proximity. Referrals usually still occur at this level, but have a higher likelihood of success because the practices are in the same location. Providers may feel like they are part of a larger team, but the team and how it operates are not clearly defined, leaving most decisions about patient care to be done independently by individual providers. In some cases this can lead to the illusion of integration, without many of the benefits.

Level 4—Close Collaboration with Some System Integration

There is closer collaboration among primary care and behavioral health care providers due to co-location, and there is the beginning of integration in care through some shared systems. A typical model may involve an embedded behavioral health practice, where the primary care front desk schedules all appointments and the behavioral health provider has access and enters notes in the medical record. As professionals have more opportunity to share patients, they have a better basic understanding of each other's roles.

9.5.3 Integrated Care

This is the least common level of care, and is seen in centers who have focused on improving health care delivery like the University of California at Davis, the University of Washington, and the various sites involved in the IMPACT study.

Level 5—Close Collaboration Approaching an Integrated Practice:

There are high levels of collaboration and integration and behavioral and primary care providers begin to function as a true team, with frequent personal communication. The team actively seeks system solutions as they recognize barriers to care integration for a broader range of patients. Some issues may not be readily resolved, but providers understand the different roles team members need to play and they have started to change their practice and the structure of care to better achieve patient goals.

Level 6—Full Collaboration in a Transformed/Merged Practice:

The highest level of integration involves the greatest amount of practice change. Extensive collaboration between providers has allowed old system cultures to blur into a single merged practice. Providers and patients view the operation as a single

health system treating the whole person, and this "whole person" principle is applied to all patients, not just targeted groups (Heath et al. 2013).

9.6 How Is Primary Care Integration Structured?

There are many ways to construct an IC program, and much is written on this topic. One of the most widely studied and implemented models of integrating mental health services into primary care is the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) model developed at the University of Washington. The original IMPACT trial followed 1,801 depressed, older adults from 18 diverse primary care clinics across the USA for 2 years. The 18 participating clinics were associated with eight health care organizations in Washington, California, Texas, Indiana, and North Carolina. The clinics included several Health Maintenance Organizations (HMOs), traditional fee-for-service clinics, an Independent Provider Association (IPA), an inner-city public health clinic and two Veteran's Administration clinics. IMPACT has now been implemented at many more sites throughout the USA, and also internationally (Unützer et al. 2001, 2002). IMPACT was originally designed to focus on the identification and treatment of depression, but has since been adapted to also address other behavioral health problems seen in primary care clinics such as generalized anxiety, PTSD, and substance abuse.

The key components of the IMPACT model include: (1) close collaboration between the primary care provider and a behavioral health care manager, (2) active participation of a behavioral health care manager in the monitoring and care of patients identified with behavioral health problems, using evidence-based screening and treatment techniques, (3) more peripheral involvement of a consulting psychiatrist who assists in the care of patients who are not responding to treatments as expected, (4) close monitoring of individual and population-level outcomes using evidence based tools, and (5) "stepped care" with closer scrutiny and level of involvement for patients who are not responding to treatment as expected. Due to its initial focus on depression, IMPACT screened for and tracked depressive symptoms using the Patient Health Questionnaire-9 (PHQ-9), a nine item self-administered depression questionnaire that completed in about 2 min (Kroenke et al. 2001). The first two items of the PHQ-9, called the PHQ-2, have been shown to perform nearly as well as the PHQ-9 in the screening function (Löwe et al. 2005). IMPACT has been adapted to use screening tools for other mental health symptoms, such as the GAD-7 for generalized anxiety (Spitzer et al. 2006). Based upon these symptom rating scales and other relevant clinical factors, treatment is adjusted based upon clinical outcomes and according to an evidence-based algorithm (Unützer et al. 2001, 2002).

The success of the IMPACT model hinges upon of all members of the team having a clear understanding of their respective duties. The patient (often accompanied by family members) is at the center of the team, and is ultimately responsible for defining goals and the direction of care. Nothing is done without the consent and participation of the patient. IMPACT is designed to engage the patient as an active participant in their treatment. Education about mental health symptoms and treatment is essential in preparing the patient to be an active member of the team, and to help prevent relapse when preparing for discontinuation of active care management (Katon et al. 1995; Unützer et al. 2001, 2002). This is further developed with objectively studied brief therapy techniques such as Motivation Interviewing (MI) for substance abuse treatment, and Problem Solving Therapy (PST) for developing new and more adaptive health behaviors.

The primary care provider (PCP) is also a critical team member in the IMPACT model, and is responsible for encouraging the patient's participation in care activities, prescribing antidepressant medications, providing treatments aimed at comorbid medical conditions, and for referrals to specialty mental health care when needed.

The care manager in the IMPACT model is responsible for supporting the patient and PCP in

depression treatment. The care manager is expected to:

- Provide patient education on pertinent behavioral health topics (e.g., sleep hygiene, antidepressant medication, etc.)
- Support medication therapy prescribed by the PCP by following up with the patient after medication is prescribed to provide education, encourage adherence, and monitor for/mitigate side effects
- Engage patients in behavioral activation at each contact
- Offer evidence-based counseling or refer the patient for such counseling or psychotherapy, when indicated
- Track depression and other behavioral health symptoms at each contact to monitor the effectiveness of treatment
- Notify the PCP when the patient has been in treatment for more than 10–12 weeks without adequate improvement
- Coordinate consultation from the psychiatrist regarding treatment changes
- Complete a relapse prevention plan with the patient when they are ready to leave active care management

Care managers can be nurses, psychologists, social workers or licensed counselors.

The usual caseload for a full-time care manager is approximately 100–150 patients. Some models split the care manager duties into the routine activities that can be handled by a paraprofessional (e.g., Medical Assistant) and those better handled by a more highly trained professional. This can be an efficient use of resources and allows the care manager to carry a larger caseload. In the literature this position has been given many different titles including: (behavioral health) care manager (CM), behavioral health consultant (BHC), expert (BHE), or provider (BHP).

The consulting psychiatrist's two primary responsibilities are clinical consultation to the care manager and the patient's PCP, and direct patient consultation for patients who are not improving after several treatment changes or who are suspected to need specialty mental health care (e.g., patients with bipolar disorder or schizophrenia). The consulting psychiatrist meets with the care manager weekly for about an hour (either in person or by telephone) and they review new patients and any patients who have been in treatment for 10–12 weeks who are not showing adequate improvement in their depression symptoms. The psychiatrist suggests treatment modifications for the PCP to consider, which are usually communicated to the PCP by the care manager and/or in the medical record. The psychiatrist is also available to both the care manager and the primary care providers for ad hoc telephone consultations and for an in-person consultation in those rare instances when that is needed. For example, in the IMPACT randomized trial for depressed elderly patients in primary care, only about 10 % of all patients receiving active care management had an in-person consultation with the consulting psychiatrist (Unützer et al. 2002).

Relative to other integrated care models, IMPACT has spread to a wide variety of settings because its developers encourage providers and organizations to adapt the program to meet the unique needs of their setting, only recommending that they adhere to the key components (defined earlier) and work toward the quality goals below:

Depression Screening: 75 % of patients will have documentation of annual screening for depression with the PHQ-2 or similar screening measure

Diagnosis: 75 % of patients who have a positive screen will receive a structured depression assessment (e.g., PHQ-9) to help confirm a diagnosis of depression within 4 weeks of screening

Initiation of Treatment: 75 % of patients diagnosed with depression will have initiated treatment (antidepressant medication, psychotherapy, or ECT) or attended a mental health specialty visit within 4 weeks of initial diagnosis

Measurement of Treatment Outcomes: 75 % of patients treated for depression will receive a structured clinical assessment (i.e., PHQ-9) of depression severity at: *baseline*: within 2 weeks prior or subsequent to treatment initiation *follow-up*: within 8–12 weeks following treatment initiation *continuation*: within 3–6 months following treatment initiation

Adjustment of Treatment Based on Outcomes: 75 % of patients treated for depression with a PHQ-9 score of ≥ 10 at follow-up will receive an adjustment to their depression treatment (e.g., change in antidepressant medication or psychotherapy) or attend a mental health specialty consult within 8–12 weeks of initiating treatment

Symptom Reduction: 50 % of patients treated for depression will have a decrease > 50 % in depression symptom levels from baseline as measured by the PHQ-9 or similar quantifiable measure and a PHQ-9 score < 10 within 6 months of initiating treatment (Source: http://impact-uw.org)

9.7 What Does Integrated Care Look Like to a Patient?

To a patient this new system looks both similar and different when compared to traditional care. They arrive at their familiar primary care office and check in at the front desk in the same way as always. Depending on the IC model, and the reason for the visit, the patient might be given a mental health screening form to fill out in addition to any other paperwork. When called into the back office they will meet with a member of the nursing staff to take their vital signs and preliminary information as usual, but this will now include a brief mental health screen if they have not already done one.

Here is where things could diverge more obviously. If mental health issues are prominent, there may be an additional phase of the appointment here before the primary care doctor becomes involved. A more detailed discussion of the mental health situation or symptoms may ensue now with the nursing staff member or with the behavioral health care manager. After this the patient will see their familiar primary care provider and discuss both their physical and mental health needs. The PCP will listen to the symptoms and advise the patient on the next phase of evaluation and treatment which may include more screenings, laboratory tests, or consultations. At this point prescription medications may be written for the treatment of either somatic or mental health conditions. The patient will then either end the appointment by scheduling a follow-up with the same office, or with a specialist which might include a therapist or psychiatrist. If more health education is required, the patient may again meet with nursing staff or care manager. The patient will likely leave the appointment with educational material on physical and mental health conditions, but also strategies for management of these and other ongoing health behaviors that can maximize overall health and well-being. The patient may be told to expect a call in a few days in order to ascertain how their treatment is going (ex: symptoms or medication side effects) or in order to determine whether they have been successful in connecting to subspecialty services.

What the patient will not observe will be the algorithm that had been developed to guide the navigation of this appointment, the integrated team meeting that discussed their case if it was difficult or unique, or the recommendations given by the psychiatrist consultant to any of the different team members individually if contacted. Although present in the process at all points in this care, the consulting psychiatrist will likely never meet directly with the patient.

9.8 Is Integrated Care Effective?

IC has consistently demonstrated excellent results in a variety of settings in both the improvement of mental health and substance abuse outcomes, but also medical illnesses as well. The IMPACT model of depression care described above is one of the most cited successes for the integration of mental health care in to the primary care setting. In this 1998–2003 study we see the care model more than doubles the effectiveness of depression treatment in primary care settings, with a decrease in cost by half. At 12 months, about half of the patients receiving IMPACT care reported at least a 50 % reduction in depressive symptoms, compared with only 19 % in the usual care. The IMPACT patients experienced more than 100 additional depression-free days over a 2-year period than those treated in usual care.

Furthermore, even 1 year after the program was discontinued, benefits of the intervention persisted (Unützer et al. 2002).

The integrated approach seems to work with patients of all ages. Results suggest that reductions in drinking can also be achieved. Other conditions, such as somatization, are earlier on the research trajectory. The potential for other mental health conditions, such as PTSD, have yet to be systematically studied, but early results appear promising (Butler et al. 2008). The new delivery method also shows benefits for severely depressed patients with suicidal ideation who are seen more quickly and delivered to more acute care in a more timely fashion (Kripalani et al. 2010).

Another program was completed in 2006 in Texas through St. David's Community Health Foundation, at People's Community Clinic and Lone Star Circle of Care. Both clinics provide primary care to "safety-net" populations. Again we see an improvement in 58 % of patients, who experienced a 50 % or greater reduction in their depression scores. This outcome far exceeds the 28 % estimates for what was expected with usual care alone and even exceeded the 40 % goals for collaborative care. Additionally, emergency room and primary care provider visits declined significantly in the follow-up period, shifting IBH patients from "heavy" to "average" utilizers. Globally, the patients report significantly better overall health, less pain, and more energy (Watt 2008).

The true scope of integrated care becomes evident when we see that when patients have better mental health, they also have better physical health. It is said that there can be no physical health without mental health. Mental disorders have repeatedly demonstrated an increased risk for communicable and non-communicable diseases, and contribute to unintentional and intentional injury. A 2010 study showed as compared with usual care, an intervention involving nurses who provided guideline-based, patient-centered management of depression and chronic disease significantly improved control of medical disease as well as depression (Katon). Research in 1999 suggested that the maintenance of emotional well-being is critical to cardiovascular health, that patients who felt "lonely, depressed, and isolated" have been found to be significantly more likely to suffer illnesses and to die prematurely of cardiovascular diseases than those who have adequate social supports (Williams). It has been found that not only is depressed mood a risk factor for the development and progression of cardiovascular disease, but that there is a strong link between depression and poor outcomes following a cardiovascular event. These patients are less likely to follow treatment such as taking aspirin, antihypertensive drugs, and lipid-lowering medications (Ford 2003). Enrollment in a co-located, integrated clinic was repeatedly associated with increased primary care use and improved attainment of cardiovascular risk goals among veterans with serious mental illness (Pirraglia et al. 2012) and in particular patients with bipolar disorder (Goodrich et al. 2012l).

Other chronic illnesses, such as obesity (Pratt et al. 2013 and Bonfioli et al. 2012), diabetes (Katon et al. 2012), inflammatory bowel disease (Mikocka-Walus et al. 2012, 2013), and hepatitis C (Groessl et al. 2013; Newman et al. 2013) all have shown marked improvement after integration of services as well.

9.9 What Is "Reverse Integration?"

Whereas by population most patients with mental health needs will be seen in the primary care settings, this does not account for the portion of the population with the most severe mental illness. These patients, particularly those with schizophrenia, have much higher incidences of heart disease and metabolic syndrome than the general population and show increased risks of infectious disease, pulmonary disease, and substance abuse (Goff and Newcomer 2007). People with serious mental illness die on average 25 years earlier than the general population, not only through suicide and injury but 60 % of premature deaths are due to preventable medical conditions. These include a high incidence of smoking (½ the cigarettes smoked in the USA), sedentary lifestyle, high rates of obesity (42 %), poor nutrition, comorbid substance use disorders, and often with very

limited access to quality health care (Real 2013). In this case, we need a second type of integration of care aimed at having medical services available to clients being treated in more long-term behavioral health settings. This second model has been called "reverse integration" or "reverse co-location" when more limited (Collins et al. 2011).

This system modifies the role of the psychiatrist in helping to maintain the physical health of patients, just as the previously described system enhanced the mental health care duties of the primary care provider. Targeted tasks for the mental health team include monitoring for weight gain and other cardiac risk factors that may be increased by psychotropic medications, and emphasis on the importance of communication between psychiatrists and primary care providers. Psychosocial interventions can include meditation or walking groups, smoking cessation classes, and yoga. Here the primary care doctor observes, teaches, and consults. Integrating care is described by the Substance Abuse and Mental Health Services Administration as "vital to addressing all the health care needs of individuals helping to maintain the physical health of patients, just as the previously described system enhanced the mental health.

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Systems and Ethical Issues in CL Psychiatry: Hospital as a Social System, Sick Role and Doctor Role, Ethical and Legal Issues

10

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Contents

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10.1 Vignettes

1. A 67-year-old woman with a hip fracture was referred to the psychiatrist, as she wished to leave the hospital against medical advice prior to surgery. The patient was described as being hostile, agitated, and irrational by the nursing staff. On interview, the patient insisted that she had to go home, but upon further questioning, it was found that the patient lived alone with three cats, and she was concerned about not being able to care for the cats. When the consultant called the social worker, she was unaware of the patient's concern about the cats, as she had only asked whether the patient had a home and family (human family!). The consultant explained to the nursing staff why the patient was so agitated: she was worried about her cats. They empathized with her concern. The social worker was able to contact a sister who lived in another city, who was willing to care for the cats while the patient was in the hospital. The patient was now willing to stay and have the necessary surgery.
2. An urgent psychiatric consultation was requested for a 47-year-old man with suspected coccidioidomycotic meningitis to evaluate his capacity to refuse a lumbar puncture. On examination, the patient was found to be mildly delirious, but he understood that the doctors wanted to put a needle into his spine to get fluid to help treat him. However, he was

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sure that he would be OK without the test as he had trust in God. The consultant contacted his wife, who turned out to be quite supportive, and was willing to try to persuade him to undergo the procedure as well as to sign the consent form as next of kin.

3. A 54-year-old woman was referred to the psychiatrist for "declaration of incompetence and institutionalization." She was admitted to the hospital with chest pains, and a myocardial infarction was ruled out. The referring physician stated that she had received a call from a psychiatrist working for the patient's managed care company, who stated that the patient should be certified by the hospital to be placed in a nursing home facility. On examination, the patient had no evidence of delirium, dementia, or any other psychiatric condition. The patient stated, however, that she had been previously "harassed" by a psychiatrist hired by the managed care company. The consultant called the managed care psychiatrist, who insisted that the patient was "subtly delusional and paranoid," which becomes manifest only when she is repeatedly confronted. On further discussion, the managed care psychiatrist confided that the patient was a drain in resources for the company as she had frequent presentations to the emergency department with chest pains, and that she would be better cared for in a nursing home under psychiatric certification for inability to function independently. Having no basis for such certification at present, and unwilling to "confront the patient repeatedly," the consultant refused any further intervention.
4. A 34-year-old man was admitted for pneumocystis pneumonia associated with AIDS. A psychiatric consultation was requested because the patient appeared depressed and expressed suicidal ideation. The nursing staff also stated that the patient's partner, who was always at the bedside, made disparaging remarks about the care the patient was receiving. Through an interview with the patient and his partner, the consultant found out that they had recently moved from another city because the partner's job was transferred, and that the patient and his partner had had a long-standing relationship with the health care system of their former city. As the patient fell ill, they did not have an opportunity to build a social support system in the new city. The consultant provided the patient's partner with contact information for gay and HIV support groups in the community, and restarted the fluoxetine that the patient was receiving previously but that had run out. The patient recovered uneventfully, was discharged, and has outpatient appointments with a psychiatrist who is associated with an HIV clinic.

10.2 Overview

The consultation process occurs in a social system. As we discussed in Chap. 3, the request for consultation usually arises as a result of a strain in the system around the patient, consisting of the doctors, nurses, allied health professionals, health care organizations, as well as the patient's family, friends, and, at times, social agencies.

To relieve the strain that led to the consultation, then, it is necessary to recognize the state of the social system around the patient. While treatment of the psychiatric condition that the patient manifests, such as depression or suicidal ideation, may often be sufficient to reduce the strain (i.e., anxiety of the nursing staff about a patient committing suicide on the floor), the most efficacious way to intervene to reduce such symptoms may be directed to the social systems as well as the individual patient (as in vignette 4).

10.3 The Hospital as a Social System

A general hospital is a complex organization with complex lines of authority and loyalties. The people who are found in a general hospital can be generally classified as follows:

1. Administrators
   (a) Health-care related (e.g., chief of staff, director of nursing)
   (b) Non-health-care related (e.g., CEO, CFO, director of food service, laundry)

2. Doctors
   (a) Employed by the hospital, medical school, or medical group (house staff, full-time attendings, hospitalists, etc.)
   (b) Not employed by hospital or medical school or medical group (visiting staff, consultants, etc.)
   (c) Medical students
3. Nurses
   (a) Registered nurses
   (b) Other nursing staff
   (c) Nursing students
4. Allied health care professionals (pharmacists, social workers, psychologists, etc., and, in some institutions, their trainees)
5. Non-health-care professional workers (housekeeping, food services, engineers, security, etc.)
6. Patients
7. Patient's visitors
8. Police/prison guards accompanying patients
9. Emissaries of regulatory agencies, auditors, etc.
10. Members of organizations that may encompass or interact with the hospital, e.g., county or city (for a municipal hospital), a for-profit or voluntary nonprofit health (managed) care company (e.g., Humana, Kaiser), a religious organization (e.g., Sisters of Charity, Roman Catholic Church), and/or a health sciences professional school (e.g., medical, nursing, psychology, dental, pharmacy school)

It is obvious that the mission and loyalties of the hospital community would be affected by the organizational structure and reporting relationship of the hospital administration. As an organization, a municipal hospital may be conflicted between its mission to serve as many of the underserved patients as possible and the mandate from the city government to cut costs or close down and the pressure from the Joint Commission on Accreditation of Health Care Organizations (JCAHO) to improve its patient care and facilities.

The physicians generally have a separate line of authority from the hospital administration with concomitant autonomy in medical decision making; that is, physicians report to physicians. There are certain exceptions in managed care organizations and government agencies such as the Veterans Administration (VA) hospitals. The nursing hierarchy, on the other hand, is generally directly responsible to the hospital administration. In the hospital hierarchy, the physicians are usually near the top, followed by RNs and allied health professionals, and at the bottom is the patient. One can often distinguish a person's status in the hierarchy by the attire: the administrators are the ones in suits and ties, the attendings are in long white coats, house staff in their respective uniforms, nurses in theirs, and dietary staff and janitors in theirs. The uniform for patients is the exposed and vulnerable hospital gown, befitting their lowly, vulnerable position. The professional hierarchy in the hospital is unbridgeable through merit promotions. A patient cannot be promoted to janitor, a janitor cannot be promoted to practical nurse, a practical nurse cannot be promoted to registered nurse, and a registered nurse cannot be promoted to physician. To get promoted to another level, one must obtain the necessary educational qualifications. The hierarchy, therefore, is rigid. A side effect of this rigid hierarchy is a tendency for segregation along professional lines. Doctors generally talk to doctors, nurses to nurses, dietitians to dietitians, except when they are dealing with patients. Therefore, the lack of cross-discipline communication can become a problem for a patient (as in vignette 1).

The lack of power patients experience in the hospital often translates into timidity in asking questions, and in an increase in anxiety and sensitivity that accentuates the patient's defense mechanisms, personality characteristics, and sometimes suspiciousness and paranoia. The psychiatric consultant can help by forming a bridge between the patient and the health care personnel (the *liaison function* of consultation-liaison psychiatry), by encouraging patients to ask questions, and by encouraging staff members to respect the patient's autonomy as much as possible.

10.4 The Sick Role and the Doctor Role

A person who is ill undergoes a change in society's role expectations. Talcott Parsons (1951) described the *sick role* as consisting of two rights and two

responsibilities: the right not to be held responsible for being sick; the right to be exempt from normal social role expectations, such as going to work or school; the responsibility to consider the state of being sick to be an undesirable state; and the responsibility to seek competent help to get well. As one is not considered to be responsible for being sick, there is the general expectation that the society has a responsibility to aid the sick. The society (or a smaller unit, such as a company or an organization) defines what the limit of role exemption (e.g., sick leave) is and what competent help means (e.g., licensing of physicians).

The sick role expectations described by Parsons obviously do not apply to a number of medical conditions, such as chronic disability and behavior-induced conditions such as lung cancer (smoking) or certain cases of HIV/AIDS (unprotected sex). The expectation that being sick is undesirable is challenged when a patient has entitlements because of the fact of being sick, as in VA and other compensation cases in which the patient's livelihood depends on being sick. Entitlements such as these often result in conflicts with physicians, who expect patients to adhere to the sick role expectation of wanting to get well. A latent dimension in such cases is a values conflict: physicians universally are imbued in the work ethic through their medical training, and cannot understand or condone patients whose livelihood depends on an unearned or arbitrarily defined entitlement. Such value conflict often results in a request for psychiatric consultation for suspicion of "psychogenic" symptom or frank malingering.

Parsons also described *societal expectations of physicians,* which include technical competence, functional specificity (confining their work to the practice of areas of medicine in which they have been trained), universalism (treating all patients who seek treatment), affective neutrality (not being overinvolved emotionally), and collectivity orientation (all in the best interests of the patient—a fiduciary relationship). Current managed care environment directly conflicts with several expectations of the classical doctor role, such as treating all patients (only treat patients belonging to the particular health plan), and in the best interest of the patient (which may conflict with the economic interest of the doctor and the organization if it involves extensive workup or expensive treatment). Such strain may be directly responsible for some psychiatric consultations (as in vignette 3).

10.5 Psychiatric Consultation and Social Systems

10.5.1 Theoretical Considerations

A number of observations have been made concerning social systems approaches in psychiatric liaison settings in which the consultant is also a participant observer of the social system of a particular unit, such as hemodialysis.

A general systems approach is usually applied by psychiatric consultants, often implicitly, when they consider the patient's biologic state, psychological state, and the social and physical milieu that might contribute to the patient's distress or comfort.

Considering the group processes of the staff of a medical unit, one might consider Bion's (1961) approach to operational groups based on his experiences at the Tavistock Clinic in London. Bion conceptualized two different aspects of a group process: the *work group* and the *basic assumption group*. The work group represents the mature, responsible, rational task-oriented aspect of the group. The basic assumption group is the unconscious aspect of the group in which it behaves as if it held certain assumptions about itself, its work, and its leader. The basic assumption group may either enhance or reduce the effectiveness of the work group. There are three commonly observed basic assumption groups: dependency, fight–flight, and pairing. The basic assumption dependency group feels helpless, needing to be led by an idealized omnipotent leader. This assumption could augment the effective functioning of a hospital unit by reifying the physician's role and decreasing physician–nurse conflict. The fight–flight group is in constant readiness to act, avoiding passivity, introspection, and reflection. It awaits only its leader's choice of action and then fulfills that choice.

The pairing group accepts the current situation that must be endured until the ideal, perfect leader arrives, who might be procreated by the pairing of two of the group members. Then, all troubles will disappear. Such unconscious belief could maintain the effectiveness of a nursing unit dealing with insufferable house staff members or attending physicians (who, the nurses hope, would rotate out) (Mohl 1980).

Another application of social systems in consultation-liaison psychiatry is A.K. Rice's model, emphasizing the open system, organizational boundaries, primary task, division of labor, and delegation of authority. An open system is one that must interact with the external environment. The consultant can diagnose the problems in the open system, and intervene at different points of the system, including the boundary management (vignette 1), the input (vignette 4), throughput, and output systems (Glazer and Astrachan 1979).

Group culture, based on Kurt Lewin's field theory, is an important consideration in understanding the social systems that produce a psychiatric consultation. Group culture consists of shared norms, beliefs, and role definitions. The consultant should be cognizant of the "mythology" of a unit, and should it be incompatible with the patient's current status (e.g., "A patient in this unit *never* dies without heroic efforts on the part of the staff"), then a transfer may be in the best interest of the patient (Karasu and Hertzman 1974). Consultation-liaison psychiatry can also be conceptualized as a commodity in a marketplace (Guggenheim 1978). Guggenheim conceptualizes the liaison psychiatrist as an "ambassador" and "salesman," with the consultation being the product. The consultee is the consumer of this product. As with any other product, effective merchandising and marketing are essential for success. Guggenheim likens the initial negotiation with the primary physician to the research and development phase of production. Patient evaluation and formulation of a therapeutic plan are comparable to the manufacturing phase, and the implementation of the plan and evaluation of outcome are comparable to the marketing phase. The goals are to gain acceptance of the product (implementation of the treatment plan) and to stimulate repurchase (further request for consultation on other patients). When one considers psychiatric consultation as merchandise in a marketplace, such issues as advertising and packaging, usually not in the forefront of the consultation psychiatrist, require careful attention (Mohl 1981).

10.5.2 Practical Considerations

An understanding of the social context in which a psychiatric consultation occurs is critical in the successful implementation of the consultation process. The consultant functions in various roles, as a physician, an educator, and a link with other physicians, professionals, and systems (e.g., health care systems, family, work, law enforcement, courts, social agencies). The consultant also serves an administrative function in clearing for discharge or transfer a patient who attempted suicide or declaring a patient to be competent/incompetent to consent to a procedure. The consultant may also be a link, if only in recommending them, to such community resources as psychiatric treatment facilities, halfway houses, board and care homes, and homeless shelters.

The consultant begins the process of systems intervention through the *operational group* described by Meyer and Mendelson (1961), consisting of the doctor, nursing staff, social worker, and patient's family. Based on the assessment of the situation by the consultation, the consultant then plans intervention strategies in the biologic, psychological, and social dimensions of the patient. For the social dimension, the consultant should select the most useful strategy of intervention, considering the various theoretical models described.

10.6 Ethical and Legal Issues in Consultation Psychiatry

The consultant often encounters questions concerning medical ethics and legal issues in the course of psychiatric consultation. Such issues include the patient's capacity to consent to or refuse procedures, the patient's capacity to sign out against medical advice, advance directive

issues, requests for assisted suicide, as well as requests for involuntary psychiatric hospitalization from the medical staff or family.

10.6.1 Medical Ethics and Bioethics

The foundations of medical ethics may be traced to the Hippocratic Oath of antiquity. The first code of medical ethics, *Formula Comitis Archiatrorum*, was published in the fifth century, during the reign of the Ostrogothic king Theodoric the Great. Thomas Percival, an English physician and author, published the first modern code of medical ethics, which was expanded in 1803, in which he coined the terms, medical ethics and medical jurisprudence (MacDouball and Langley 2013).

In 1847, the American Medical Association adopted its first code of ethics, based in large part upon Percival's code of ethics.

In the twentieth century, following the revelation of Nazi atrocities with "medical research" performed by physicians during the Nuremberg war crimes trials, the presiding judges created the Nuremberg Code to define international standards for ethical use of human subjects. Concerned physicians founded the World Medical Association, whose "Declaration of Geneva" included clauses that stated: "I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient" (World Medical Association 1949)

Since 1960s and 1970s, technological developments in medicine and biological sciences resulted in an explosion of ethical issues and dilemmas such as in organ transplantation, hemodialysis, cloning, recombinant DNA, gene therapy, electronic medical records, etc. The term, bioethics, is generally used to address the greatly expanded field of human inquiry concerning ethics and biological sciences (Crowley 2008).

10.6.2 Values in Medical Ethics

Beauchamp and Childress proposed four principles in medical ethics in their textbook, *Principles of Medical Ethics* (2001). They are

1. Respect for autonomy—the right to refuse or choose their treatment. (*Voluntas aegroti suprema lex*.)
2. Beneficence—a clinician should act in the best interest of the patient. (*Salus aegroti suprema lex*.)
3. Non-maleficence—"first, do no harm" (*primum non nocere*).
4. Justice—in the distribution of scarce health resources, and in the decision of who gets what treatment (fairness and equality).

In addition, the following values are generally accepted in medical ethics:

5. Respect for persons—the patient (and the person treating the patient) have the right to be treated with dignity.
6. Truthfulness and honesty—the concept of informed consent in view of the historical events of such as the Nuremberg trials on medical experimentation and Tuskegee syphilis experiment (The Dark History of Medical Experimentation from the Nazis to Tuskegee to Puerto Rico http://www.democracynow.org/2010/10/5/the_dark_history_of_medical_experimentation)

10.6.3 Issues on Autonomy, Informed Consent, Advance Directive, Competency, and Capacity

The principle of *autonomy* is rooted in the belief that individuals have the ability to make informed decisions about personal matters. Autonomy in the medical setting has become more important as social values have shifted from "paternalistic medicine" where the medical professionals' views were paramount to defining medical quality in terms of outcomes that are important to the patient. Respect for autonomy is the basis for *informed consent* and *advance directives*. In general, autonomy is an indicator of good health as the ability to exercise autonomy is often compromised in serious illness. Consultant psychiatrists are often asked to evaluate a seriously ill patient's competency and/or capacity to make life and death decisions. *Competency* is a legal term, and any adult is

considered legally competent unless a Court pronounces the person incompetent. Thus, the consultant psychiatrist *does not* determine competency. The Consultant can, however, render an opinion concerning a patient's *capacity* to make specific decisions. When a patient is seriously mentally ill to the extent that they are unable to live independently or make decisions concerning their treatment, or when a patient has advanced dementia and thus lacks basic decision making capacity, the psychiatrist may petition the court to declare the patient *incompetent*, and assign a conservator for the patient. Such a conservator may be for limited decision making, such as financial affairs, or may be for the person. Psychiatrists may also be required to make decisions in depriving patient's autonomy through emergency holds, involuntary hospitalizations, and involuntary treatments.

Beneficence, considering patient's interests first, is a core value in medicine. It may, however, be subject to modification when a particular patient's interest (such as a scarce and expensive treatment) conflicts with justice that posits an equitable distribution of resources to patients in need (which may be codified by law, institutional policy, or insurance, such as non-reimbursement of a life-saving transplantation surgery).

Non-maleficence is also a core value in medicine, but many medical treatments and drugs have both beneficial effects as well as harmful side effects. An example of this is *double effect*, in which a drug (or treatment) such as a powerful narcotic analgesic may alleviate terminal cancer pain in adequate doses (beneficence), but it may simultaneously cause respiratory arrest and death (contrary to non-maleficence).

Autonomy, beneficence, non-maleficence, and justice may in certain situations conflict with one or more of the other values in difficult ethical decisions. Involuntary hold, hospitalization, and the double effect have already been mentioned. In addition, end-of-life care, euthanasia, assisted suicide, in vitro fertilization, abortion, paid organ transplantation, genetic testing are only some of the known areas of ethical controversy.

10.6.4 Issues Relating to Consenting to or to Refuse Treatment, or Placement, or to Sign Out Against Medical Advice

When these issues arise, the consultant should consider the following points:

1. Often, ethical and legal issues arise because of a lack of communication/understanding between the patient and the medical staff (as in vignettes 1 and 4). The consultant can be a catalyst in opening avenues of communication and understanding. The patient's significant other, family, or a friend may be able to persuade the patient to follow medical recommendations.
2. When a patient has diminished mental capacity, always try to obtain the consent of the next of kin. As a hospital lawyer remarked, "Think of who might sue you if something goes wrong, and have that person sign the consent form."
3. When a capacity evaluation is requested, the first question should be "Capacity to do what?" The capacity to consent to a medically indicated procedure should have a lower threshold than that for refusing a potentially life-saving procedure. In general, the following questions should be asked for capacity/competence evaluation concerning informed consent:
   (a) What information was given to the patient, and how much information has the patient retained?
   (b) What is the patient's understanding of the nature of the illness?
   (c) What is the patient's understanding of the risks and benefits of the proposed treatment or treatment alternatives?
   (d) What are the possible consequences of treatment refusal?
4. The consultant does not determine *competence*. A patient is presumed to be competent unless declared otherwise by a judge. A consultant can, however, render a professional opinion concerning whether the patient has the capacity to make the decision.

5. The ethics committee of the institution is usually available for difficult cases, and the consultant should recommend referral to it when indicated. The ethics committee can often untangle ethical dilemmas by bringing the patient, family, and hospital administration together. It can also "bless" a medically indicated course of action.
6. The consultant should have an open line of communication with the institution's legal counsel and risk management and consult them as indicated.

10.6.4.1 Capacity to Live Independently

Adults are presumed to be capable of living independently unless declared incompetent by a court. Generally, patients who show moderate to severe dementia may be incapable of living independently unless help is provided. Such help may be found in families, relatives, and friends as well as assisted living facilities without the patient being declared incompetent. Some patients may become temporarily and repeatedly delirious due to poorly controlled chronic conditions such as diabetes mellitus, and may require hospitalization for the acute metabolic crisis. Once the delirium clears, however, the patients may exhibit no or minimal dementia. It may be in such patients' interest to be placed in a supervised facility, but repeated episodes of delirium per se is not sufficient reason to declare a person permanently incompetent. For such patients, the consulting psychiatrist may render the opinion that the patient lacks the capacity to leave the hospital or refuse treatment while delirious, and recommend obtaining consent from next of kin temporarily. Even relatively brief periods of independent living may provide a superior quality of life to nursing home placement.

10.6.4.2 Testamentary Capacity

The criteria for the testamentary capacity, that is, the capacity to draw up a will, require that individuals are rational and cognizant at the time they draw up the will, and consist of the individuals' understanding or being aware of the following:

1. The nature of the act, i.e., a will is being written
2. The nature and extent of their estate or property
3. Who would inherit the property if no will has been drawn, i.e., who might reasonably have a claim to the property
4. To whom and in what manner they are distributing the estate

10.6.4.3 Involuntary Hold, Hospitalization, and Treatment

Most states allow an involuntary hold of a person for psychiatric reasons, usually up to 72 h, usually for being a danger to self or a danger to others, or for grave disability. Depending on the jurisdiction, such emergency certificate may be executed by one or more psychiatrists, physicians, psychiatric clinicians, emergency medical personnel, etc.

Some states allow patients in general hospitals to be held involuntarily on an emergency certificate for psychiatric treatment. Danger to self or others generally means clear and imminent danger, and grave disability is confined to being unable to provide basic food and shelter. Psychotic symptoms per se, such as hallucinations or delusions, are not sufficient grounds for emergency certification.

In many states, psychiatric patients may be given medications involuntarily in emergencies and under certain non-emergency circumstances. Often a judicial process such as a court hearing is required for such involuntary use of psychotropic drugs.

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Cultural Aspects of Consultation-Liaison Psychiatry

11

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Culture influences thoughts, emotions, and behaviors in individuals, groups, and communities, and thus it can have a significant impact on illness behavior and the practice of health care. Culture can influence disease through a variety of mediating factors such as diet, smoking, use of alcohol and other drugs, activity levels, and compliance with medical management. Increasingly culturally competent medical practice is the goal for psychiatrists consulting to patients of diverse ethnic or cultural backgrounds (Bigby 2003; Tseng and Streltzer 2008), The consultation-liaison psychiatrist should not only be aware of cultural aspects of the assessment of the patient but also of the consultation process itself. This chapter elaborates broadly on cultural aspects of consultation-liaison service, including: the process of referral; the nature of the clinical problems; the interview; and clinical management and liaison work.

11.1 Obtaining a Psychiatric Consultation: The Influence of Culture

Associated with the increase of medical knowledge in contemporary society, patients and families have become more familiar and comfortable with the work of psychiatry. However, perceptions by people of different cultural backgrounds vary about psychiatrists and their patients. In some cultures, the terms like "brain doctor" or "psychological doctor" are used to avoid negative connotations of "psychiatrist." This reflects culturally stimulated stigma.

11.1.1 The physician's Referral for "Psychiatric Consultation"

Before performing the consultation, it is desirable to know from the referring physician why psychiatric consultation is sought, how the referral has been explained to the patient, and how the patient reacted to the idea of psychiatric consultation.

For patients or families who have misconceptions about psychiatry, and equate psychiatric problems with psychosis or insanity, the primary physician's explanation about the need for psychiatric consultation is critical. If not done carefully, the patient might react negatively, interpreting that the physician was dismissing him or her as a "crazy" person, and then failing to cooperate with the consulting psychiatrist.

11.1.2 The consultant's Introduction to the Patient and Family

Ordinarily, the consultant will introduce himself or herself as a consulting psychiatrist, or simply a psychiatrist, or doctor, depending on the situation. The interaction and relationship that is going to develop with the patient is more important than the particular form of introduction. A relaxed, confident manner is far more likely to initiate a therapeutic alliance than a timid, apologetic tone, in which the patient may feel that he or she is being asked to put the consultant at ease.

11.2 Culture Influences the Exploration of Clinical Problems

Factors that shape the process of exploration of clinical problems include such things as the personality of the clinician, professional orientation and experiences, and the medical culture within which the service is provided. In addition, the cultural backgrounds of the patient and the physician are going to interact during the process of the clinical exploration and assessment.

11.2.1 The Dynamic Nature of the Patient's Presentation of Complaints

The presentation of complaints by the patient and the assessment of problems by the doctor occur as a process that is subject to various factors (Tseng 2001, pp. 446–449). On the patient's side, it starts with the experience of problems or distress, which is subject to the patient's personality,

personal background, and environmental context. The nature of the stress encountered is subject to the patient's perception of the stress and coping style. Finally, the presentation of the problems by the patient to others depends on additional factors including the patient's conception and understanding of the problems, motivation and expectations, and the patient's orientation about the care system and the physician, psychiatrist or other medical staff. The patient's presentation will then influence how the clinician interacts with the patient while making an assessment.

As for the clinician's side, the process of assessment and diagnosis will be influenced by the clinician's sensitivity, perception of a morbid condition, familiarity with the problems, and professional definition of pathology. Furthermore, the clinician is subject to the influence of professional training, choice of theoretical background, classification system utilized, and the medical culture within which he or she practices, in addition to clinician's personality and personal experience. In another words, clinical assessment is a dynamic process subject to impact of various factors, including social and cultural factors of both the patient and the clinician.

11.2.2 Understanding the Potential Gap Between "Disease" and "Illness"

The consultation-liaison psychiatrist needs to understand the potential conceptual gap between "illness" and "disease," a distinction related to professional and popular ideas of sickness (Eisenberg 1977).

The term "disease" refers to the pathological or malfunctioning condition that is diagnosed by a clinician. It is the physician's conceptualization of the patient's problem, which derives from the paradigm of disease in which the physician (including psychiatrists) was trained. For example, a biomedically oriented psychiatrist is trained to diagnose "mental disease," a pathological condition that can be grasped and comprehended from a medical point of view, providing an objective and professional perspective on how the sickness may occur, how it is manifested, how it progresses, and how it ends.

In contrast, the term "illness" refers to the sickness that is experienced and perceived by the patient and his/her family. It is patient's subjective perception, experience, and interpretation of his/her suffering. Although the terms "disease" and "illness" are linguistically almost synonymous, they are purposely used differently to refer to two separate conditions. It is intended to illustrate that "disease" as perceived by the physicians healer may or may not be similar to "illness" as perceived and experienced by the person in suffering. This artificial distinction is useful from a cultural perspective, because it illustrates a potential gap between the healer (physician) and the help-seeker (patient) in viewing the problems. Although the biomedically oriented physician tends to assume that "disease" is a universal and medical entity, from a medical anthropological point of view, all clinicians' diagnoses, as well as patients' illness experiences, are cognitive constructions based on cultural schema.

The potential gap between disease and illness is an area that deserves the clinician's attention in order to make the clinical assessment meaningful and useful, particularly in a cross-cultural situation.

11.2.2.1 The Cross-Cultural Consultation

11.2.2.1.1 Vignette

A Caucasian-American psychiatric consultant was called to consult on a 58 year-old, second generation, Japanese-American man, suffering from terminal stomach cancer. The consultant introduced himself, but before he could explain why he was consulting, the patient spontaneously reported that he had gone to Japan and received vials of a special injectable medicine to treat his cancer. He wondered if the consultant knew of this treatment and could help him take the formula correctly. The consultant expressed interest, but responded that he had no knowledge of such treatment. The patient was enthusiastic about this medicine and seemed to be in denial of his terminal illness (indeed, he died 3 weeks later). His wife was present during the session. At the end,

she asked to talk to the psychiatric consultant separately out of the room. She complained that her husband was driving her crazy and was also not relating on any meaningful level with their only child, a 19-year-old daughter, who felt quite alienated from him. The consultant assured her that he would be back to talk to her husband further. The next day the consultant met with the patient alone. The consultant focused the conversation on the family, and the patient stopped talking about his miracle cure. The patient acknowledged that his first priority was the well-being of his wife and daughter. It was for this reason that he was obsessed with a cure. He needed to regain his health, so he could continue to be the provider for his family. He was not good at expressing himself in words, and did not know how to relate to his family, other than by being a good provider. He was unable to communicate with his daughter, and it bothered him a lot.

The consultant helped him articulate his love for his wife and daughter, and then arranged a meeting so that he might have the opportunity to say what had always been unsaid, and to leave them with positive memories of him. The consultant agreed to be at the meeting to facilitate the discussion, which alleviated somewhat the patient's anxiety about such a conversation. The meeting began with tension, but soon the family members cried and hugged each other, and they talked at length. The positive feelings and open communication continued the next few days until the patient became too ill to talk. The family grieved without ambivalence when he died.

Denial is often useful in medical illness, and in terminal disease. It is compatible with some cultures including Japanese, and tends to be fostered by the family and the doctors. In this case, however, there was much unfinished business within the family. For the dying process to be successful, the patient needed to feel that he was leaving the family with good memories of him, a positive legacy. The family needed to resolve their anger and disappointment with the patient.

This case has been described in great detail as an example of a psychotherapeutic intervention by a consultation-liaison psychiatrist (Streltzer 2001). Cultural issues were involved at several levels. The alternative treatment of the Japanese cure turned out to be a superficial issue covering more meaningful concerns. The patient was the provider but not the manager of the family, a traditional role for a second-generation Japanese man. The wife had acculturated more to the host culture, and was more "liberated" in philosophy, but not to the point that she could directly confront her husband. The "cultural gap" between the patient and the consulting psychiatrist allowed the psychiatrist to serve in effect as a "cultural broker" to resolve the conflict.

11.2.2.2 Culture-Related Mind–Body Issues

A cultural perspective is particularly helpful in understanding the clinical ramifications of beliefs about the mind–body relationship. Often unaware of the philosophical implications, Western physicians commonly view the issue in dualistic terms, body and mind conceptualized as separate, dichotomized things. Closely associated with this epistemological view is the notion that it is more mature or superior to express psychological problems through psychological complaints rather than somatic complaints. Eastern medical philosophies do not necessarily hold the same view. By viewing body and mind as integrated parts of a whole being, they do not distinguish distinctly between them, and do not try to view psychological or somatic manifestations in a hierarchical way. For many cultures, people learn how to express their emotions through language pertaining to the body.

11.2.2.3 The patient's History of Self-Management: Utilization of Indigenous and/or Traditional Remedies

The consultation-liaison psychiatrist may want to explore the patient's and family's folk concept of sickness and history of possible utilization of indigenous and/or traditional remedies. Patients from both Eastern and Western cultures, developed modern societies and undeveloped traditional societies, use traditional remedies to try to heal their medical condition. They often do not inform their physician about their use of

traditional remedies, because they may believe that it is a separate matter. It may not be so separate, however, as in the case of drug interactions between modern and traditional medicine, for example. They may hesitate to reveal that they are using indigenous healing methods, concerned that the modern physician will look down upon their behavior. The consultation-liaison psychiatrist needs to gently ask if traditional and modern treatments are being utilized simultaneously by the patient.

11.3 The Interview Process

In order to carry out culture-relevant and competent clinical assessment, there are several issues that deserve attention. It starts with how to maintaining culture-appropriate physician–patient relationship.

11.3.1 Culturally Appropriate Physician–Patient Relationship

Most consultations are not initiated by the patient, and, therefore, rapidly building rapport is a special skill extremely desirable for the consultation-liaison psychiatrist. The relationship is itself a therapeutic tool and the outcome of the consultation may vary significantly depending on the quality of this relationship. This is particularly true with patients of different cultural backgrounds from the consultation-liaison psychiatrist.

An important perspective can be seen by examining contemporary American culture. In the medical setting, the predominant form of physician–patient relationship is egalitarian, based on an implied contractual agreement between the two that is influenced heavily by an ideological emphasis on individualism, autonomy, and consumerism. In contrast, in many traditional Asian cultures, there is more emphasis on an ideal form of hierarchical relationship. The physician is seen as an authority figure who is endowed with knowledge and experience. An ideal doctor should have great virtue and be concerned, caring, and conscientiously responsible for the patient's welfare. In return, the patient must show respect and deference for the physician's authority and suggestions. This respect and deference may inhibit the patient from asking questions and discussing choices and alternatives.

The psychiatric consultant has the task of rapidly developing a working alliance with a patient who usually did not request the doctor's services (see Chapter on Interviewing). This task is all the more difficult if a cultural gap exists between them. Bridging this gap may become critical to gaining rapport, making a correct assessment, and engaging in therapeutic interventions. One should not assume that having an ethnic or cultural mismatch with the patient is a disadvantage. A patient may feel less likely to lose face to an outsider, who may be perceived as less judgmental and more accepting. The doctor may also plead ignorance of the patient's background, expressing an interest in learning about it. This may promote a connection with the patient (Tseng and Streltzer 2001).

When cultural issues are suspected at all, the patient should be encouraged to explain his or her culture, in essence becoming the cultural guide to help the doctor put the issue into proper cultural perspective. The objective is to demonstrate to the patient that one's concerns are synchronous with the patient's interests. This increases the chances of developing a working relationship quickly.

Such communication works best when there is a shared language. If there is not, interpreters are often required, and cultural differences are more difficult to overcome.

11.3.2 Culturally Appropriate History-Taking

The interview is the major aspect of psychiatrist-patient interaction. How the patient presents complaints and informs the consultation-liaison psychiatrist of his or her problems and how the psychiatrist, reciprocally, listens, asks questions, and provides relevant explanations to the patient are key areas of communication that closely relate to the achievement of meaningful and effective clinical service.

From a cultural point of view, the clinician should judge to what extent the patient is familiar with the psychiatric interview, and provide explanations if necessary for those who feel unfamiliar with this type of communication. Whenever appropriate, the interviewer should ask the patient whether he/she identifies with his/her ethnic or parental culture. If the patient does, it would be a good idea to tell the patient to let the interviewer know if some of the questions or discussions touch on culturally sensitive areas. The interviewer should then use an active style to obtain basic information needed for assessment of "disease," but make sure that the patient is given the opportunity to communicate concerns and problems from the perspective of "illness." The ability to skillfully intertwine these two interview styles is an indication of competence from a clinical as well as a cultural perspective.

Although it is desirable for a patient to communicate freely about his or her personal background, illness history, and other related information to the consultation-liaison psychiatrist, this does not always happen in clinical situations. The patient's ability to describe things and willingness to communicate are often influenced by clinical condition, motivation, and understanding of the purpose of doing so. In addition, there is a cultural impact on the process of problem communication.

Emotional problems and personal feelings are generally considered highly private matters, not to be revealed to strangers. In many cultures, doctors are exempt from this prohibition, but there is variation. In some cultures, talking about one's inner feelings is almost as taboo as parading nude in public. Family conflicts are often regarded as "inside" problems that should not be revealed, even to a doctor.

11.3.3 Culturally Relevant Mental Status Examination

As a part of the initial diagnostic interview, the consultation-liaison psychiatrist will often perform a formal mental status examination. The contemporary method of mental status examination taught to the medical students or psychiatric residents is derived from clinical experience with Western patients, mostly with American patients. However, it may not suitable for patients of other cultures, and may need to be modified (Tseng 2003, pp. 231–232).

For example, asking "Do you hear any voices?" may not be understood by the patient as inquiring into the presence of auditory hallucinations. Instead, he/she may answer that his/her hearing ability is intact. This caution is needed for all patients, particularly those who are unfamiliar with psychiatric terms and concepts, and especially those whose cultural backgrounds include few experiences with psychiatric jargon. "How do you feel?" "Are you depressed?" are other examples of questions that sound simple in daily English, but can be very confusing from the language and conceptual perspectives of those who use language without referring to "feeling" or states of "depression." Questions such as "Do you feel tired? Do you have the energy to do daily work? How is your appetite for eating? Do you have interest in your daily activities?" may be more suitable to ask.

As a part of the mental status examination, clinicians often ask questions such as "Who is the President of the USA?" to examine the patient's level of general knowledge. This is a proper question to ask if the patient is a citizen of the USA with adequate contact with the social environment through news media. However, failure to answer such a question means little when it is addressed to a foreigner or someone who hardly ever has access to social media.

When communication is difficult, as is more frequently the case when there are cultural differences, a clinician may wonder if a thought disorder is present. A psychiatrist may choose to ask for proverb interpretations to test abstracting ability. Proverbs, however, are a cultural product and their interpretations are subject to cultural influence. The commonly used proverbs, "A rolling stone gathers no moss," or "The grass is greener on the other side of the fence," for example have their roots in British language and culture, and are foreign to the point of meaninglessness to many non-Westerners.

Asians and others may use their own proverbs to express certain issues that may or may not be familiar to the Westerners. For example, a Japanese proverb is "Even *kappa* (a legendary animal good at swimming) would drown in the river," a Chinese one is "Monkeys will fall from trees." Interestingly, a German proverb is "The best swimmer drowns first." These proverbs have the same basic meaning, yet are expressed in different ways. However, some proverbs are culturally unique. For instance, a Korean proverb says: "After 3 years, even a dog in school will learn how to bark poems" implying the virtues of persistence and diligence. A Japanese proverb says: "Fortune is contained in the leftover (food)," suggesting that a person should not compete with others. These proverbs may be entirely unfamiliar to other cultures.

A useful technique to determine if a proverb is culturally appropriate is to ask the patient if he or she has ever heard that proverb or old saying. If the patient has heard of it, but still fails to abstract it, the information is potentially useful. Somewhat culturally universal proverbs include, "Don't judge a book by its cover," and, "Don't count your chickens before they hatch."

11.3.4 Use of Interpreters

Problems of communication between consultation-liaison psychiatrist and patient are highlighted when the consultation-liaison psychiatrist and the patient do not share the same language and have to rely on the assistance of interpreters to communicate. Who serves as the interpreter, whether a close family member, a friend, a member of the same ethnic group, or a trained interpreter with mental health knowledge and experience, will affect significantly the process and quality of translation and interpretation. Proper translation that is relevant and meaningful for clinical purposes is difficult to achieve (Tseng 2003, pp. 231).

Selecting the proper interpreter and utilizing the interpreter to effectively communicate with the patient during a psychiatric consultation is a matter of clinical skill and art. Ideally, an interpreter trained to work in medical or mental health settings is employed. There are several different ways to use an interpreter, namely: word-for-word translation is needed for areas that are delicate and significant; summary translation for areas that require abstract interpretation; and meaning interpretation for areas that need elaboration and explanation in addition to translation. By coaching the interpreter in these different styles of interpretation, the process will be more efficient and useful.

In a consultation setting, sometimes a family member is visiting the patient and may be capable of interpreting. There are pros and cons when a family member is the translator. The bilingual relative will have been acculturated to a greater or lesser extent and may be able to provide insight into the cultural factors influencing the patient's behavior, motivations, and expectations. On the other hand, if the psychiatric assessment involves complicated personal emotional issues or delicate interpersonal or family matters, the family member may perform one of the common translation errors: deletion or omission of information, distortion of meaning, exaggeration or adding of information. The consultation-liaison psychiatrist should be sensitive to the possibility of bias affecting the translation, as well as a reluctance on the part of the patient to be forthright because of the lack of confidentiality or because of an anticipated reaction from the relative.

Sometimes, a member of the hospital staff is available as a translator, such as a nurse, or nurse's aide. If this person is medically knowledgeable, and experienced as an interpreter this may work out very well. This is not always the case, however, and even if the person is not a relative, he or she may be a member of the patient's same community. The patient may not reveal a reluctance to speak in front of this person, or the cultural expectations of this interpreter may distort the translation.

In general, the interpreter needs orientation, and perhaps training, for the work that is to be done.

11.4 Culture and Consultation-Liaison Psychiatry

11.4.1 Respecting Culturally Suitable Privacy and Confidentiality

The concept of privacy and confidentiality varies greatly among people of different cultural backgrounds. For cultures that emphasize the importance of individuality, as exemplified by the USA, medical practice tends to respect the privacy of individual patients as much as possible. Physicians have the professional and ethical duty to keep medical information confidential, not revealing it to others, even the patient's parents, spouse, or other family members, without permission from the patient. In contrast to this, for cultures that value family and interdependence more than individual autonomy, parents may demand that physicians inform them about the medical condition or problems of their adult children. Similarly, a spouse may expect medical information to be shared about their marital partner. Protecting individual privacy and confidentiality, but at the same time, not defy the cultural expectation of sharing information within the family, or even the relatives or friends, is a challenge for the consultation-liaison psychiatrist.

11.4.2 Breaking the News: Informing the Patient and Family of the Diagnosis

Another important and delicate issue is how to inform the patient and family of the medical diagnosis. In Western Europe or North America, following contemporary medical practice, a physician often openly and frankly informs the patient of the diagnosis of the disorder from which the patient is suffering, even when the news is ominous and expected to be frightening to the patient. Otherwise, the physician would fear a malpractice suit.

However, in contrast, in many societies, such as Japan and other East Asian societies, it is normal for a physician to conceal the actual medical diagnosis from the patient, particularly of a serious or fatal illness, to protect the "vulnerable" patient. (This was a practice also common in the USA prior to the 1960s) The actual diagnosis is told only to the family. If the physician were to reveal a potentially fatal diagnosis to the patient without the family's consent, he or she may be subject to resentment from the family. This is a complex matter, in which the physician needs to act according to proper medical ethics as well as the culture of the society.

11.4.3 Family Involvement

Involving the family in the patient's medical care, including examination, assessment, and even treatment, will be particularly challenging to clinicians in Western societies. The consultation-liaison psychiatrist sometimes has referrals generated primarily because the primary physician is uncomfortable dealing with family members who are attempting to be actively involved in a patient's care. It is almost impossible to exclude the family in cultures that are very family-oriented (rather than individually oriented), such as is common in Eastern societies. Based on clinical experience, we know that involvement of the family in an interview sessions has both advantages and disadvantages.

Among the advantages, in addition to relieving the family's anxiety, is the enabling of the clinician to obtain needed collateral information to assist in the process of assessment, and to provide an opportunity for the interviewer to observe how the patient and family interact. Working with the family increases their ability to support the patient's recovery.

Disadvantages are that family involvement may discourage the patient from expressing personal concerns or communicating about family conflicts. This is also true in reverse, with family members hesitant to express concerns about the patient in front of the patient. Therefore, it is sometimes best to approach the patient and family separately at some time during the interview process.

From a cultural point of view, however, family can serve not only as a resource for collateral

information but also as a base from which to check cultural reality. Unless major family pathology is present, the consultation-liaison psychiatrist can obtain from the family members a culturally objective indication as to what extent the thoughts and behaviors manifested by the patient are normal, unusual, or deviating from the sociocultural norm. The interviewer also can learn culturally relevant coping techniques available to the patient to resolve problems. Generally speaking, family involvement is helpful to the process of liaison work. This is particularly so for patients with a strong family-oriented background.

11.4.4 Ethnic Consideration for Recommendation of Medication

Modern Western medicine is based on a technology that prepares drugs in pure abstract forms to perform specific pharmacological functions. Modern physicians usually prescribe a single medication for a specific purpose, and for multiple problems they may prescribe multiple medications. Usually the least number of medications possible is considered to be the goal. In contrast, herbal medicines used in traditional medical practice are thought to work by combining multiple remedies in their raw forms. Multiple herbs are always prescribed, as there is not too much concern over combining medications. In general, in societies where traditional medicine is still used, Western medicine is considered "strong" and useful for combating the specific etiology of a disorder, but there are usually unwelcome side effects. Traditional herbal medicine is viewed as "harmonious," with fewer side effects, and will "strengthen" the body so that it can overcome the disorder, or not get it in the first place.

Modern Western physicians make no secret about the name and nature of prescriptions, and often make it a goal to explain to the patient the drug mechanism as well as potential side effects. Traditional physicians, on the other hand, sometimes keep prescriptions "secret" and in some Asian countries, such as Japan, China, and Korea, the patient may not expect or desire the physician to give a full explanation.

Associated with this is the tendency of patients to feel that there is no need to follow the physician's orders in taking the medication. If the medicine works immediately (within a day or so), the patient will take it. If the symptoms subside, the patient may feel no obligation to continue the medication, even when directed by the physician.

Beyond psychological issues relating to prescribing and receiving medication, there are also biological issues as well. There are potential ethnic differences in the pharmacokinetics and pharmacodynamics of drugs that are used. In general, Asian patients and patients of some other ethnic/racial groups need smaller doses than textbook recommendations, which are based on studies of Caucasians.

11.4.5 Communication to the Referring Physician and Staff

The consultation-liaison psychiatrist communicates to the referring physician in several ways. For uncomplicated consults, a note in the chart may suffice, but direct communication is usually preferable. Increasingly, clinicians are becoming sensitive to cultural issues, and they are likely to be interested if the consultation-liaison psychiatrist discusses cultural issues as part of the recommendations for care.

Case example: An internist known to be rather autocratic asked a consultation-liaison psychiatrist to see his patient to determine if he needed to be committed to a mental hospital. The patient was a Russian immigrant who had been working as a radiology technician. The patient was in his final few days of intravenous antibiotics for a cellulitis. The patient, a diabetic, had been arguing with the nurses about his insulin doses. The psychiatrist discovered that the patient was a physician who had not been licensed the USA. He had always managed his diabetes without difficulty and was rather obsessional about how it should be done, and about his need to care for himself.

The consultation-liaison psychiatrist reported to the internist that the patient was not committable to a psychiatric facility.

In this case, the patient was a Russian man, brought up in a society where his status as a physician made him an authority, well respected and valued for his competence and self-confidence. In addition to personality factors, the patient's demanding behavior could be partly explained on the basis of a cultural need for self-management. This formulation allowed the consultation-liaison psychiatrist to suggest that, since the patient had never demonstrated difficulty, why not let him have more say about his insulin dosing? The internist was able to comfortably relax his control of the diabetic management by viewing this as culturally appropriate, and the rest of the hospital course passed uneventfully.

11.4.6 Some Specific Clinical Issues

The variety of clinical issues encountered by consultation-liaison psychiatrists is endless. Some of them are heavily related to culture and deserve to be mentioned.

11.4.6.1 Culturally Stigmatized Medical Diseases

Because of their poor prognoses and historically limited effectiveness of treatment, the diagnoses of certain medical diseases still carry substantial stigma, despite an improvement in medical management. Leprosy, pulmonary tuberculosis, epilepsy, and venereal disease, as well as mental disease, are some examples of diseases that are still associated with strong negative views as a result of cultural beliefs, which intensely influence patients' emotional lives as well as their illness behavior. The patient's and his or her family's medical knowledge has an impact on attitude toward various kinds of disease.

11.4.6.2 Sex-Related Medical Conditions or Issues

There are certain medical disorders that are perceived as sex-related and, in turn, subject to cultural interpretation and reaction. For example, breast cancer is one of them. The varying degrees to which female breasts have a sexual role in different cultures may influence the patient's understanding of the causes of breast cancer. Concerning attitudes toward risk factors for breast cancer, there have been two broad cultural models. The Anglo-American model emphasizes family history and age as risk factors. The Latin model associates breast trauma and "bad" behaviors (such as alcohol and illegal drug use) as risk factors for breast cancer. This reflects a moral framework within which disease is interpreted.

Pregnancy and giving birth are not only major events in the parents' lives but they also have substantial cultural significance and are impacted by cultural beliefs. For instance, when the ideas and experiences of pregnancy and childbirth of Asian and non-Asian women in east London was compared, it was revealed that, although Asian women demonstrated a strong commitment to Western maternity care, they continued to follow traditional cultural practices such as observing a special diet in pregnancy and following restrictions on certain activities in the post-partum period. Asian women tended to want their partners present at delivery and to express a greater concern with the gender of the child.

In some ethnic groups, great attention is paid to post-partum care. In traditional Chinese belief, a woman is expected to observe 1 month of confinement after giving birth. She is not allowed to go outside of her house, to take "cold" foods (such as fruits), or to bath or even wash her hair. A woman is supposed to eat a lot of "hot" foods (such as chicken cooked with sesame oil and ginger). These customs were observed in the past, perhaps to prevent post-partum infection, and are still faithfully observed by some traditional women. In Micronesia, a traditional "pregnancy taboo" requires the wife to return to her family of origin once she discovers she is pregnant. She does not return to her husband's house until her child is old enough to hold his or her breath under water or to jump across a ditch, activities that ensure a greater likelihood of survival.

Breast-feeding is a very natural way to feed a newborn baby. However, despite the widely acknowledged evidence supporting the benefits of

breast-feeding (fewer childhood infections and allergies), the prevalence of breast-feeding in Western countries remains low. This may be due to the development of baby formula or time demands on a working mom. However, the cultural notion of the female breast as a primarily sexual object places the act of breast-feeding in a controversial light and can be one of the most influential factors in a woman's decision not to breast-feed.

In many cultures, reproduction is considered one of the major functions of women, and losing the uterus is considered to be losing the power of being a woman. Many women fear a change in sexual desire after a hysterectomy, and that their husbands will not want them because they are "incomplete" women. As a result, they might refuse to have their uteruses removed, or develop anxiety and depression after a hysterectomy.

Although menopause is a biological phenomenon, the intensity of menopausal symptoms varies among ethnic or racial groups. This may be due partially to diet, with a recent study revealing that Asian women may experience fewer hot flashes because of estrogen derived from soybean products in their meals. To what extent sexual attitudes contribute to emotional adjustment or attitudes toward menopause is a subject that requires future investigation.

11.4.6.3 Culturally and Ethically Controversial Medical Practices

Many medical practices are culturally proscribed, or prescribed, and are often as a result, ethically controversial. Following are some of the examples:

Artificial abortion is the subject of an intense emotional, political, and ethical debate in many countries. In the USA, there is no foreseeable resolution to the conflict, which has involved radical acts such as the bombing of abortion clinics and the shooting of physicians who perform abortions. However, in many countries, abortion is an accepted and uncontroversial part of family planning. This is particularly true where there is societal acceptance of the concept of population control. Thus, abortion is not merely a medical choice, but also a social, cultural, and political matter.

From a medical point of view, sterilization is a simple surgical operation and a way of family planning. However, there may be a significant psychological impact depending on how the procedure is seen by the patient's culture. In some cultures, particularly those that strongly emphasize the need for many children, sterilization can be most unwelcome. In such cases, sterilization for men may even be considered nearly equal to castration, even though medically it is not.

Whether physicians are allowed to offer active assistance for patients to end their lives is a controversial subject in many societies. In Holland, euthanasia is actively practiced by physicians. In Germany, assisted suicide is a legal option, but is usually practiced outside of the medical setting. In almost all of the USA, withdrawing from or refusing treatment is the only means currently permitted by law, and then only with legal documentation from the patient or his or her family.

It is important that the consultation-liaison psychiatrist know that medical practices developed by physicians for treatment of disease may be perceived and reacted to in various ways by patients and families not only because of personality-specific factors but also because of cultural background. This is the foundation for providing a culturally competent consultation service.

11.5 Medical Culture

In addition to cultural issues associated with patients and with staff, the consultation-liaison psychiatrist should recognize the presence of a medical culture that determines the manner in which care is provided (Tirrell 2001). Effective communication between doctor and patient requires an alignment of the medical culture with the cultural perpective by which the patient views the world and puts his or her illness in context.

For example, role expectations differ for patients with acute or chronic illness (Streltzer l983). The hospitalized acutely ill medical patient is expected to be a passive recipient of care. Diet, bathroom privileges, and all activities of daily living are prescribed by the doctor and taken care

of by others. In return, the patient is relieved of personal responsibilities, such as work, household chores, childcare, even personal grooming. By this tradition, the patient does not interfere with a doctor's treatment, and the patient is content because he or she usually gets better and resumes normal activities.

With chronic illness, however, the patient is expected to become responsible for accepting and managing the illness. An example is the diabetic who monitors glucose and adjusts insulin levels. Essentially the message is, "You are responsible for your illness: become educated about it and learn how to take care of it." Sometimes, however, the physician manages the chronic patient with an acute model. The message from the physician becomes, "You are responsible for your illness and activities, but at the same time you must do exactly as I say with regard to the medical management of your illness." For some patients, these two messages are difficult to resolve, leading to conflict, misunderstandings, and noncompliance (Alexander 1976). When this occurs, a psychiatric consultation is often requested. Factors associated with the medical culture can interact with the the patient's, as well as the physician's, cultural background, and should be taken into account.

11.5.1 Vignette

A 62-year-old man, treated with maintenance hemodialysis for 2 years, who threatened to kill the head nurse of his outpatient dialysis unit. He was a Caucasian-American retired cook in the merchant marines. The head nurse had emigrated from the Philippines 15 years before. She had a distinct but understandable accident, and she had a reputation for being very efficient and competent technically.

One day, seemingly out of the blue, the patient, who rarely talked much, finished his dialysis, then walked up to the head nurse, and said that he would come after her one day, and kill her. Although the head nurse did not take the threat seriously, other staff did. The unit manager phoned the psychiatric consultant asking for advice, adding that the patient refused psychiatric consultation. The consultant stated that in this situation he needed to see the patient despite his refusal, and asked that the patient be informed that he would be coming at a designated time.

The patient anticipated the visit of the psychiatric consultant and immediately spoke of his concerns. He was certain that the nurses were tampering with his dialysis machine when he was looking the other way. Possibly, they planned to put sugar water into his machine. The nurses, on the other hand, had reported that the patient often fell asleep during his dialysis.

In this unit the patients had all learned self dialysis. The nurses only helped the patient on and off of their machines, and were present in case there were problems during dialysis. In the case of this patient, they had begun watching his machine more closely as he often fell asleep and they found that his settings were often not ideal. When he woke up, he realized he had not been monitoring the machine. He suspected that he was being drugged. He came to the conclusion that the head nurse was trying to kill him, because of her presumed prejudice against Caucasians.

The psychiatrist assured him that he would talk to the head nurse, and also to the chief physician in charge, and make sure that no harm come to the patient. Furthermore, he would monitor the situation himself. The patient then discussed his life in response to the psychiatrist's interest. Raised in foster homes, at 13 he ran away and lied about his age to join the merchant marines. He became a cook, kept to himself, and was a heavy drinker. Kidney failure forced him to retire a few years ago. He married late in life, had no children, and did not socialize.

He had learned early on, that one must take care of himself because no one will do it for you. He liked to work independently of others, which he was able to do as a cook. He feared being dependent on others for dialysis, and had learned self dialysis. He demonstrated mild cognitive deficits along with paranoia on the mental status examination. The psychiatrist thought he was mildly demented and probably making mistakes in his dialysis without realizing it.

The psychiatrist placed him on 0.5 mg of haloperidol nightly, and arranged for his transfer to a dialysis unit where the patients were not required to dialyze themselves. He explained this to the patient in terms that allowed the patient to feel in control. The patient was satisfied and caused no problems in the new unit.

In this case, the patient had a chronic illness and the medical staff wanted him to be in charge of his own care as much as possible, simply making up for his deteriorating memory whenever needed. Because of his paranoid personality style and developing dementia, however, he misinterpreted their help in projected the blame for his own failings onto them. It was now necessary to structure his medical care and expect less from him, while presenting the changes in a way compatible with his personality style.

An important area where medical culture comes into play is the interpretation of somatization. Historically, somatoform symptoms in Western culture tended to be seizures, twitches, and paralyses until the twentiethcentury, when these symptoms became less common, replaced by chronic fatigue and pain (Shorter 1997). In medical practice, the somatizing patient can cause the practitioner to pursue an exhaustive and fruitless search for underlying medical pathology. The practitioner can be confused or even angered by the patient whose complaints do not conform to the expectation that that they must be stimulated by a somatic cause. All of this is consistent with the Western conception of mind–body dualism (Tseng 2001). Eastern cultures tend to have a more holistic conception of mind and body, and somatic complaints are often thought to have communication intentions and are not resistances to psychological issues, which may readily come to light if the doctor is sensitive enough to look for them. Somatization can have multiple implications, including being a culturally coded expression of distress, and being a mechanism for patients to negotiate their status in a medical context (Kirmayer and Young 1998). Somatization can reflect aspects of the underlying societal culture, and the corresponding medical culture may be consonant with this, but it also may not be. If the medical culture seems too alien to the patient, the patient may seek some sort of alternative healing.

11.6 Culture and Pain

Culture is known to influence the experience of pain, be it acute, chronic, cancer-related, or experimental (Green et al. 2003). Perhaps the best-known cross-cultural study of chronic pain is that of Zborowski (Zborowski 1952). He compared the responses of different ethnic groups to chronic pain by observing them in the hospital. He concluded that "old Americans" tended to be stoic and uncomplaining about their pain. In contrast, Italians and Jews readily voiced their complaints. He described the Italians as being present oriented, wanting immediate relief, whereas the Jews were future oriented, not wanting the pain to be taken away by medication, in order to monitor how their condition was doing. This study provided no data, not even the numbers of patients observed, however. No mention was made of the types of pain, the duration, the medications used, or concomitant psychiatric and medical conditions. It was even stated that not all patients fit these stereotypes! More sophisticated recent studies demonstrate how difficult it is to sort out the role of ethnicity because of many confounding factors.

A study that used multiple regression to sort out the influence of different factors on the management of pain found that ethnicity was a highly statistically significant variable, but accounted for at most 6 % of the variance (Streltzer and Wade 1981). It is reasonable to conclude that culture influences pain management, but not a great deal. Nevertheless psychosocial and cultural factors are clearly important in individual cases, even if generalities are difficult to make.

Perhaps even more importantly, the prevailing medical culture greatly influences the treatment of painful conditions. For example, the relationship of low back pain to physical findings explaining the pain and the related psychosocial dysfunction varies substantially by country (Sanders et al. 1992). Some of this may be directly related to culture of the society, and

some of it may be related to the medical care system, including the presence of entitlements for disability.

11.6.1 A Culture of Chronic Pain Management

In recent years, a pain management culture has influenced American medicine and that of some European countries. It may be considered a culture because it has specific values, beliefs, and practices with regard to the use of opioids for chronic pain. It minimizes or discounts and scientific evidence that does not conform to this belief system.

This new pain management culture developed as a reaction to the undertreatment of acute pain that was prevalent during the 1960s and 1970s in the USA, which itself probably was a reaction to the epidemic of drug abuse at the time (Marks and Sachar 1973). As this undertreatment became recognized, developments led to greatly improved management of acute pain and terminal pain, utilizing such technologies as epidural and patient controlled analgesia.

Chronic pain patients were known to have very different characteristics, however, and psychological and behavioral factors were recognized as extremely important in the development and maintenance of chronic syndromes. Pain clinics that usually required detoxification from dependency producing drugs developed to care for these patients, and they reported success (Malec et al. 1981).

Then in the mid 1980s, it was suggested that patients with chronic pain could do well if maintained on opioids. Cases appeared in the literature briefly described, usually on low maintenance doses of opioids (Portenoy and Foley 1986). This ushered in a new approach to chronic pain in the 1990s, involving chronic opioids, which were used in increasingly higher doses. Problematic cases began being seen in ever greater frequency by consultation liaison psychiatrists (Streltzer 1994).

Pain medicine became a subspecialty in its own right. In the USA, this subspecialty was originally certified only by the American Board of Anesthesiology beginning in 1993, but in recognition of the complexity and frustrations in treating chronic pain patients, the subspecialty became multidisciplinary in the year 2000, with certification available in physical medicine and rehabilitation, psychiatry, and neurology, as well as anesthesiology.

A review of opinions from the medical literature, Internet discussion groups, pain societies, and patient advocacy groups in the USA reveals a firm belief that opioids are efficacious analgesics even when given chronically on a daily basis (Streltzer 2000.). This belief requires that one accept a number of other propositions to be consistent. One such belief is that tolerance does not occur in the face of pain, or at least only to a certain point, and that higher doses mean that there is more pain, not that the opioids are losing their effectiveness. If pain becomes a problem again, the solution, therefore, is to raise the dose, or switch or rotate to another opioid. There is said to be "no upper limit" to opioid dose, and consequently maintenance with ultra high doses of opioids is being increasingly seen in problem patients referred to the consultation-liaison psychiatrist, usually after a period of several years of escalating doses.

Scientific evidence is weak in support of these beliefs, however, and in fact there is much evidence contradicting them. In particular, chronic opioids result in a cascade of cellular adaptations, such that physiological responses chronic opioids are quite distinct from responses to acutely administered opioids. The chronic adaptation includes tolerance, hyperalgesia, and probably craving, all by different distinct mechanisms. Thus, chronic opioids actually enhance sensitivity to pain, let alone induce tolerance to analgesia (see pain chapter) .

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Part II

Syndromes, Disorders, and Treatment in Consultation-Liaison Psychiatry

Delirium

12

José R. Maldonado

Contents

12.1 Introduction

Delirium is one of the most common psychiatric syndromes found in the general hospital setting. Phenomenologically, delirium is an acute or subacute organic mental syndrome characterized by disturbance of consciousness, global cognitive impairment, disorientation, perceptual disturbance, deficits in attention, changes in psychomotor activity, disordered sleep–wake cycle, and fluctuation in symptom severity. Mechanistically, delirium is a neurobehavioral syndrome caused by the transient disruption of normal neuronal activity secondary to disturbances of systemic physiology.

Many terms other than delirium have been used to describe the same phenomenon, e.g., "ICU psychosis," "sundowning," "acute confusional state," "toxic confusional state," "post-anesthetic excitement," "acute postoperative psychosis," "post-cardiotomy delirium," and "toxic-metabolic encephalopathy." While there might be differences in contributing etiologies and some manifestations, all these terms represent a similar phenomenon. The author personally prefers the term *acute brain failure*, as it is compatible with multiple etiologies and settings, and it carries the implication of significant morbidity and mortality.

12.2 Diagnostic Criteria

To date, the diagnostic gold standard for delirium remains the neuropsychiatric assessment based on the Diagnostic and Statistical Manual for Mental Disorders criteria, 5th Edition (DSM-5) (APA 2013). Given the characteristic waxing and waning of this syndrome, it is imperative that a comprehensive neuropsychiatric evaluation takes into consideration all available clinical information, including interview of the family members and caregivers, nursing and medical staff, and a

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thorough review of the chart for behaviors exhibited during the preceding 24-h to the clinical examination.

The most current DSM criteria (DSM-5) (APA 2013) changes its diagnostic focus away from a "disturbance of consciousness" to a "disturbance in attention and awareness"—criterion A. Criterion B established that delirium is an acute or subacute onset of symptoms (from hours to days) to differentiate from more chronic disorders such as dementia. Criterion C refers to additional disturbances in cognition (e.g., deficits in memory, orientation, language, visuospatial ability, perception) not better explained by another neurocognitive disorder. New to DSM is Criterion D which stipulates that A and C "do not occur in the context of severely reduced level of arousal or coma." And finally criterion E reiterates the presence of physical evidence which can explain an organic etiology for the syndrome. Notice that the presence of psychotic symptomatology (e.g., illusions, hallucinations, delusions) is not an official part of DSM-5 criteria. The new criteria provide for categorization of delirium based in etiology; duration (i.e., acute [hours to days] vs. persistent [weeks to months]), and motoric presentation (i.e., hypoactive, hyperactive, or mixed).

12.3 Delirium Subtypes

While initially described based on behavioral and motoric characteristics (Liptzin and Levkoff 1992), factor analysis has confirmed the existence of at least two different cluster of symptoms: hyperalert/hyperactive features (e.g., agitation, hyperreactivity, aggressiveness, hallucinations, delusions); and the hypoalert/hypoactive features (e.g., decreased reactivity, motor and speech retardation, facial inexpressiveness) (Camus et al. 2000). Subsequent studies have suggested there are at least three types of delirium based on their clinical (motoric) manifestations: hyperactive, hypoactive, and mixed (Meagher et al. 2000; Meagher and Trzepacz 2000). It is important to notice that the motoric subtypes of delirium may vary, depending on the population under study. Studies in the general adult in-patient medical population suggested that the most common was the mixed type (46 %), followed by the hyperactive (30 %) and the hypoactive (24 %) (Meagher et al. 1996). But among the critically ill populations the hypoactive type was the most common among with 43.5 % in the medical ICU, 64 % in the surgical ICU, and 65 % among the hospitalized elderly patient (Peterson et al. 2006; Pandharipande et al. 2007; Khurana et al. 2011).

Not only is hypoactive delirium often missed or misdiagnosed (Liptzin and Levkoff 1992), but these patients usually experience longer hospital stay, higher morbidity and mortality than hyperactive and mixed types (Kiely et al. 2007). Often the classic symptoms of hypoactive delirium (e.g., unawareness of the environment, lethargy, apathy, decreased level of alertness, psychomotor retardation, decreased speech production, and episodes of unresponsiveness or staring) prompt a misdiagnosis of depression in up to 42 % of cases in which psychiatry was consulted for management of "depression" (Farrell and Ganzini 1995, Maldonado et al. 2003a, b; Kishi et al. 2007).

Studies have demonstrated that delirium is misdiagnosed, detected late, or missed altogether in >50 % of cases across the various healthcare settings (Kean and Ryan 2008). Despite its high prevalence in critical ill patients delirium remains unrecognized in as many as 66–84 % of patients experiencing this complication (Francis et al. 1990; Inouye 1994; Rolfson et al. 1999, Ely et al. 2001a, b; Inouye et al. 2001; Pisani et al. 2003a, b; Pandharipande et al. 2007; Steis and Fick 2008; Swigart et al. 2008; Steis et al. 2012). There are a series of factors that contribute to delirium's poor detection rate. These can be divided into three large groups: Patient factors, Clinician/Practitioner factors, and System factors (Table 12.1)

There are a number of clinically available instruments have been developed to screen for the presence of delirium (screening tools, e.g., Confusion Assessment Method [CAM], Confusion Assessment Method for the ICU [CAM-ICU] both based on DSM-III-R criteria), while others allow for a measure of the progression of delirium (severity scales, e.g., Delirium Rating Scale-revised-1998 [DRS-R-98]; Memorial Delirium Assessment Scale [MDAS]; Intensive Care

Table 12.1 Factors contributing to the poor detection rate of delirium

Patient Factors	Clinician/Practitioner Factors	Systems Factors
• Older subjects • Patients experiencing comorbid dementia • Fluctuating course of presentation • Presence of hypoactive features	• Lack of knowledge and training • Lack of confidence • Lack of suspicion • Lack of time of the clinical staff • Expectation that altered mental status or delirium are a "normal occurrence" in certain medical settings, such as the ICU	• Lack of consensus over the optimal assessment of delirium • Location of care [worse in surgical rather than medical settings] • Busy clinical settings [especially low nurse to patient ration] • Inadequate application of sedation holidays in sedated-ventilated patients • The rapid transfer of patients from one unit to another which may decrease the proper documentation and diagnosis

Adapted from Maldonado JR, Delirium: Neurobiology, Characteristics and Management, in Psychiatric Care of the Medical Patient, Fogel, B., Greenberg, D. (Eds). Oxford University Press, 2014 (In Press). (Maldonado 2014)

Delirium Screening Checklist [ICDSC], all based on DSM-IV criteria). A significant advantage of diagnostic tools that measure delirium severity is that they provide clinicians a tool to measure the severity of the episode and determine whether the condition seems to be worsening or improving. Severity scales may also provide the ability to diagnose subsyndromal delirium (SSD) (i.e., patients presenting with mental status changes that do not rise to full DSM or ICD diagnostic criteria). Studies suggest that patients suffering from SSD in the general medical wards experienced longer acute care hospital and ICU stay, increased post-discharge mortality, more symptoms of delirium, lower cognitive and functional level at follow-up than patients with no SSD, and greater rate of nursing home placement or death at 6 months post-discharge; even after adjusting for illness severity, and baseline cognitive status and severity of baseline functional status (Marcantonio et al. 2002; Cole et al. 2003, Ouimet et al. 2007a, b).

Unfortunately, no tool is perfect. In fact, a recent study comparing the CAM-ICU and the ICDSC demonstrate an agreement in diagnosing delirium diagnosis between the two methods in only 42 of 162 patients (27.8 %) (Tomasi et al. 2012). Others have demonstrated that the agreement rates between CAM-ICU and ICDSC may vary between different groups of ICU patients (e.g., elective vs. emergency surgery) and seems to be affected by disease severity (Fagundes et al. 2012).

All currently available scales have been derived from and have been validated against expert psychiatric assessments using earlier versions of DSM or ICD diagnostic criteria. It is unclear as of yet, what the new DSM-5 diagnostic criteria will mean to the diagnostic accuracy of existing tools.

As of yet, there are no objective diagnostic tests for delirium. Some have advocated the use of the electroencephalogram (EEG) with its characteristic slowing of peak and average frequencies, and decreased alpha activity, but the clinical usefulness of EEG may be limited by its low specificity (given there are a number of conditions and medications that may affect the EEG) and the impracticality of conducting the test (particularly in the case of agitated and combative patients). Still, the EEG can be useful in differentiating delirium from other psychiatric and neurological conditions such as catatonic states, seizure activity (e.g., non-convulsive status), medication side effects (e.g., posterior reversible encephalopathy syndrome due to the use of calcineurin inhibitors) or the manifestations of the behavioral and psychological symptoms associated with dementia (BPSD). Others have advocated the use of a 24-hr accelerometer-based activity monitor. The continuous wavelet transform (CWT) provided by the instrument can then be used to characterize the phenotypic presentation of delirium as hyperactive, hypoactive, or mixed (Godfrey et al. 2009; Meagher 2009; Godfrey et al. 2010).

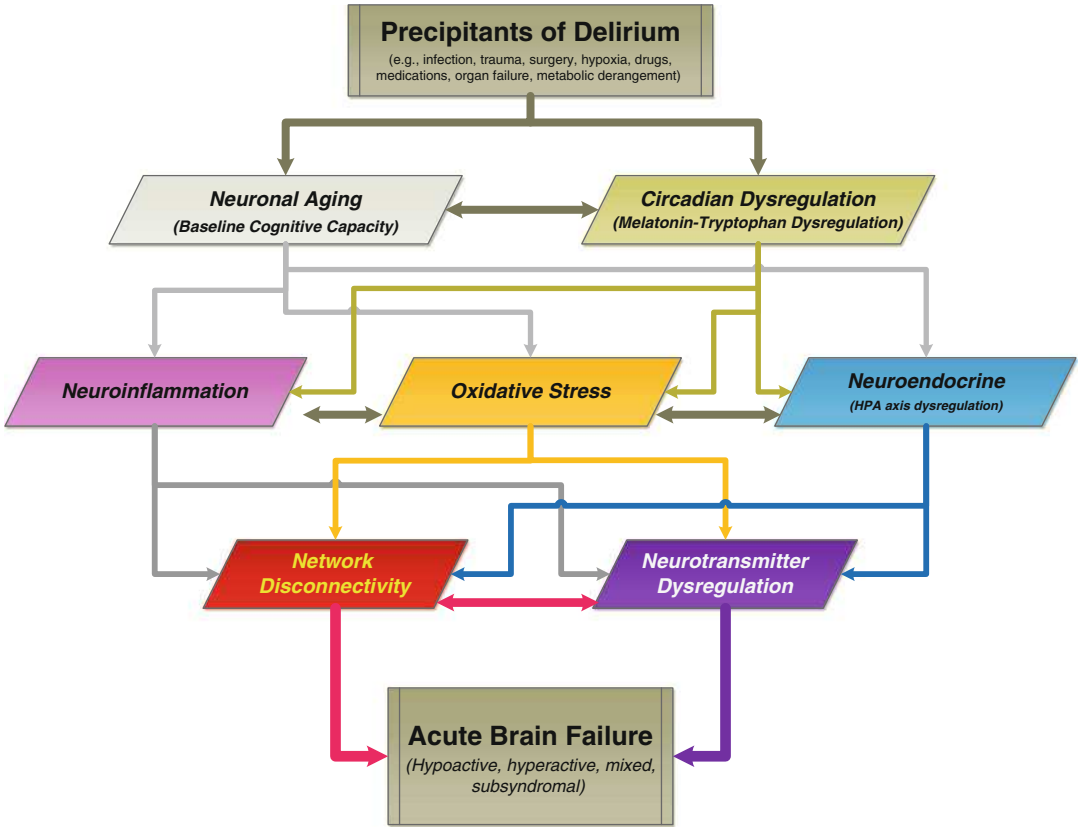


Fig. 12.1 Theories on the Development of Delirium. Schematics of the interrelationship of current theories on the pathophysiology of delirium and how they may relate to each other. Each proposed theory has focused on a specific mechanism or pathologic process (e.g., dopamine excess or acetylcholine deficiency theories), observational and experiential evidence (e.g., sleep deprivation, aging), or empirical data (e.g., specific pharmacological agents' association with postoperative delirium; intraoperative hypoxia). Most of these theories are complementary, rather than competing, with many areas of intersection and reciprocal influence. The literature suggests that many factors or mechanisms included in these theories lead to a final common outcome associated with an alteration in neurotransmitter synthesis, function, and/or availability, coupled with an acute breakdown in brain network connectivity, leading to the complex behavioral and cognitive changes observed in delirium. In the end, it is unlikely that any one of these theories is fully capable of explaining the etiology or phenomenological manifestations of delirium, but rather that their interaction lead to the biochemical derangement and, ultimately to the complex cognitive and behavioral changes characteristic of delirium. Adapted from (Maldonado 2013)

12.4 Neuropathogenesis of Delirium

By now it is rather clear that delirium is a neurobehavioral syndrome caused by the transient disruption of normal neuronal activity secondary to systemic disturbances (Engel and Romano 1959; Lipowski 1992; Brown 2000). A number of scientific theories have been proposed in an attempt to explain the processes leading to the development of delirium (Maldonado 2008a, b). Most of these theories are complementary, rather than competing (see Fig. 12.1). It is likely that none of these theories by themselves explain the phenomena of delirium, but rather that two or more of these, if not all, act together to lead to the biochemical derangement we know as delirium (see Table 12.2). A recent detailed review of the most salient theories has been published elsewhere (Maldonado 2013).

Regardless of which of these theories is correct (e.g., due to changes in oxidative metabolism,

aging, endocrine disturbances, neuroinflammation, changes in sleep–wake pattern), the literature suggests that changes in neurotransmitter concentration or receptor sensitivity are likely to create the substrate conducive to the brain dysfunction characteristic of delirium. In general, the most commonly described neurotransmitter changes associated with delirium include: excess release of norepinephrine (↑ NE), dopamine (↑ DA), and/or glutamate (↑ GLU) and increased Ca + channel activity (↑ Ca + Ch); reduced availability of acetylcholine (↓ Ach) and/or melatonin (↓ MEL); and either a decreased and increased activity in serotonin (↑↓ 5HT); histamine (↑↓ H1&2), and/or gamma-amino butyric acid (↑↓ GABA) likely depending on the etiology or motoric presentation (see Table 12.2). Similarly, it appears that an acute breakdown in brain network connectivity, and the level of inhibitory tone caused by the breakdown, may produce the various motoric phenotypes associated with delirium (e.g., hyperactive, hypoactive, mixed) (Ross 1991; Sanders 2011; Maldonado 2013).

12.5 Etiology of Delirium

Many factors may potentially contribute to the development of delirium. The author uses the mnemonic "E*nd Acute Brain Failure,*" to help recall 20 of the most common contributing factors (see Table 12.3). Several factors are discussed here; readers are referred to the author's comprehensive review of delirium risk factors for further details (Maldonado 2008a, b; Maldonado 2014) Risk factors can be grouped as *non-modifiable* and potentially *modifiable* (Table 12.4).

Recognition of the non-modifiable factors can help identify patients at high risk for delirium; attention would then turn to those patients' potentially modifiable factors. Four of the most important non-modifiable factors are older age, baseline cognitive impairment, severity of underlying medical illness, and preexisting mental disorders. *Old age* is likely a contributor due to increased number of medical comorbidities; overall frailty, decreased volume of ACh producing cells; decreased cerebral oxidative metabolism; cognitive deficits and increased risk of dementia, and age-related cerebral changes in stress-regulating neurotransmitter, intracellular signal transduction systems, and chronic neurodegeneration with an increased production of inflammatory mediators, including cytokines and acute phase proteins. *Baseline cognitive deficits* even subtle ones, have been associated with an increased the risk of developing delirium. The presence of dementia, more than double the risk for postoperative delirium. Studies have also shown that the *severity of the patient's underlying medical problems* has a significant influence in the development and progression of delirium. Finally, the presence of *pre-existing mental disorders* has been associated with an increased rate of delirium (especially bipolar disorder, major depression alcohol use, and anxiety states).

Among the potentially modifiable risk factors, which many be amenable to early intervention and/or prevention include: the use of various pharmacological agents, especially GABA-ergic and opioid agents, and medications with anticholinergic effects; prolonged and/or uninterrupted sedation; immobility; substance intoxication and withdrawal states; the use of physical restraints; water and electrolyte imbalances; nutritional deficiencies; metabolic disturbances and endocrinopathies (primarily deficiency or excess of cortisol); poor oxygenation states (e.g., hypo-perfusion, hypoxemia, anemia); environmental factors impeding adequate rest or causing disruption of the sleep–wake cycle; both the experience of pain and some of the pharmacological agents used for the treatment of pain have been associated with the development of delirium; and the development of emergence delirium (i.e., an altered mental status occurring as a patient "emerges" from deep sedation or medication induced coma).

12.6 Epidemiology

Delirium's prevalence often surpasses all other psychiatric syndromes in the general medical setting (Maldonado 2008a, b; NICE 2010a, b). Among the "general" population aged 85 + years, the prevalence of delirium is about 10 %, rising

Table 12.2 Theorized neurochemical mechanisms associated with conditions leading to delirium

Delirium Source	ACH	DA	GLU	GABA	5HT	NE	Trp	Phe	His	Cytok	HPA axis	NMDA activity	Changes in RBF	EEG	Mel	Inflam	Cort
Anoxia/hypoxia	↓	↑	↑	↑	↓	↓	⇔	↑	╬↓	╬↑	╬	↑	╬	↓	↓	↑	↑
Aging	↓	↓	↓	↓	↓	↓	↓	↓	↓	╬↑	╬	↓	╬	↓	↓	↑	↑
TBI	↑	↑	↑	↑	↑	↑	↑	↑	↓	↑╬	↑	↑	↑	↓	↓	↑ ╬	↑
CVA	↓	↑	↑	↑	↑	↑	↑	↑	↓	↑╬	↑	↑	╬	↓	↓	↑ ╬	↑
Hepatic Failure (encephalopathy)	⇔	↓	↑	↑	↑	↓	↑	↑	↑	↑╬	╬	↑	╬	↓	↓	↑	↑
Sleep deprivation	↓	↓	╬	↑	↑	↑	↓	↑	↑	↑	╬	↑	↑	↓	↓ ╬	↑ ╬	↑
Trauma, Sx, and Post-op	↓	↑	↑	↑	↓	↑	↓	↑	↑	↑	↑	↑	╬	↓	↓	↑	↑
ETOH and CNS-Dep Withdrawal	↑	↑	↑	↓	↑	↑	↓	↑	↑	↑	↑ ╬	↑	↓	↓	↓	↑	↑
Infection/Sepsis	↓	↓	↑	↑	↓	↓	↓	↓	↓	↑	↑ ╬	↑ ╬	╬	↓	↓	↑	↑
Dehydration and Electrolyte Imbalance	⇔	↑	↑	↑	↓	↑	?	?	↑	↑	╬	↑	↓	╬	↓	╬↑	↑
Medical Illness	↓	↑	↑	╬	↓	↑	↓	↑	↑	↑	↓	↑	╬	╬	↓	╬	↑

↑ = likely to be increased or activated; ↓ = likely to be decreased or slowed; ⇔ = no significant changes; (╬) = probably a contributor, exact mechanism is unclear; (−) = likely not to be a contributing factor; ? = effect unclear; CVA = cerebro-vascular accident; Sx = surgery; ETOH = alcohol; CNS-Dep = central nervous system depressant agent; ACH = acetylcholine; DA = dopamine; GLU = glutamate; GABA = gamma-aminobutyric acid; 5HT = 5-hydroxytryptamine or serotonin; NE = norepinephrine; Trp = tryptophan; Phe = phenylalanine; His = histamine; Cytok = cytokines; HPA axis = hypothalamic-pituitary-adrenocortical axis; NMDA = N-methyl-D-aspartic acid; RBF = regional blood flow; EEG = electroencephalograph; Mel = melatonin; Inflam = inflammation; Cort = Cortisol.

Table 12.3 Delirium: predisposing and precipitating risk factors—"*end acute brain failure*"

Risk Factor	Examples
Electrolyte imbalance and dehydration	Electrolyte disturbances (e.g., hyperammonemia, hypercalcemia, hypokalemia/hyperkalemia, hypomagnesemia, hyponatremia/hypernatremia)
Neurological disorder and injury	All neurological disorders, e.g., CNS malignancies, abscesses, cerebrovascular accident (CVA), vasculitis, multiple sclerosis (MS), epilepsy, Parkinson's disease, normal pressure hydrocephalus (NPH), traumatic brain injury (TBI), diffuse axonal injury (DAI), limbic encephalitis (both non-paraneoplastic and paraneoplastic syndrome). Of the various forms of sensory impairment, only visual impairment has been shown to contribute to delirium. Visual impairment can increase the risk of delirium 3.5-fold.
Deficiencies (nutritional)	Nutritional deficiencies (e.g., malnutrition, low serum protein/albumin, low caloric intake, "failure to thrive"), malabsorption disorders (e.g., celiac disease), and hypovitaminosis; specifically deficiencies in cobalamine (B12), folate (B9), niacin (B3; leading to pellagra), thiamine (B1; leading to beriberi and Wernicke's disorder).
Age	Age [>65] and Gender [m>f]
Cognition	*Baseline cognitive functioning, including dementia and other cognitive disorders; h/o delirium* have all been shown to increase the likelihood of delirium.
U-Tox (intoxication and withdrawal)	*Substances of abuse*—Acute illicit substance intoxication (e.g., cocaine, PCP, LSD, hallucinogens), as well as poisons, pesticides, solvents, and heavy metals (i.e., lead, manganese, mercury)—and S*ubstances Withdrawal*.
Trauma Toxins	Physical trauma and injury; heat stroke, hyperthermia, hypothermia, severe burns, including trauma of surgical procedures. *Various, including biotoxins [animal poison]; heavy metals (lead, manganese, mercury); insecticides; poisons; carbon dioxide; toxic effect of pharmacological agents [*i.e.*, serotonin syndrome, neuroleptic malignant syndrome, anticholinergic states); Blood levels [toxic levels of various therapeutic substances (*e.g.*, lithium, VPA, carbamazepine, immunosuppressant agents).*
Endocrine disturbance	Endocrinopathies such as hyper/hypo-adrenal corticoid; hyperglycemia/hypoglycemia; hyperthyroidism/hypothyroidism.
Behavioral-Psychiatric	Certain psychiatric diagnoses, including undue emotional distress; a history of alcohol and other substance abuse, as well as depression, schizophrenia and bipolar disorder have been associated with a higher incidence of delirium
Rx and other toxins	Several pharmacological agents have been identified, especially those with high anticholinergic activity, including prescribed agents (especially narcotics and GABA-ergic agents)] and various OTC agents [especially anticholinergic substances; polypharmacy]
Anemia, anoxia, hypoxia, and Low perfusion states	Any state that may contribute to decreased oxygenation (e.g., pulmonary or cardiac failure, hypotension, anemia, hypoperfusion, intraoperative complications, hypoxia, anoxia, carbon monoxide poisoning, shock).
Infectious	Pneumonia, urinary tract infections, sepsis, encephalitis, meningitis, HIV/AIDS.
Noxious stimuli (Pain)	Data suggests that both pain and medications used for the treatment of pain have been associated with the development of delirium. Studies have demonstrated that the presence of postoperative pain is an independent predictor of delirium after surgery. On the other hand, the use of opioid agents has been implicated in the development of delirium.
Failure (organ)	Cardiac, hepatic, pulmonary, and renal failure.
Apache score (severity of illness)	Evidence shows that the probability of transitioning to delirium increases dramatically for each additional point in the Acute Physiology and Chronic Health Evaluation (APACHE II) severity of illness score.

(continued)

Table 12.3 (continued)

Risk Factor	Examples
Intracranial processes	*Stroke (especially non-dominant hemispheric); Intracranial bleed; Meningitis; Encephalitis; Neoplasms*
Light, sleep, and Circadian Rhythm	Sleep deprivation and insomnia, sleep disorders (e.g., obstructive sleep apnea) and disturbances/reversal in sleep–wake cycle.
Uremia and other Metabolic Disorders	Acidosis, alkalosis, hyperammonemia, hypersensitivity reactions; *glucose, acid–base disturbances*
Restraints and any factors causing immobility	The use of restraints, including endotracheal tubes (ventilator),soft and leather restraints, intravenous lines, bladder catheters, and intermittent pneumatic leg compression devices, casts, and traction devices all have been associated with an increased incidence of delirium
Emergence delirium	Emergence from medication induced sedation, coma or paralysis; which may be associated with CNS depressant withdrawal, opioid withdrawal, REM-rebound, sleep deprivation.

Adapted from Maldonado JR, Delirium: Neurobiology, Characteristics and Management, in Psychiatric Care of the Medical Patient, Fogel, B., Greenberg, D. (Eds). Oxford University Press, 2014 (In Press). (Maldonado 2014)

Table 12.4 Delirium risk factors

Modifiable factors	Non-modifiable factors
• Various pharmacological agents, especially GABA-ergic and opioid agents, and medications with anticholinergic effects • Prolonged and/or uninterrupted sedation • immobility • Acute substance intoxication • Substance withdrawal states • Use of physical restraints • Water and electrolyte imbalances • Nutritional deficiencies • Metabolic disturbances and endocrinopathies (primarily deficiency or excess of cortisol) • Poor oxygenation states (e.g., hypo-perfusion, hypoxemia, anemia) • Disruption of the sleep–wake cycle • Uncontrolled pain • Emergence delirium	• Older age • Baseline cognitive impairment • Severity of underlying medical illness • Preexisting mental disorders

up to 22 % in populations with higher percentages of demented elder; and as high as 70 % for those in long-term care (de Lange et al. 2013); making delirium one of the six leading causes of preventable conditions in hospitalized elderly patients (Rothschild and Leape 2000).

The frequency of delirium varies from 15 % to 60 % in hospitalized general medical and surgical patients (Smith and Dimsdale 1989; Francis et al. 1990; Levkoff et al. 1992; Schor et al. 1992; Williams-Russo et al. 1992; Pompei et al. 1994; Parikh and Chung 1995; van der Mast and Roest 1996; Elie et al. 1998; Bucht et al. 1999; Fann 2000; Aldemir et al. 2001; Lepouse et al. 2006; Siddiqi et al. 2006; Hala 2007; Lundstrom et al. 2007; Maldonado 2008a, b; Katznelson et al. 2009; Maldonado et al. 2009; NICE 2010a, b; Tognoni et al. 2011; Ryan et al. 2013). The reported rate of postoperative delirium has been reported to range from 10 % to 74 % (Dyer et al. 1995; Vaurio et al. 2006; Bruce et al. 2007; Maldonado et al. 2009; NICE 2010a, b; Wiesel et al. 2011). Studies have demonstrated that up to 87 % of critically ill patients develop delirium during their ICU stay (Ely et al. 2001a, b). Delirium is common among cancer patients (Adams 1988; Weinrich and Sarna 1994; Morita et al. 2001; Breitbart et al. 2002; Centeno et al. 2004; Gaudreau et al. 2005).

Terminally ill cancer patients, patients with moderate to severe traumatic brain injury, frail elders, and the critically ill are clinical populations generally recognized to have a high incidence of delirium over their course of illness, due to factors such as polypharmacy, comorbid medical conditions, and metabolic dysfunction. Among patients with advanced cancer, delirium was diagnosed in 42 % of patients on admission,

while it developed in 45 % of hospitalized cancer patients (not delirious at the time of admission) (Lawlor et al. 2000). Terminal delirium occurred in 88 % of patients dying of cancer (Lawlor et al. 2000).

The large variation of incidence and prevalence data reported reflects differences in patient populations studied and diagnostic criteria used.

12.7 Management of Delirium

The management of delirium has four main components: (1) recognition of patients at risk; (2) implementation of prevention techniques (with pharmacological and non-pharmacological approaches), especially in those populations identified to be at high risk; (3) enhanced surveillance and screening; and (4) treatment of all forms of delirium (with pharmacological and non-pharmacological approaches). In the discussion that follows we combine prevention and treatment methods as some of the pharmacological and non-pharmacological approaches have been shown to be of benefits in both, delirium prevention and amelioration of symptoms and shortening the duration of delirium once it has started (Table 12.5).

The *recognition of patients at risk* begins by knowledge of the patient's characteristic, an assessment of the predisposing and precipitating medical risk factors the patient is or may be exposed to (Table 12.3), and the modifiable and non-modifiable risk factors for that particular patient or patient population (Table 12.4). Finally, certain medical conditions and surgical procedures are more likely to be associated with the development of delirium than others. It is likely that a particular patient's odds of developing delirium are associated with the interaction between these four sets of conditions. These have been discussed in detail elsewhere (Maldonado 2008a, b; Maldonado 2014).

Prevention techniques have been found to be rather effective, especially when targeted to patients at high risk for developing delirium. There are a whole host of pharmacological and non-pharmacological techniques available (See Table 12.5). It is important that providers carefully consider the fear of potential side effects versus the benefits associated with effective delirium prevention.

The early *recognition of delirium* is of upmost importance given the serious negative consequences of misdiagnosis or delayed treatment, including increased morbidity and mortality. A study among ICU patients demonstrated that whose delirium treatment was delayed were more frequently mechanically ventilated (50.0 % vs. 22.3 %; $p = 0.012$), had more nosocomial infections (including pneumonia) ($p < 0.05$), and had a higher mortality rate ($p < 0.001$) than patients whose treatment was promptly started (Heymann et al. 2010).

The most important aspects of an *adequate surveillance and early detection* include knowledge about the condition and presenting symptoms (of all motor forms) and a high level of suspicion, especially in populations at risk. There are a number of surveillance tools and techniques (discussed above under Diagnosis of Delirium section) that can be used to efficiently screen subjects, especially those at greatest risk. Adequate training of medical personnel at all levels is paramount. Surveillance should be effectively implemented by all practitioners.

Once diagnosed, adequate *management of delirium* includes the following steps: (1) management of the behavioral and psychiatric manifestations and symptoms to prevent the patient from self-harm or harming of others (e.g., use of tranquilizing agents to manage agitation); (2) treatment or correction of underlying medical problems and potential reversible factors (e.g., correction of electrolyte imbalances, infection, end organ failure, sleep deprivation, pain, metabolic and endocrinological disturbances, substance or medication intoxication or withdrawal); and (3) correction of the neurochemical derangement (triggered by the underlying cause) which leads to the behavioral manifestations of delirium (see Table 12.5).

We advocate an integrative approach which we like to call the "CNS Pharmacotherapy Algorithm" for the prevention and management of delirium in the ICU (Fig. 12.2) (Maldonado

Table 12.5 Delirium management algorithm: prevention and management

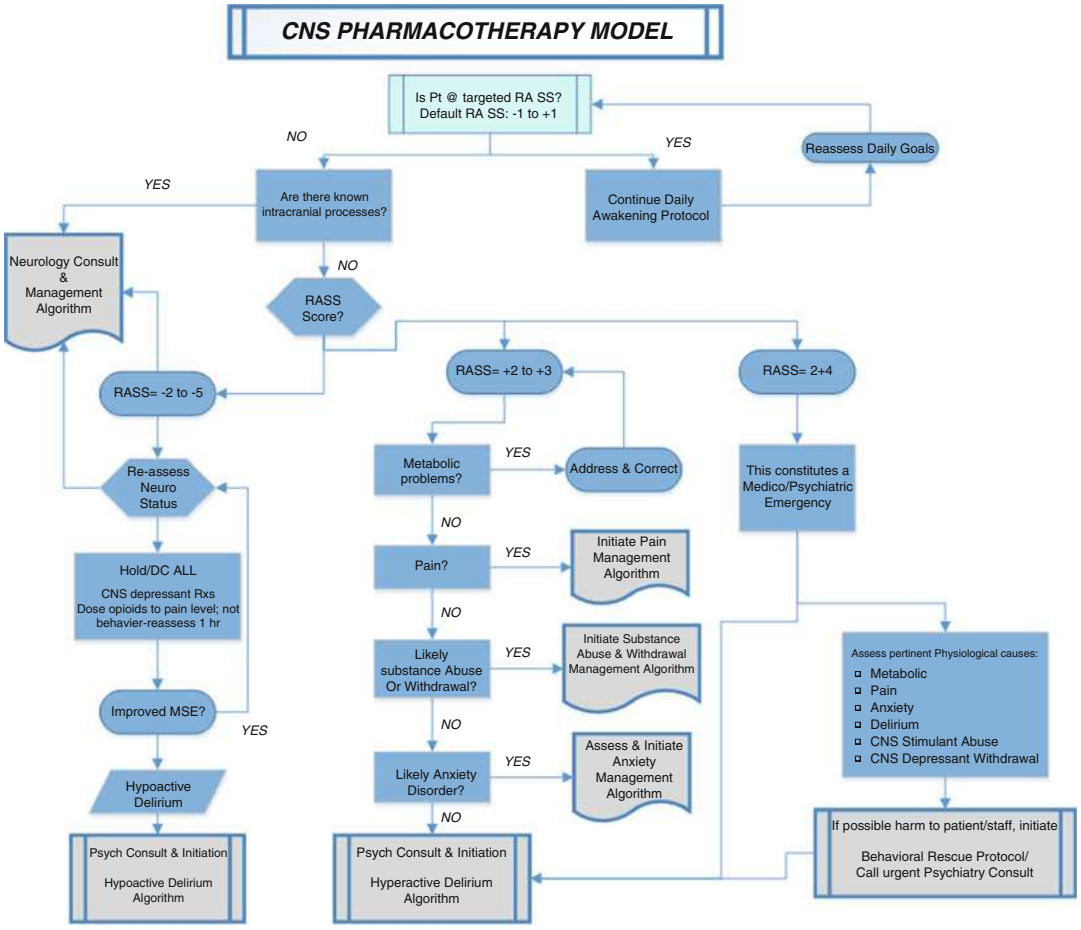
I. Recognition of patients at risk
A. A particular patient's odds of developing delirium are associated with the interaction among the following conditions:
i. Knowledge of a patient's characteristic
ii. Predisposing and precipitating medical risk factors (Table 12.3)
iii. Modifiable and non-modifiable risk factors for that particular patient or patient population (table 12.4)
iv. Specific medical conditions and surgical procedures the patient is exposed to
B. Obtaining the patient's baseline level of cognitive functioning using information from accessory sources (e.g., IQCODE)
II. Implementation of prevention techniques
A. A key focus should be placed on prevention strategies, particularly in "at risk" populations
i. Avoid all pharmacological agents with high deliriogenic potential or anticholinergic load, if possible
ii. Promote a non-pharmacological sleep protocol
iii. Early mobilization (see below for details)
B. For patients in the ICU, especially those on ventilation or IV sedation, consider:
i. Sedate to a prescribed or target sedation level (e.g., RASS)
ii. Consider using the sedative agent with lowest deliriogenic potential:
• Dexmedetomidine use is associated with the lowest incidence of delirium
• Propofol use is a good second choice; followed by midazolam
iii. Reassess pain levels daily and titrate opioid agents to the lowest effective required to maintain adequate analgesia
• Hydromorphone is preferred as baseline agent of choice for pain management
• Limit the use of fentanyl for rapid initiation of analgesia and as rescue agent
• Avoid the use of opioid agents for sedation or management of agitation or delirium
iv. Provide daily sedation holidays, this includes:
a. Interrupt sedative infusions daily until the patient is awake
b. Restart sedation, if needed, at the lowest effective dose
c. Reassess target sedation level (e.g., RASS)
III. Enhanced surveillance, screening, and early detection
A. Most important aspects surveillance:
i. Knowledge about the condition and presenting symptoms
ii. A high level of suspicion
B. Be vigilant for the development of delirium in high risk groups:
i. Use a standardized surveillance tools (e.g., DRS-R-98; MDAS; CAM)
ii. Use of psychiatric consultants (i.e., DSM-5/ICD-10 criteria)
iii. Be particularly aware of the presence of hypoactive delirium and its different manifestation
C. Use psychiatric consultants to help with assessment and design of the treatment plan, if available
D. Training of medical personnel at all levels
IV. Treatment of all forms of delirium
A. Identify and treat underlying medical causes
B. Treatment or correction of underlying medical problems and potential reversible factors
C. Conduct an inventory of all pharmacological agents administered to the patient
i. Any medication or agent known to cause delirium or to have high anticholinergic potential should be discontinued, if possible, or a suitable alternative instituted
D. Implement early mobilization techniques, to include ALL of the following components:
i. Daily awakening protocols (sedation holiday)—as described above
ii. Remove IV lines, bladder catheters physical restraints and any other immobilizing apparatuses as early as possible
iii. Aggressive PT and OT as soon as it is medically safe to do
a. In bedridden patients this may be limited to daily passive range of motion
b. Once medically stable, get the patient up and moving as early as possible

(continued)

Table 12.5 (continued)

iv. Provide patients with any required sensory aids (i.e., eyeglasses, hearing aids)
v. Promote as normal a circadian light rhythm as possible
a. Better if this can be achieved by environmental manipulations, such as light control (i.e., lights on and curtains drawn during the day; off at night) and noise control (i.e., provide ear plugs, turn off TVs, minimize night staff chatter)
b. Provide as much natural light as possible during the daytime
vi. Provide adequate intellectual and environmental stimulation as early as possible
E. Avoid using GABAergic agents to control agitation, if possible
• *Exception*: cases of CNS-depressant withdrawal (i.e., alcohol, benzodiazepines, barbiturates); or when more appropriate agents have failed and sedations are needed to prevent patient's harm
F. Adequately assess and treat pain
i. Yet avoid the use of opioid agents for behavioral control of agitation
ii. Rotate opioid agents from morphine to hydromorphone or fentanyl
G. For the treatment of delirium (all types) consider using:
i. Acetylcholinesterase inhibitor (e.g., rivastigmine)—for patients with a history of recurrent delirium or delirium superimposed on known cognitive deficits. Physostigmine, for known causes of anticholinergic delirium
ii. Melatonin (e.g., 3 mg q HS) or melatonin agonists (e.g., ramelteon 8 mg q HS) to promote a more natural sleep. If that is ineffective, consider trazodone (e.g., 25-100 mg q HS) or mirtazapine (e.g., 3.75 – 7.5 mg q HS)
iii. Serotonin antagonist (e.g., ondansetron)
H. In case of *hyperactive delirium* consider the use of the following agents:
i. Dopamine antagonist agents (to address DA excess) (e.g., haloperidol, risperidone, quetiapine, aripiprazole)
a. Moderate dose haloperidol (e.g., < 20 mg/24 h in divided doses), is still considered the treatment of choice, if the patient's cardiac condition allows it
b. Before using haloperidol:
• Obtain 12-lead ECG; measure QTc and
• Check electrolytes; correct K + and Mg+, if needed
• Carefully review the patient's medication list and identify any other agents with the ability to prolong QTc
• If possible avoid other medications known to increase QTc and/or inhibitors of CPY3A4
c. When the use of haloperidol is contraindicated or not desirable, atypical antipsychotics should be considered:
• Better evidence for: risperidone, quetiapine
• Limited data for: olanzapine, aripripazole, perospirone
• Avoid: clozapine, ziprasidone
d. Discontinue dopamine antagonist agents use if QTc increases to >25 % of baseline or >500 msec
ii. Alpha-2 agonist agents (to address the NE excess) (e.g., dexmedetomidine, clonidine, guanfacine)
a. Consider changing primary sedative agents from GABA-ergic agents (e.g., propofol or midazolam) to an alpha-2 agent (e.g., dexmedetomidine), starting at 0.4mcg/kg/h, then titrate dose every 20 min to targeted RASS goal
iii. Anticonvulsant and other agents with glutamate antagonism or Ca + Ch modulation (e.g., VPA, gabapentin, amantadine, memantine)
F. Consider the use of NMDA-receptor blocking agents, to minimize glutamate-induced neuronal injury (e.g., amantadine, memantine), particularly in cases of TBI and CVA.
G. In case of hypoactive delirium:
i. Evidence suggests that DA antagonists may still have a place given the excess DA theory.
a. If haloperidol is use, recommended doses are in the very-low range (i.e., 0.25 to 1 mg / 24 h). This is usually given as a single nighttime dose, just before sun down
b. If an atypical is preferred, consider an agent with low sedation (i.e., risperidone, aripiprazole)
ii. In cases of extreme psychomotor retardation or catatonic features, in the absence of agitation or psychosis, consider the use of psychostimulant agents (e.g., methylphenidate, dextroamphetamine, modafinil) or conventional dopamine agonists (e.g., bromocriptine, amantadine, memantine)

Modified from (Maldonado 2008a, b; 2009; 2011)



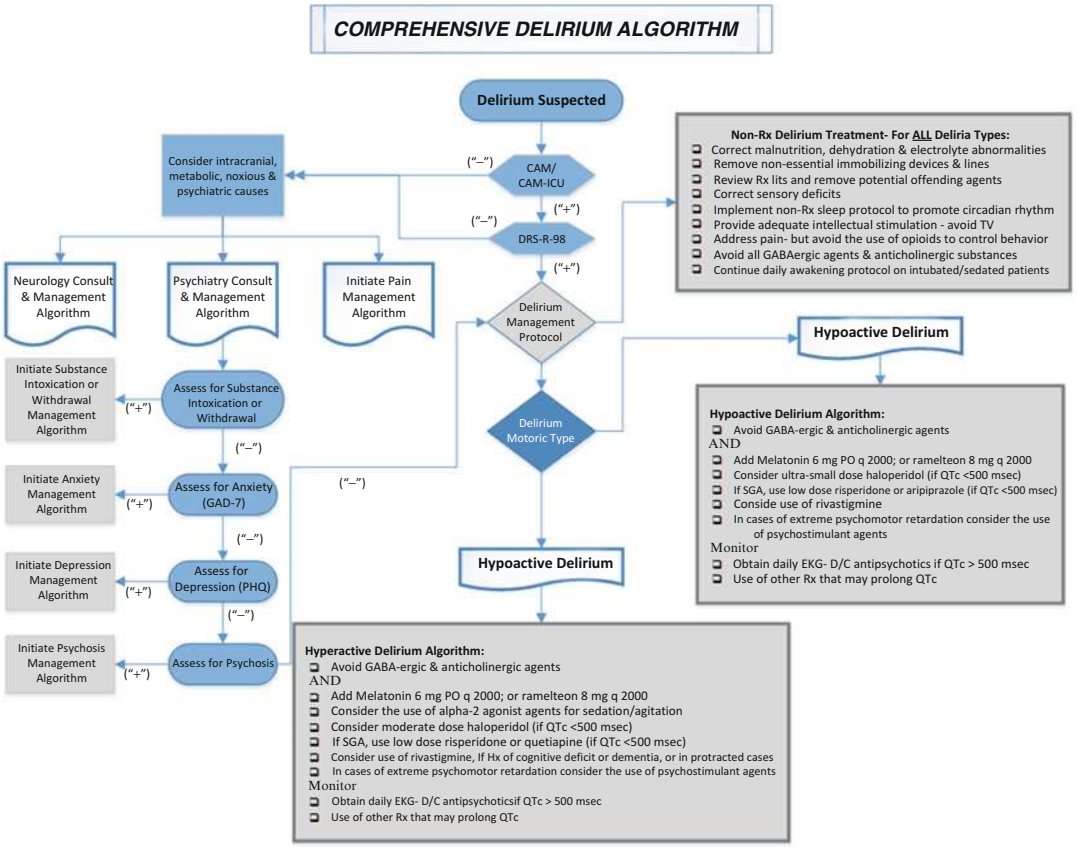
|Adapted from (Maldonado 2008, Maldonado 2014, Maldonado 2014)

Fig. 12.2 CNS Pharmacotherapy Model

2008a, b; Maldonado 2009; Maldonado 2011). This approach incorporates input and collaboration among all pertinent medical teams including primary treatment team and its consultants (including the CL service), nursing personnel, and members of the various ancillary teams (e.g., respiratory, physical and occupational therapy) and is directed at early mobilization, restoration of the sleep–wake pattern, optimizing patient comfort (i.e., adequate sedation), minimizing pain (i.e., adequate analgesia), prevention or treatment of delirium. This approach is directed at improving physical and cognitive recovery and return to baseline functional level as soon as possible (Fig. 12.3).

12.7.1 Non-pharmacological Management Strategies

To date, there are 12 studies published on the use of non-pharmacological prevention strategies in the non-ICU environment, with equal number of studies claiming benefits as those suggesting the intervention has limited or no effect in delirium prevention. The multicomponent protocol consisted of simple techniques applied by the hospital staff, including reorientation, appropriate cognitive stimulation three times a day, the implementation of a non-pharmacologic sleep protocol to help normalize patient's sleep–wake cycle, early mobilization after surgery or extubation, timely



|Adapted from Maldonado (Maldonado 2008, Maldonado 2014, Maldonado 2014)

Fig. 12.3 Comprehensive Delirium Algorithm

removal of catheters and restraints, correction of sensory deficiencies (i.e., eyeglasses and hearing aids), and early correction of dehydration and electrolyte abnormalities. This has evolved into the Hospital Elder Life Program (HELP) (Inouye and Charpentier 1996, Inouye et al. 1999a, b; Inouye et al. 2000). This program involves the implementation of targeted interventions for known risk factors (i.e., cognitive impairment, sleep deprivation, immobility, dehydration, vision or hearing impairment) for cognitive decline in the elderly by an interdisciplinary team A number of studies have demonstrated the usefulness of the multicomponent approach in preventing delirium (Marcantonio et al. 2001; Tabet et al. 2005; Vidan et al. 2005; Caplan and Harper 2007; Lundstrom et al. 2007; Colombo et al. 2012).

Yet a number of studies have failed to demonstrate the benefits of the multicomponent protocol in delirium prevention (Schindler et al. 1989; Wanich et al. 1992; Milisen et al. 2001; Benedict et al. 2009; Bjorkelund et al. 2010; Gagnon et al. 2012). In fact, recent studies have found that the intervention had no effect on the overall delirium rate ($p=0.84$), and made no significant difference on secondary measures (i.e., mean length of hospital stay ($p=0.74$), falls ($p=0.43$), or discharge to long-term care facilities ($p=0.20$) (Holroyd-Leduc et al. 2010a, b). A meta-analysis of published studies found that although the multicomponent interventions appeared to be effective in reducing the incidence of delirium among postoperative patients, it made no difference in a number of important secondary

measures, including discharge location or post-discharge dependency, length of hospital stay ($p=0.12$), or mortality rate ($p=0.77$) between intervention and control groups (Holroyd-Leduc et al. 2010a, b). Of note, a recent study found that the administration of the multicomponent intervention by non-professional, family members lead to a significant reduction in the occurrence of delirium ($p=0.027$) (Martinez et al. 2012), suggesting the negative studies mentioned above are a reflection of the mode of administration, rather the approach itself. Of interest, a recent study demonstrated that a relatively simple intervention consisting of daily reorientation, supplemented with environmental, acoustic and visual stimulation significantly lowered the occurrence of delirium (Colombo et al. 2012).

To date, there is only one non-pharmacological intervention that has proven effective in preventing delirium in the intensive care units (ICU). Researchers have found that a combination of early physical and occupational therapy during periods of daily interruption of sedation was accompanied with a significantly greater return to independent functional status ($p=0.02$), shorter duration of delirium ($p=0.02$), and more ventilator-free days ($p=0.05$) (Schweickert et al. 2009). Others have confirmed that a combination of sedation reduction and early mobilization with physical rehabilitation leads to improved outcomes (i.e., lower total amount benzodiazepine use, higher level of functional mobility, and reduction in delirium rates) (Needham and Korupolu 2010).

Finally, some small recent studies have suggested that the use of bright light therapy (i.e., 3000–5000 lux at a distance of 100 cm between light source and patient's eyes) may be useful in both, prevention (Yang et al. 2012; Chong et al. 2013) and treatment of delirium (Taguchi et al. 2007; Ono et al. 2011). In fact these studies suggest the use of bright light was also associated with an increased mean sleep time (7.7 from 6.4 h; $P<0.05$).

In addition, there are a number of steps the primary team can take to effectively decrease the risk of delirium and/or assist in its recovery (Table 12.5). These include conducting an inventory of all pharmacological agents being administered to the patient and discontinuing or substituting potentially offending agents, if possible, especially those with high anticholinergic load. Early discontinuation of all immobilizing lines and devices (e.g., chest tubes, IV lines, bladder catheters), including physical restraints. Early titration of sedation and early mobilization (as described above) has proven to be a key factor in minimizing delirium and improving the odds of return to independent functioning upon discharge home.

Early correction of sensory deficits should be undertaken (e.g., replacement of eyeglasses and hearing aids) as soon as possible. Encouragement of healthy social interaction with family and friends should be made to decrease environmental isolation. Correct malnutrition, dehydration, and electrolyte abnormalities as quickly and safely as possible. Implement environmental manipulations (e.g., increase the amount of natural light during daytime hours, reduce noise levels and artificial lights at nighttime, decrease nighttime tests and procedures) to normalize the sleep–wake cycle and avoid the need of pharmacological sleep agents. In the case of intubated, sedated ICU patients, sedative and pain regimens should be titrated to manage the patients' symptoms, while allowing for early extubation and mobilization.

The British National Institute for Health and Clinical Excellence (NICE) provided a set of guidelines for the prevention of delirium in elderly at-risk patients, mostly based on the correction of modifiable of factors and the implementation of the multicomponent intervention package (O'Mahony et al. 2011). The full version of these recommendations can be found at <http://guidance.nice.org.uk/CG103/Guidance/pdf/English>.

12.7.2 Pharmacological Management Strategies

While pharmacological agents may assist in the management of agitated patients and in the correction of the neurotransmitter derangements associated with delirium symptoms (Table 12.2),

it is important to note that to date no pharmacological agent has received FDA approval for the prevention or treatment of delirium. Also, a systematic review of prospective delirium trials, including prospective randomized and nonrandomized double-blind, single-blind, and open-label clinical trials of any pharmacological agent for the prevention or treatment of delirium demonstrated that pharmacological strategies (e.g., haloperidol, second-generation antipsychotics, gabapentin, melatonin, single dose of ketamine during anesthetic induction, and dexmedetomidine-based sedation compared with other sedation strategies for mechanically ventilated patients) showed *greater success in preventing delirium* than in treating it (Friedman et al. 2013).

We base the use of pharmacological agents on the premise that the phenomenon of delirium is caused by an underlying metabolic derangement leading to alterations in the neurotransmitter function and the available evidence-based literature. Thus, this section, we address possible pharmacological interventions, based on the neurotransmitter being targeted.

12.7.2.1 Norepinephrine Excess

α_2-Adrenergic Receptors Agonists versus Conventional Sedative Agents: Effect on Delirium Prevention: There have been several randomized clinical trials looking at anesthetic practice and delirium prevention. Most ICU patients, particularly those who are mechanically ventilated, receive some form of sedation in order to reduce anxiety, encourage sleep and to increase tolerance to the critical care environment, including multiple lines, pain management, endotracheal tubes, and ventilators. Sedative agents (mostly GABA-ergic) and opioids may contribute to the development of delirium by one of six mechanisms: interfering with physiologic sleep patterns; interfering with central cholinergic function; increasing compensatory upregulation of NMDA and kainite receptors and Ca^{2+} channels; disrupting the circadian rhythm of melatonin release; disrupting thalamic gating function; and leading to CNS depressant dependence and withdrawal (Maldonado 2008a, b).

The author and his team were the first to report on the use of the novel sedative agent, dexmedetomidine (DEX) as an alternative to the use of benzodiazepines and related agents (e.g., midazolam (MID), propofol (PRO)) during the postoperative state (Maldonado et al. 2003a, b). We studied patients ($n = 118$) undergoing cardiac surgery (i.e., repair or replacement) with cardiopulmonary bypass (CPB) (Maldonado et al. 2003a, b; Maldonado et al. 2009). After successful weaning from CPB, patients were started on one of three randomly assigned, postoperative sedation regimens: dexmedetomidine (DEX), propofol (PRO), or midazolam (MID). There were no significant preoperative or intraoperative differences between treatment groups (e.g., age, sex, ASA classes, bypass time, clamp time, or lowest temperature achieved), except for the type of postoperative sedation. The study found an incidence of delirium of 3 % for patients on DEX, compared to 50 % for propofol or midazolam ($p < 0.01$) suggesting a "*delirium-sparing effect*." Similarly, the number of delirious days was also significantly lower in the DEX group compared to PROP and MID (1 % vs. 16 % vs. 29 %, respectively; $p < 0.001$) (Maldonado et al. 2009).

Subsequent DBRPCTs have confirmed the original findings and demonstrated the delirium sparing effects of dexmedetomidine (DEX) as compared to conventional sedation (i.e., midazolam) (Pandharipande et al. 2007; Reade et al. 2009; Riker et al. 2009; Shehabi et al. 2009; Jakob et al. 2012). There is evidence suggesting that other α2-agonists (e.g., clonidine) may have similar deliriolytic effects (Rubino et al. 2010). Despite evidence demonstrating that prophylactic use of dexmedetomidine in reducing the incidence of delirium and plenty of clinical evidence that it is useful in the management of agitation related to hyperactive delirium, there is no study to date confirming its potential in the treatment of delirium.

12.7.2.2 Dopamine Excess

Dopamine Antagonists for Delirium Prevention: Of the seven studies published on the use of various antipsychotic agents for delirium

prevention five demonstrated positive results (i.e., the Intensity and duration of postoperative delirium were more severe and lasted longer in the control group) (Kaneko et al. 1999; Prakanrattana and Prapaitrakool 2007; Larsen et al. 2010; Wang et al. 2012; van den Boogaard et al. 2013) Of note, two of the studies showing the most significant effects used relatively small doses of risperidone or olanzapine (a single dose preoperatively; or a dose pre-op and a second dose immediately after surgery, respectively) (Prakanrattana and Prapaitrakool 2007; Larsen et al. 2010).

Of the negative studies, one compared haloperidol (0.5 mg/d preoperatively and until postoperative day #3) to placebo, also in at-risk patients, elderly orthopedic patients (Kalisvaart et al. 2005). Although the incidence of delirium was not significantly lower, the use of haloperidol was associated with lower severity ($p < 0.001$) and shorter duration ($p < 0.001$) of delirium and shortened length of hospital stay ($p < 0.001$).

Two recent meta-analyses of studies using dopamine antagonist agents for delirium prophylaxis found that pooled relative risk of published studies suggested a 50 % reduction in the relative risk of delirium among those receiving antipsychotic medication compared with placebo ($p < 0.01$). The studies suggest that perioperative use of prophylactic dopamine antagonist agents (both typical and second generation antipsychotics), when compared to placebo, may effectively reduce the overall risk of postoperative delirium, thereby potentially reducing mortality, disease burden, length of hospital stay, and associated healthcare costs (Hirota and Kishi 2013; Teslyar et al. 2013)

Dopamine Antagonists for Delirium Treatment: Intravenous neuroleptic agents have been the treatment of choice for agitated and mixed type delirium, particularly in the ICU (Adams et al. 1986; Fernandez et al. 1988; Sanders et al. 1989; Ziehm 1991; Riker et al. 1994; Inouye et al. 1999a, b). Similarly, a number of national and international organizations (i.e., Britain's National Institute for Health and Clinical Excellence (NICE 2010a, b); American Psychiatric Association (Association 1999); Society of Critical Care Medicine (SCCM) (Shapiro et al. 1995; Jacobi et al. 2002)) have recognized IV haloperidol as the agent of choice for the management of critically ill delirious patients. Similarly, a "best evidence topic in cardiac surgery" suggested that haloperidol should be considered the first line drug for agitated patients post cardiac surgery (Khasati et al. 2004). Keep in mind that haloperidol has never been approved by the FDA for IV use and that the Federal Drug Administration (FDA) issued a "black-box" warning for the "off-label" clinical practice of using IV-haloperidol (FDA 2007).

Repeated studies have demonstrated that haloperidol is effective in treating delirium, yet due to the stigma and potential side effects associated with typical antipsychotics, second-generation antipsychotics (SGA) have been increasingly used in recent years for the management of delirium in medically ill patients (Breitbart et al. 1996; Han and Kim 2004; Hu et al. 2004; Skrobik et al. 2004; Lee et al. 2005; Devlin et al. 2010; Girard et al. 2010a, b; Kim et al. 2010; Tahir et al. 2010; Hakim et al. 2012; Maneeton et al. 2013).

Regarding effectiveness of different classes (i.e., typical vs. SGA) a Cochrane database review compared haloperidol with risperidone, olanzapine, and placebo and concluded that there was no significant difference between low dose haloperidol (<3.0 mg per day) and the atypical antipsychotics olanzapine and risperidone in the treatment of delirium (Odds ratio 0.63 ($p = 0.25$) (Lonergan et al. 2007). The same study revealed that low dose haloperidol did not have a higher incidence of adverse effects than the atypical antipsychotics; and that low dose haloperidol was effective in decreasing the intensity and duration of delirium in postoperative patients, compared with placebo (Lonergan et al. 2007). Risperidone is a rather effective (80–85 %) and the most thoroughly studied SGA for the management of delirium, at doses of 0.5–4 mg per day; while olanzapine was found to be 70–76 % effective in treating delirium at doses of 2.5–11.6 mg per day (Ozbolt et al. 2008).

A systematic literature review of 28 delirium treatment studies with antipsychotic agents concluded: (1) that around 75 % of delirious patients who receive short-term treatment with low-dose antipsychotics experience clinical response; (2) that this response rates appear quite consistent across different patient groups and treatment settings; (3) that evidence does not indicate major differences in response rates between clinical subtypes of delirium; (4) that there is no significant differences in efficacy for haloperidol versus atypical agents (Meagher et al. 2013).

There are some steps to remember before and during delirium treatment with dopamine antagonist agents: review the patient's medication list to identify any other agents with the ability to prolong QTc; monitor electrolytes (especially K + and Mg+) and QTc (via 12-lead ECG) before and during the use of continuous antipsychotic management; discontinue their use as soon as possible, and avoid discharging patients on dopamine antagonist agents, if possible. Some have suggested that haloperidol may have the lowest ratio of cardiac death among all dopamine antagonist agents, both typical and atypical (Hatta et al. 2001; Harrigan et al. 2004).

Data available suggests that antipsychotic use helps prevent and treat all forms of deliria, including the hypoactive type (Maldonado 2008a, b; Meagher et al. 2013). In these cases, it is usually given as a single nighttime, low dose (i.e., haloperidol or risperidone in the 0.25 to 1 mg/24 h range). In cases of hypoactive delirium it is best to avoid sedating agents (e.g., quetiapine, olanzapine). In addition, because of its partial dopamine antagonist–agonist properties, aripiprazole may prove being a particularly good choice for hypoactive cases (usually starting at doses as low as 1–5 mg q AM), although others have described the need of much higher doses (e.g., 15–30 mg/day (Alao and Moskowitz 2006; Straker et al. 2006; Boettger and Breitbart 2011). This agent may have positive effects on attention, concentration, and sleep–wake cycle reversal in delirium; and minimal muscarinic and histaminic antagonist activity (thus minimizing adverse cognitive effects). Until recently, aripiprazole had enjoyed the reputation of being the only SGA not associated with significant cardiac side effects. Yet, an increasing number of case reports have demonstrated that the use of SGA, including aripiprazole (either by themselves or in combination with SSRIs) has been associated with cases of arrhythmias, prolonged QTc interval on electrocardiogram (ECG) and orthostatic hypotension, even in patients lacking cardiovascular disorders, likely by inhibiting cardiac and vascular Na(+), Ca(2+) and K(+) channels (Leo et al. 2008; Straker, et al. 2006; Suzuki, et al. 2011; Pacher and Kecskemeti 2004; Hategan and Bourgeois 2014; LoVecchio et al. 2014; LoVecchio et al. 2005; Nelson and Leung 2013).

12.7.2.3 Glutamate Excess

Glutamate Antagonists and Ca + Channel Modulators for Delirium Management: A number of agents with antiglutamatergic and Ca + Ch blocking qualities are worth considering here: lamotrigine, amantadine, memantine, gabapentin, and valproic acid (VPA). Both amantadine and memantine have been recognized as having neuroprotective effects, likely mediated by their protection from glutamate (GLU)-induced exocytosis (by blocking excessive N-methyl-D-aspartic acid receptors (NMDAR) without disrupting physiological synaptic activity, thus preventing excessive calcium influx into neurons—believed to be the key early step in GLU-induced exocytosis); reducing the release of pro-inflammatory factors from activated microglia; inducing expression of neurotrophic factors such as Glial cell line derived Neurotrophic Factor (GNDF) in astroglia; and limiting oxidative injury and dendritic degeneration induced by anticholinesterase neurotoxicity (Giacino and Whyte 2003; Zaja-Milatovic et al. 2009; Ossola et al. 2011; Kutzing et al. 2012). Thus, it makes sense to consider their use in various syndromes associated with excess glutamate and subsequently cognitive decline (e.g., traumatic brain injury, stroke, delirium). In fact, amantadine has been shown to enhance cognitive recovery and minimize delirium after severe traumatic brain injury in humans (Giacino et al. 2012). Similarly, gabapentin has been found to be superior to placebo in reducing delirium

occurrence among postoperative patients (0 % vs. 42 %, $p=0.045$) (Leung et al. 2006), likely due to its modulation of voltage-sensitive Ca^{2+} channels, NMDA receptor antagonism, activation of spinal alpha-2 receptors, attenuation of Na + dependent action potentials

Valproic acid (VPA; either PO or IV) is increasingly used in the management of agitated delirious patients who either are not responsive or cannot tolerate conventional treatment, yet there is very little data regarding its effectiveness, limited to two case series (Bourgeois et al. 2005; Sher et al. 2013).

12.7.2.4 Cholinergic Deficit

Acetylcholinesterase Inhibitors for Delirium Prevention: Acetylcholine deficiency has been postulated as one of the potential causes of delirium, whether this is caused by natural physiological process (e.g., aging) or due to exogenous factors (e.g., use of anticholinergic substances). Given long-standing theories suggesting that a cholinergic deficit may be one of the mechanisms causing delirium and early positive trials it seemed reasonable to expect a benefit from the prophylactic use of acetylcholinesterase inhibitor agents (Dautzenberg et al. 2004; Moretti et al. 2004). Yet studies have not consistently demonstrated positive results; in fact, most recent studies have been rather disappointing (Gamberini et al. 2009) (Liptzin et al. 2005; Sampson et al. 2007)

Early positive results of these agents may suggest these agents may need to be in use for an extended period of time before they have any prophylactic effect (as in the case of Dautzenberg and Moretti's study); or that they need to be used at doses much higher than we currently use them in order to achieve acute clinical efficacy.

Acetylcholinesterase Inhibitors for Delirium Treatment: Addressing the theory that proposes delirium is caused by a central cholinergic deficiency state, some researchers and clinicians have experimented with the use of acetylcholinesterase inhibitor agents. There are a number of published papers, mostly case reports, suggest that acetylcholinesterase inhibitor agents (e.g., donepezil, galantamine, physostigmine, rivastigmine) may be effective in the treatment of delirium. Most of the published data consists of small series of case reports associated with the use of rivastigmine in the treatment of delirium in older persons (van den Bliek and Maas 2004; Sampson et al. 2007).

In general, the use of these agents for the treatment of delirium has proven problematic, with positive results not significant to risk the side effects. For example, a study on the adjunct use (to haloperidol) of rivastigmine for the treatment of delirium in critically ill patients was stopped after only about 25 % of the sample had been recruited due to a higher mortality in the treatment group ($n=12$, 22 %) compared to placebo ($n=4$, 8 %) and no beneficial effect. The study titrated the dose of rivastigmine at a very fast pace (i.e., every 3 days) to a total dose of 12 mg/day. Unfortunately, the authors did not share the mortality data, thus it is difficult to assess how much of a role rivastigmine played on the increased mortality rates (van Eijk et al. 2010).

As per the previous discussion, the use of physostigmine, a short-acting acetylcholinesterase inhibitor, should be considered. Physostigmine increases synaptic acetylcholine concentrations and can overcome the postsynaptic muscarinic receptor blockade produced by anticholinergic agents. As a tertiary amine, it can pass freely into the central nervous system (CNS) and reverse both central and peripheral anticholinergic effects. Many reports have demonstrated the utility and safety in cases when delirium has been caused by medication overdose (whether accidental or intentional) (Stern 1983; Lipowski 1992; Beaver and Gavin 1998; Richardson et al. 2004; Eyer et al. 2011; Hail et al. 2013). Various studies have suggested that despite its reputation, its use is safe when used under controlled circumstances (Burns et al. 2000; Schneir et al. 2003) Given its safety profile and effectiveness, physostigmine should be considered when a delirious patient's examination exhibits signs of a central anticholinergic state (e.g., confusion, sinus tachycardia, markedly dilated and fixed pupils, dry mouth, hypoactive bowels sounds, dry and flushed skin) and/or when it is known that the patient's altered mental status is due to the use of known anticholinergic substances (e.g., diphenhydramine).

12.7.2.5 Melatonin/Sleep Deficit

Sleep deprivation is one of the major theories on the development of delirium, whether caused by medication effect, environmental factors, or patient characteristics. Many sedative and hypnotic agents may worsen sleep and thus are not recommended. An alternative to these is the use of non-benzodiazepine agents, such as melatonin or melatonin agonists (i.e., ramelteon).

Melatonin has been shown to play an important role in the regulation of circadian rhythm and maintenance of a physiological, well-regulated sleep–wake pattern (Brzezinski 1997).

Melatonin Physiological Effects (adapted from (Maldonado 2008a, b)):

– Melatonin play important roles in multiple bodily functions which may have potential implications regarding the development of delirium in the medically ill:
  - Chronobiotic effect (affecting aspects of biological time structure)
  - Sleep–wake cycle regulatory effects
  - Helps reset circadian rhythm disturbances
  - Extensive antioxidant activity (with a particular role in the protection of nuclear and mitochondrial DNA)
  - Extensive anti-inflammatory activity
  - Antinociceptive and analgesic effects
  - Melatonin receptors appear to be important in mechanisms of learning and memory
  - Inhibits the aggregation of the amyloid beta protein into neurotoxic microaggregates responsible for the neurofibrillary tangles characteristics of Alzheimer's disease and it prevents the hyperphosphorylation of the tau protein.

12.7.2.6 Melatonin in Delirium Prevention

Melatonin plays many important roles in multiple physiological roles besides the well-known chronobiotic effect (Reiter 1991a, b; Brzezinski 1997; Hanania and Kitain 2002; Bourne et al. 2008; Maldonado 2008a, b; Verster 2009; Maldonado 2013) These may contribute to melatonin's ability to cause a statistically significant decrement in postoperative delirium (9.43 % vs. 2.65 %, $p=0.003$) (Sultan 2010); and medically ill hospitalized elderly patients (12.0 % vs. 31.0 %, $p=0.014$), when compared to placebo and after adjusting for dementia and other comorbidities (Al-Aama et al. 2011).

12.7.2.7 Sleep Restoration in Delirium Treatment

As described above, we highly recommend starting with the implementation of non-pharmacological sleep protocols. If the patient still has difficulty sleeping, the use of melatonin (or melatonin agonists) is probably the best first pharmacological option (e.g., 3 mg PO q 2000, for prophylaxis). Several case reports have described the successful use of melatonin (e.g., 6 mg HS PO, for treatment) and melatonin agonists in treating severe postoperative delirium unresponsive to antipsychotics or benzodiazepines (Sultan 2010; Kimura et al. 2011; Furuya et al. 2012)

If that fails, clinicians should consider the use of non-benzodiazepine agents, such as trazodone or mirtazapine. If absolutely necessary zolpidem may be an acceptable choice, but taking into consideration the moderately high incidence of disordered sleep behaviors while on zolpidem and like drugs. Given its short half-life and high sedation, low-dose quetiapine may also be an acceptable short-term solution, especially in patients experiencing sundowning.

12.7.2.8 Delirium Management: Summary

A systematic review and meta-analysis of randomized trials identified 38 RCTs with interventions ranging from perioperative managements to pharmacological, psychological or multicomponent interventions. The meta-analysis showed that multicomponent interventions (2 RCTs with 325 patients, RR = 0.71; 95 % CI = 0.58–0.86) were effective in preventing delirium; dexmedetomidine sedation was associated with less delirium compared to sedation produced by other drugs (2 RCTs with 415 patients, pooled risk ratio (RR) = 0.39; 95 % confidence interval (CI) = 0.16–0.95); and that both typical (3 RCTs with 965 patients, RR = 0.71; 95 % CI = 0.54–0.93) and atypical antipsychotics (3 RCTs with 627 patients, RR = 0.36; 95 % CI = 0.26–0.50)

decreased delirium occurrence when compared to placebos (Zhang et al. 2013a, b). A subsequent systematic review found that perioperative psychogeriatric consultation (OR 0.46, 95 % CI 0.32–0.67) and lighter sedation (OR 2.66, 95 % CI 1.27–5.56) were associated with a decreased incidence of postoperative delirium; while prophylactic haloperidol use (OR 0.62, 95 % CI 0.36–1.05) and bright light therapy use (OR 0.20, 95 % CI 0.03–1.19) provided possible protection (Moyce et al. 2014).

Thus, in general, the data suggests that non-pharmacological approaches (when regularly applied) may be useful in both preventing and treating delirium. The most efficacious non-pharmacological techniques include sedation holidays, minimization of sedation, and early mobility. The pharmacological approaches with most evidence include the use of alpha-2 agonists rather than GABA-ergic agents for ICU sedation; the judicious use of antipsychotic agents for the treatment of delirium, and some evidence in for their prophylactic use in patients at high risk (best evidence for haloperidol, risperidone, and quetiapine; some evidence for olanzapine for hyperactive and aripiprazole for hypoactive delirium. There is evidence for the prophylactic and therapeutic use of melatonin and bright-light therapy. Finally, clinical evidence suggests that some antiglutamatergic agents (e.g., VPA, gabapentin) may be effective, as an adjunct to antipsychotics, in management of hyperactive delirium.

12.8 Impact of Delirium

After controlling for demographics, apparent illness severity, age, and medical comorbidities, patients who develop delirium fare much worse than their non-delirious counterparts. The mortality rate for elderly patients in acute care hospitals is much higher among those with delirium than those without delirium: 8 % versus 1 % in one study (Francis et al. 1990). Studies have found an independent association between delirium present within 24 h after ICU admission, and an increased in-hospital mortality (i.e., 16.2 % for delirious patients vs. 5.7 % for non-delirious) (van den Boogaard et al. 2010). Patients in the medical ICU who developed delirium have higher mortality both at 90-days (11 % vs. 3 %) and at 6 months mortality rates (34 % vs. 15 %) (Pompei et al. 1994; Ely et al. 2004). The number of days of delirium older patients experience during an intensive care unit admission is significantly associated with mortality up to 1 year after admission after controlling for severity of illness ($p = 0.001$) (Fig. 12.3) (Pisani et al. 2009).

In the intensive care units, when compared with patients suffering from the same medical problem who do not develop delirium as a complication, delirious patients experienced higher mortality rate; longer length of stay in both ICU and general hospital; and a higher rate (6X) of complications (i.e., acute respiratory distress syndrome, nosocomial pneumonia, cardiopulmonary edema, reintubation, self-extubation, removal of catheter, cardiac arrhythmia (Zhang et al. 2013a, b). Delirious ICU patients also spent more time on mechanical ventilation and were more likely to be discharged to skilled placement (Zhang et al. 2013a, b).

Similarly, among the general medical population those who developed delirium experienced prolonged hospital stays—5 to 10 days longer on average (Francis et al. 1990; O'Keeffe and Lavan 1997; Ely et al. 2001a, b; Maldonado et al. 2003a, b; Ely et al. 2004); increased short- and long-term mortality; decreased long-term cognitive function; increased length of hospital stay and increased complications of hospital care (Vasilevskis et al. 2012); and required a higher rate of institutional post-acute care (e.g., 16 % versus 3 %) (Francis et al. 1990; O'Keeffe and Lavan 1997). These bleak prognoses apply not only to severe cases, but even to patients experiencing prevalent subsyndromal delirium (SSD) (Cole et al. 2003; Ouimet et al. 2007a, b).

While it is clear from available evidence that the presence of baseline cognitive deficits, including dementia lowers the threshold to develop delirium (Franco et al. 1998; Litaker et al. 2001; McNicoll et al. 2003, Benoit et al. 2005; Smith et al. 2009; Kalisvaart et al. 2006; Wacker et al. 2006; Wahlund and Bjorlin 1999; Tognoni et al. 2011), data suggests that among elderly patient, there is a significant acceleration in the slope of

cognitive decline in patients with Alzheimer's disease (AD) following an episode of delirium (Fong et al. 2009). Emerging data suggests that a substantial proportions of patients who survive delirium are left with post-delirium long-term cognitive impairment (LTCI) (Macdonald 1999; Rockwood et al. 1999; Jackson et al. 2004; Wacker et al. 2006; Griffiths and Jones 2007; Gunther et al. 2007; Bickel et al. 2008; Kat et al. 2008; Maldonado 2008a, b; Cole et al. 2009; Fong et al. 2009; MacLullich et al. 2009; Girard et al. 2010a, b). Prospectively collected data from a nested cohort of hospitalized patients with AD ($n=263$); median follow-up duration, 3.2 years) found that after adjusting for dementia severity, comorbidity, and demographic characteristics, patients who had developed in-hospital delirium experienced greater cognitive deterioration in the year following hospitalization (3.1 [95 % CI, 2.1–4.1] IMC points per year) relative to patients who had not developed delirium (1.4 [95 % CI, 0.2–2.6] IMC points per year) (Gross et al. 2012). Similarly, cognitive deterioration following delirium proceeded at twice the rate in the year after hospitalization compared with patients who did not develop delirium; the more rapid rate of cognitive deterioration among delirious patients continued throughout a 5-year period following hospitalization (Gross et al. 2012). The Vantaa 85+ study (population based cohort; $n=553$ patients aged ≥85 years at baseline) followed examined individuals at 3, 5, 8 and 10 years after delirium. Results suggest that delirium increased the risk of incident dementia (odds ratio 8.7, 95 % confidence interval 2.1–35) and was associated with the loss of an additional 1 point per year in the Mini-Mental State Examination compared to those with no history of delirium (95 % confidence interval 0.11–1.89) (Davis et al. 2012).

A study of elderly, hospitalized delirious patients found that only 4 % had experienced full resolution at the time of discharge from the hospital; with only an additional 20.8 % experiencing symptom resolution by month 3 and an additional 17.7 % by the sixth month after discharge from the hospital (Levkoff et al. 1992). The occurrence of delirium was a strong independent predictor of cognitive impairment and severe dependency in activities of daily living among elderly hip surgery patients (Bickel et al. 2008). Similarly, a prospective matched controlled cohort study of elderly hip surgery patients demonstrated that the risk of dementia or mild cognitive impairment (MCI) over a 30-months follow-up was almost twice as high in patients with postoperative delirium as in those without (Kat et al. 2008).

The data suggests that many older hospital patients do not recover from delirium and that the persistence of delirium is associated with adverse outcomes. In fact, there appears to be a reciprocal relationship between delirium and cognitive decline: dementia is the strongest risk factor for delirium among older patients (Elie et al. 1998, McCusker et al. 2003, McAvay et al. 2006, Inouye et al. 2007); and the development of delirium appears to increase the risk of cognitive decline, including dementia (Rockwood et al. 1999). Over 20 prospective studies (> 5,000 patients) during the last 3 decades demonstrate a significant association was found between delirium and long-term cognitive dysfunction (MacLullich et al. 2009; Witlox et al. 2010). The studies suggest that about 40 % of patients with delirium develop some form of cognitive impairment when followed up about 3 months to 5 years after an episode of delirium (Levkoff et al. 1992; McCusker et al. 2001; Jackson et al. 2004; Witlox et al. 2010). In fact, a meta-analysis with adjusted hazard ratios demonstrated that the occurrence of delirium is associated with an increased risk of dementia (average follow-up, 4.1 years; odds ratio:12.52 [95 % CI, 1.86–84.21]; I^2, 52.4 %). Furthermore, the data shows that subsyndromal delirium (associated with critical illness), in the absence of full-blown delirium, has also been found to result in long-term cognitive dysfunction 2 months to 6 years following critical illness (e.g., 46–70 % of patients showed signs of cognitive dysfunction at 1 year; and 25 % at 6 years) (Cole et al. 2003; Morandi et al. 2012).

Furthermore, longer duration of delirium has been found to be associated with worse average performance on neuropsychological testing at 3 and 12 months follow-up ($p=0.02$ and $p=0.03$, respectively) (Girard et al. 2010a, b). In fact, an increase from 1 to 5 days of delirium was

independently associated with a 7-point decline in the cognitive battery mean score at 12 months follow-up ($p = 0.03$) (Girard et al. 2010a, b). A possible explanation for the relationship between delirium and cognitive functioning may be related to an association between longer duration of delirium and greater brain atrophy as measured by a larger ventricle-to-brain ratio at hospital discharge ($p = 0.03$) and at 3-month follow-up ($p = 0.05$) (Gunther et al. 2012). As expected, greater brain atrophy (higher ventricle-to-brain ratio) at 3 months was associated with worse cognitive performances (executive functioning and visual attention) at 12 months ($p = 0.04$) (Gunther et al. 2012).

Similarly, the incidence of PTSD related to postoperative delirium has been shown to be related to the nature and level of the sedation and analgesia, degree of factual memory recall, incidence of delirium, and underlying prevalence of preexisting psychiatric morbidity (Blank and Perry 1984; Bourgon 1985; Stukas et al. 1999; Dew et al. 2001; Jones et al. 2001; Breitbart et al. 2002; DiMartini et al. 2007; Griffiths and Jones 2007; Roberts et al. 2007; O'Malley et al. 2008; Basinski et al. 2010).

The economic impact of delirium is substantial as their increased morbidity leads to prolonged lengths of stay and require increased nursing time per patient, higher per-diem hospital costs (Inouye 2000; Ely et al. 2004; Milbrandt et al. 2004; Siddiqi et al. 2007) In fact, some have estimated that the care of delirious hospital inpatients rivals the health care costs of falls and myocardial infarction (Hall et al. 1988; Rizzo et al. 1996; Inouye 2000). A study of ICU delirium demonstrated that even after adjusting for age, comorbidity, severity of illness, degree of organ dysfunction, nosocomial infection, hospital mortality, and other potential confounders, delirium was associated with 39 % higher intensive care unit and 31 % higher hospital costs (Milbrandt et al. 2004). Similarly, a study of hospitalized medically ill elderly patients the average cost per day was 2.5-fold greater in those with delirium, and the total excess cost attributable to delirium ranged from $16,303 to $64,421 per patient (Leslie et al. 2008).

The costs of caring for in-hospital, post-delirium patients continue to mount after hospital discharge due to greater need for long-term care or additional home health care. A recent study looking at costs over 1 year following an episode of delirium estimated that delirium is responsible an additional cost of $60,000–$64,000 per patient for the year following the index hospitalization. The total annual direct healthcare costs attributable to delirium in the USA might be as high as $152 billion (Leslie et al. 2008).

12.9 Conclusion

Delirium is a neurobehavioral syndrome caused by the transient disruption of normal neuronal activity secondary to systemic disturbances. Its occurrence leads to patient and caregiver distress, and has been associated with increased morbidity and mortality, increased cost of care, increased hospital-acquired complications, poor functional and cognitive recovery, decreased quality of life, prolonged hospital stays, and increased placement in specialized intermediate and long term care facilities. Unfortunately, once delirium has occurred it is possible the patients may never return to their previous level of cognitive functioning.

Therefore, clinicians are encouraged to implement as many prevention strategies as are available to them in order to improve patient outcome and prevent/minimize the occurrence of delirium, thus minimizing its morbidity. Because delirium is common, it is important medical personnel and hospital staff implements surveillance and monitoring strategies to facilitate early detection and allow the implementation of techniques that may shorten its duration. Treatment should first be directed at patient safety, then to search and correct the underlying causes contributing to its development. The early use of treatment strategies may shorten the duration of the delirium episode, thus improving the odds of recovering baseline functional status. CL psychiatrists in consultation with members of the multidisciplinary team may facilitate the recognition and management of these patients (Fig. 12.4).

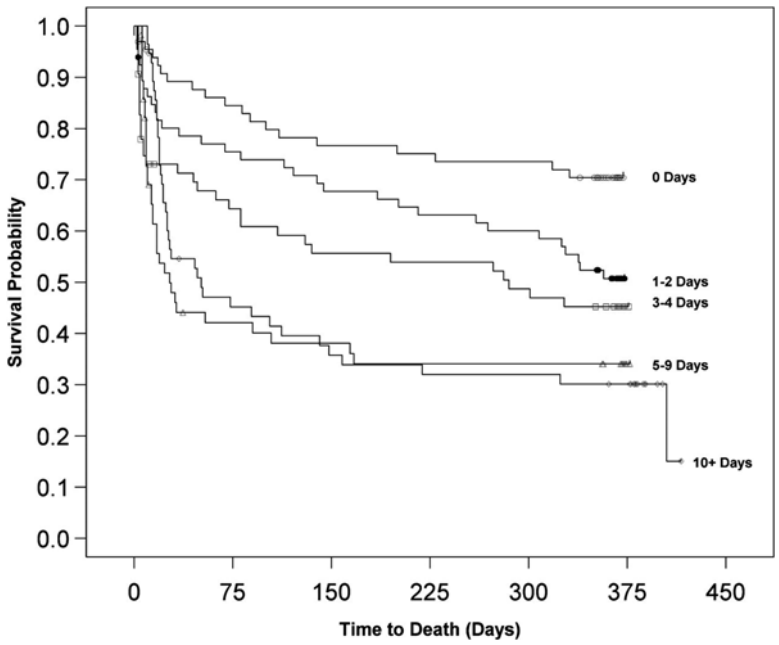


Fig. 12.4 Kaplan-Meier survival curves were calculated using the five-level days of ICU delirium variable

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Major Neurocognitive Disorders (Dementias)

13

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13.1 Introduction

Consultation-Liaison (CL) Psychiatrists are frequently consulted on patients with Major Neurocognitive Disorders (MNCDs; DSM-5), formerly known as dementia. The questions usually posed include determination of decisional making capacity, management of delirium superimposed on MNCD, diagnosing the etiology of and assisting with the management of behavioral and psychiatric symptoms (e.g., mood, psychotic or behavioral symptoms) due to MNCD.

Thus, it is imperative for CL psychiatrists to be able to recognize and diagnose MNCD, differentiate among the various types and causes of MNCD, and be familiar with management strategies of the various psychological and behavioral manifestations.

Here is a common scenario of such a consult:

> A 72-year-old man with diagnosed "Alzheimer's Dementia" was brought to the hospital by his wife and children, for increased agitation and confusion. The patient had demonstrated worsening of his memory over the last 7 years. During the same period, his wife took over managing the household and finances, the patient stopped driving, and eventually he was no longer allowed to leave the house on his own. Progressively, he required assistance in dressing and bathing and had difficulty recognizing distant family members when they visited. Over the last year, he started accusing his family members of stealing his personal items. During the same period, he called 911 several times to report non-existing intruders. During the week prior to admission, the patient became increasingly irritable and agitated, threatening and scaring his family.

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He charged and attempted to hit his son. He had forcefully pushed his wife when she was attending to him, and was later found barricading in the bathroom. He reported that he saw "a gang of thugs" in his living room and was hiding from them. At this point, his family members feel they can no longer safely manage his behavior at home and thus are requesting evaluation and treatment.

In the emergency department, a medical and laboratory evaluation revealed a urinary tract infection (UTI). Other laboratory data were within normal levels, including normal hepatic and renal function. Electrocardiogram (EKG) revealed normal sinus rhythm without prolonged QTc. The patient was admitted to the medicine unit and started on oral antibiotics.

In the hospital, the patient was agitated, yelling at and attempting to hit the nurse offering him medications. He appeared to swing at imaginary objects and exhibited a reversal of his sleep–wake cycle (i.e., not sleeping at night, but somnolent during the daytime). The patient was disoriented, unable to state where he was or why he was in the hospital.

The CL psychiatrist was consulted to aid in management of the patient's symptoms. After an assessment, the patient was diagnosed with delirium superimposed on MNCD. In addition, to treating his infection, the CL psychiatrist recommended starting a short-term, low dose antipsychotic to treat delirium, as well as to manage the patient's agitation and psychotic symptoms due to MNCD. In addition, the CL psychiatrist recommended initiating treatment with an acetylcholinesterase inhibitor and a selective serotonin reuptake inhibitor (SSRI) for the long-term management of his behavioral symptoms. The staff was instructed on the use of behavioral interventions for redirecting the patient's unsafe behavior.

After 5 days of treatment the patient appeared to be calmer. Yet, due to past experiences, the family did not feel safe having the patient return home and the team thought it was appropriate to pursue a specialized skilled nursing facility. However, the patient expressed a firm desire to return home. Psychiatry was asked to comment on patient's capacity to make decisions regarding discharge planning. The CL psychiatrist again met with the patient, discussing the patient's choice, and further elucidating the patient's understanding of his condition, the team's recommendations, and the risks versus benefits of returning home versus going to a skilled nursing facility (Appelbaum 2007). The patient was found to be unable to appreciate that he had a progressive cognitive impairment and could not verbalize his needs or risks of being at home. He did not understand his family's concerns or the team's recommendations. Thus, he was deemed not to have capacity to make medical or placement decisions, and his family was thought to be an appropriate surrogate decision maker. Finally, the family was encouraged to pursue probate conservatorship in order to facilitate the patient's future care.

Major Neurocognitive Disorders (MNCDs; DSM-5), are major neuropsychiatric conditions affecting an individual's cognitive functioning leading to interference with independence in everyday life activities (APA 2013). By definition, DSM-5 requires that the presenting deficits represent a decline from a previously attained level of cognitive functioning; this will allow distinguishing them from the neurodevelopmental disorders in which a neurocognitive deficit is present at birth or interferes with development. It is possible, however, to develop a neurocognitive disorder superimposed on a neurodevelopmental disorder, for example Alzheimer's disease (AD) in a patient with developmental delay associated with Trisomy 21.

In MNCD various cognitive domains are affected, including complex attention, executive function, learning and memory, language, perceptual-motor, and/or social cognition (Table 13.1). DSM-5 requires that in order to diagnose major NCD, the patient must demonstrate BOTH an acquired cognitive decline in one or more cognitive domains (based on concern about cognition either on the part of the individual, informants, or clinician) AND substantial cognitive impairment preferably documented with evidence from objective testing or quantifiable clinical assessment. In cases of MNCD, performance on objective neuropsychiatric assessment falls usually two or more standard deviations below standardized norms (3rd percentile or below) (APA 2013). These cognitive deficits are attributable to changes in brain structure, function, or chemistry.

13.1.1 Epidemiology

By 2005, 24.2 million people worldwide had MNCD and 4.6 million new cases were arising every year (Ferri et al. 2005; Reitz and Mayeux 2014). It is estimated that the highest prevalence and incidence rates of MNCD can be found in North America and Western Europe, followed by populations in Latin

Table 13.1 Neurocognitive domains affected in MNCD

Complex attention	The patient has increased difficulty in environments with multiple stimuli (e.g., TV, radio, conversation); has difficulty holding new information in mind (e.g., recalling phone numbers or addresses just given; or reporting what was just said).
Executive function	The patient is not able to perform complex projects; needs to rely on others to plan instrumental activities of daily living or make decisions.
Learning and memory	The patient repeats self in conversation, often within the same conversation; cannot keep track of short list of items when shopping or of plans for the day. Requires frequent reminders to complete task in hand.
Language	The patient has significant difficulties with expressive or receptive language; often uses general terms such as "the thing" and "you know what I mean."
	With severe impairment patients may not even recall names of close family and friends.
Perceptual–Motor	The patient has significant difficulties with previously familiar activities (e.g., using tools, driving motor vehicle), and navigating in familiar environments.
Social cognition	The patient may exhibit changes in behavior (e.g., shows insensitivity to social standards); makes decisions without regard to safety. Usually patients have little insight into these changes.

America and China and the western-Pacific region (Ferri et al. 2005). Studies predict that global prevalence of MNCD will quadruple by the year 2050 (Reitz and Mayeux 2014). Much of the increase will be in the developing countries (Alzheimer's Disease International 2013).

Studies have found that the prevalence of MNCD increases exponentially with age (Table 13.2) (Lobo et al. 2000; Alzheimer's Disease International 2008). In 2002, the Aging, Demographics, and Memory Study (ADAMS) estimated the prevalence of MNCD in the USA among individuals aged 71 and older to be 14 %, comprising about 3.4 million individuals, and in those aged 90 and older 37.4 % (Plassman et al. 2007).

Overall, AD accounted for approximately 69.9 % of all dementia, while vascular dementia (VaD) accounted for 17.4 %. Other types of dementia such as "dementia, undetermined etiology," Parkinson's dementia, normal-pressure hydrocephalus, frontal lobe dementia, alcoholic dementia, traumatic brain injury, and Lewy body dementia accounted for the remaining 12.7 % of cases (Plassman et al. 2007). The Global Burden of Disease project DISMOD-II software estimated incidence rates of 4.6 million new cases of dementia every year (about one new case every 7 s). Estimating the number of people living with dementia worldwide in 2001 at 24.3 million, but predicting the number will almost double every 20 years, translates to 42.3 million in 2020 and 81.1 million in 2040 (Ferri et al. 2005).

Table 13.2 Incidence and prevalence rates of dementia from the EURODEM meta-analyses for European studies

Age group	Annual incidence per 100		Prevalence (%)	
	Males	Females	Males	Females
60–64	0.2	0.2	0.4	0.4
65–69	0.2	0.3	1.6	1.0
70–74	0.6	0.5	2.9	3.1
75–79	1.4	1.8	5.6	6.0
80–84	2.8	3.4	11.0	12.6
85–89	3.9	5.4	12.8	20.2
90+	4.0	8.2	22.1	30.8

Sources: (Lobo et al. 2000; International 2008)

MNCD has widespread effects on affected individuals, their families, and society. In the report on the state of US Health, Alzheimer's Disease (AD) was ranked as the ninth cause of the years of life lost due to premature mortality and the 12th cause of the years lived with disability (Murray et al. 2013).

Early-onset neurocognitive disorder (NCD) has been increasingly recognized. A study conducted at the university hospital in Cambridge, UK found that the overall prevalence of early-MNCD (i.e., onset <65 y/o) was 81 per 100,000 in the 45–64-year age group (Ratnavalli et al. 2002). Furthermore, they found that AD accounted for 35 % of this early onset dementia, while frontotemporal lobar degeneration (FTLD) accounted for 22 %. As mentioned above, there are multiple etiologies contributing to the dementias, each with its own characteristics and presentation.

Table 13.3 Major neurocognitive disorders—subtypes (as recognized by DSM-5)

Subtypes based on etiology (*in alphabetical order*)
Alzheimer's disease
Due to another medical condition
Due to multiple etiologies
Frontotemporal lobar degeneration
HIV infection
Huntington's disease
Lewy body disease
Parkinson's disease
Prion disease
Substance/medication induced
Traumatic brain injury
Unspecified
Vascular disease
Subtypes based on severity level
Mild—Instrumental ADL's are preserved
Moderate—Basic ADL's affected
Severe—Fully dependent
Subtypes based behavior
With behavioral disturbance
Without behavioral disturbance

Table 13.4 Major neurocognitive disorder due to Alzheimer's disease

1. Diagnostic criteria for major neurocognitive disorder are met.
2. There is insidious onset and gradual progression of impairment in one or more cognitive domains.
3. Criteria met for either probable or possible Alzheimer's disease are as follows:
   (a) *Probable* Alzheimer's disease is diagnosed if either of the following is present:
   - Evidence of a causative Alzheimer's disease genetic mutation from family history or genetic testing.
   - All three of the following are present:
     – Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detail history or serial neuropsychological testing).
     – Steadily progressive, gradual decline in cognition, without extended plateaus.
     – No evidence of mixed etiology (e.g., absence of other neurodegenerative or cerebrovascular disease or another neurological, mental or systemic disease likely contributing to cognitive decline).

   (b) Otherwise, *possible* Alzheimer's disease should be diagnosed.

The commonest subtypes of MNCD include AD, vascular dementia (VaD), dementia with Lewy bodies, and FTLD. DSM-5 subtypes the various MNCD syndromes based on their etiology, if known (Table 13.3) (APA 2013). These are discussed below.

13.2 Etiologic Factors and Subtypes

13.2.1 Alzheimer's Disease

Alzheimer's disease (AD) is the leading cause of MNCD, estimated to occur in 50–75 % of those afflicted by dementia (Gouras 2009). It is estimated that by 2013 about five million Americans older than 65 have Alzheimer's disease. Further estimates suggest that by the year 2025 up to 7.1 million of Americans older than 65 will suffer from the condition. The disease slowly erodes memory and thinking skills, and eventually makes the affected individual incapable of taking care of their activities of daily living (ADLs). It is characterized by slow progression with an average time from its diagnosis until death ranging from 5 years (Larson et al. 2004) to 10 years (Brookmeyer et al. 2002). MNCD due to AD usually presents with loss of recent episodic memory, with affected individuals becoming forgetful, losing objects, repeating stories, and missing appointments. Word-finding difficulty is common and presents early. Memory deficits are followed months to years by deficits in executive function, visuospatial function, language, and praxis. It eventually manifests in global cognitive deterioration, difficulty with long-term memory and overlearned visuospatial tasks, such as eating and dressing (Table 13.4).

Of note, behavioral changes are common and eventually up to 88 % of patients experience NCD-associated behavioral and psychiatric symptoms, formerly known as Behavioral and Psychiatric Symptoms of Dementia (BPSD) (Mega et al. 1996). These symptoms are usually differentiated into three clusters, i.e., affective symptoms (dysphoria, anxiety, apathy), psychotic symptoms (delusions and hallucinations), and verbal and physical agitation. Of note, psychotic symptoms

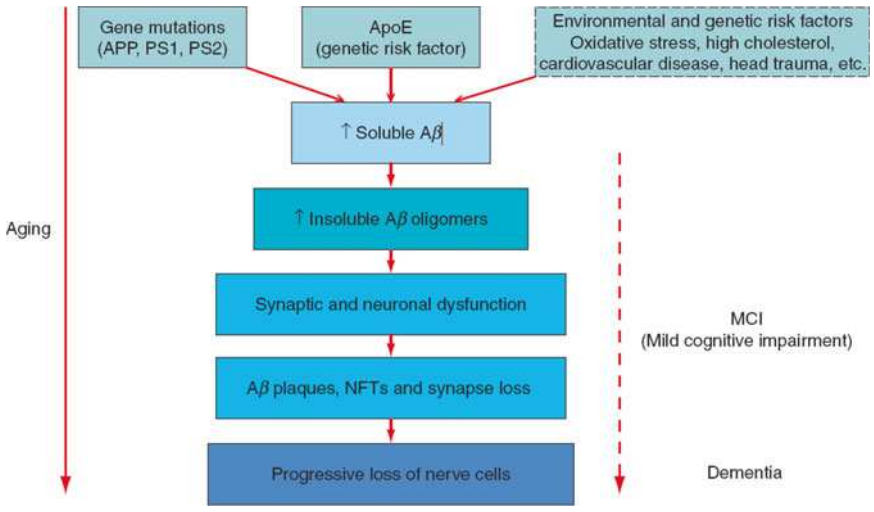

Fig. 13.1 The amyloid cascade hypothesis. *APP* amyloid precursor protein, *PS1, PS2* presenilin proteins 1 and 2, *Apo E* apolipoprotein E, *Ab* b-amyloid, *NFTs* neurofibrillary tangles. From (Gouras 2009 p. 405)

are different from the psychotic symptoms in primary psychotic illnesses: hallucinations are more commonly visual and delusions often relate to the faulty memories. For example, a patient misplaces items and thus concludes that there are intruders in the house who steal, or they have difficult time remembering their spouse and conclude that he/she was replaced with an impostor (Capgras delusion). Usually these behavioral symptoms bring these patients to the attention of a CL psychiatrist and management of agitation in a patient with MNCD is not an uncommon consult question in the general hospital. These neuropsychiatric symptoms also place a huge burden on the family and are frequently the reason behind nursing home placement of such patients. Eventually patients are bedridden, unable to feed themselves or mobilize and they often die from dehydration or sepsis.

The greatest risk factor for developing AD is aging; in addition, history of head trauma and small head size (McDowell 2001) also increase this risk. Higher level of education and occupational attainment may be protective factors (Ngandu et al. 2007), although studies supporting this might have had multiple confounders.

13.2.1.1 Pathology

The "amyloid hypothesis" is at the core of the demonstrated neuropathology of AD development. It proposes that an overproduction and decreased degradation of β-amyloid (Aβ) protein lead to cerebral amyloid angiopathy (CAA), which is characterized by progressive loss of smooth muscle cells in arterioles and accumulation of eosinophilic hyaline material, and formation of senile plaques (SPs), which are comprised of the core of amorphous eosinophilic globule of amyloid surrounded by neuritic corona (Fig. 13.1). Several lines of evidence support that Aβ accumulation precedes and can induce tangle pathology (Gouras 2009). Amyloid precursor protein (APP) is a precursor to β-amyloid and is coded on chromosome 21. Further support comes from the fact that nearly all persons with trisomy 21 (Down's Syndrome) who live long enough develop AD pathology and an accompanying behavioral syndrome. Moreover, mutations in the APP gene lead to the early-onset AD (Goate et al. 1991) as do mutations in two additional identified genes (PSEN1 and PSEN2) (Lippa et al. 2000).

In addition, there has been an established association between polymorphisms of the apolipoprotein E gene (APOE), pleiotropic protein with effects on neurotoxicity, tau phosphorylation, synaptic plasticity, and inflammation, and the risk of onset of AD at least in white populations (Corder et al. 1993). The greatest risk of AD with earlier age of onset is associated with

presence of two copies of ε4 allele; presence of ε3 carries a diminished risk, and ε2—even lower risk.

In addition to senile plaques, the microscopic lesions of AD include neurofibrillary tangles (NFTs), which are dense intraneuronal cytoplasmic aggregates of paired helical filaments and granulovacuolar degeneration (GVD), characterized by neuronal cytoplasm of hippocampal pyramidal cells replaced by vacuoles with small basophilic granules. Moreover, there is significant synapse loss that can be demonstrated biochemically or by immunohistochemistry in AD brain.

13.2.1.2 Diagnosis

Patients presenting with impairing cognitive or behavioral symptoms should be evaluated carefully and diagnosis of MNCD, and in particular AD, should be considered. Repetition is important to rule out other reversible causes of cognitive impairment, such as etiologies contributing to delirium (infection, medication side effect), hypothyroidism or hyperthyroidism, cobalamin deficiency, and neurosyphilis in some geographical regions. Computed Tomography (CT) brain scan can help to identify significant brain pathology for which interventions might be possible (brain tumor, hydrocephalus, subdural hematoma, large stroke). Brain Magnetic Resonance Imaging (MRI) can provide additional information about subtle white matter ischemic changes and regional cerebral atrophy pattern. It is important to screen for depression and other psychiatric morbidity, as these etiologies can contribute or solely explain the presentation. However, these symptoms might also be a part of MNCD. Cognitive testing must be done, such as the Mini Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MOCA) (see Chap. 4 Appendix for these tests) and if not possible or not enough, formal neuropsychological testing is recommended.

The imaging of the AD patient brain with head CT scan or brain MRI demonstrates cerebral atrophy globally, but in particular in medial temporal lobes. Nuclear Imaging with fluorodeoxyglucose positron emission tomography (FDG-PET) (Benson et al. 1983) or single-photon emission computed tomography (SPECT) (Jagust et al. 1987) shows hypometabolism or hypoperfusion in temporoparietal regions with the sensitivity of 94 % and specificity of 73 % in pathologically proven AD (Silverman et al. 2001). Because this pattern of hypometabolism is so distinctive from that of FTD, distinguishing patterns of hypometabolism between AD and FTD is Medicare-approved indication for nuclear imaging.

13.2.2 Frontotemporal Lobar Degeneration

Frontotemporal Lobar Degeneration (FTLD, *frontotemporal dementia*, FTD) is a heterogeneous group of conditions with prominent early behavioral disinhibition, encompassing a variety of clinical syndromes and pathological substrates. The mean age at onset of FTLD is 52.8 years and there is a striking male preponderance (14:3). (Ratnavalli et al. 2002)

FTLD is usually divided into three clinical variants. These include the frontal-variant or behavioral-variant (fvFTLD); progressive nonfluent aphasia (PNFA); and semantic dementia (SD). The motor syndromes of corticobasal degeneration (CBD); progressive supranuclear palsy (PSP); and motor neuron disease (MND) may also be associated with features of FTLD and its pathology (Weder et al. 2007).

FTLD presents earlier as compared to AD with age of onset varying from 35 to 75, but most typically in 5th and 6th decades. It represents 20 % of degenerative dementias of pre-senile onset. Up to 40 % of patients have family history of FTLD, with another prominent risk factor being history of head trauma (Weder et al. 2007). Median survival from symptom onset is approximately 6 years for FTLD and 3 years for FTLD-MND (Hodges et al. 2003; Weder et al. 2007). Median survival for the entire group is 3 years from initial diagnosis, related to common significant delay in diagnosis.

Patients present with behavioral alterations and tend to lack appropriate basic and social

emotions. Some patients with FTLD present with disinhibition and overactivity, while others show apathy and blunted affect.

Frontal variant of FTLD (fvFTLD) is characterized by insidious onset of personality changes, behavioral abnormalities and poor insight (Weder et al. 2007). Symptoms include disinhibition, poor impulse control, antisocial behavior, and stereotyped/perseverative behaviors. Patients might be interpersonally inappropriate, tactless, and offer and display improper sexual comments and gestures. Apathy and emotional blunting are common. Speech output is attenuated and mutism eventually develops. The most common cognitive deficit in fvFTD is an impairment of executive function or working memory, with other frequently encountered cognitive abnormalities including attentional deficits, poor abstraction, difficulty shifting mental set, and perseverative tendencies. Deficits in planning, organization and other aspects of executive function become universal as the disease progresses.

Semantic dementia (SD) or temporal FTD is associated with bilateral atrophy of the middle and inferior neocortex and is characterized by a loss of word meaning/knowledge. Patients present with abnormal speech, where speech is fluent, but words might be substituted for less specific ones and patients are often unaware of their difficulties with comprehension. Patients lose the ability to name and understand words and to recognize the significance of faces, objects and other sensory stimuli. In addition, they might demonstrate deficits on nonverbal tasks using visual, auditory, and other modalities. Behavioral symptoms may appear early or late.

Progressive nonfluent aphasia (PNFA) is associated with asymmetric atrophy of left hemisphere and is characterized by agrammatic nonfluent speech and decreased speech output leading to mutism. Patients present with changes in fluency, pronunciation, or word finding difficulty. Behavioral problems appear later in the disease.

13.2.2.1 Pathology

Pathology of FTD is heterogeneous and is characterized by gliosis, neuronal loss, and superficial spongiform degeneration in the frontal and/or temporal cortexes. Ballooned neurons, i.e., Pick cells, occur with variable frequency in all subtypes (Kertesz and Munoz 2002). Some cases show tau- or ubiquitin-positive inclusions, or lack any distinctive histological features (Mariani et al. 2006). Mutations in the tau gene, which is involved in the regulation of microtubule assembly and disassembly, lead to tau deposition in neurons and glia; while mutations in the progranulin gene lead to ubiquitin-only immunoreactive inclusions. Both genes are located on chromosome 17.

Neuroimaging shows anterior temporal and frontal atrophy, while functional imaging shows decreased perfusion of both frontal and temporal lobes. The focus of the atrophy is in the left temporal lobe in progressive nonfluent aphasia (PNFA) patients and in both frontal lobes in frontal variety frontotemporal dementia (FvFTD) patients.

Neurochemical changes of FTD differ from those of AD. There is evidence of less cholinergic deficit and more serotonergic disturbance in FTD as compared to AD (Weder et al. 2007). This might explain early increased impulsivity, irritability, affective change, and changes in eating behavior in patients with FTD since these behaviors are modulated by serotonergic dysfunction. Thus, serotonergic agents might have a greater role in managing behavioral symptoms of FTD as compared to cholinergic medications, as is discussed later in the chapter.

13.2.3 Vascular Disease

Vascular disease (VaD) encompasses a variety of vascular etiologies, including multi-infarct MNCD with cortical and subcortical involvement as well as the smaller lacunar and micro-infarcts (Erkinjuntti 2007).

VaD is considered the second most common cause of MNCD accounting for 10–50 % of the cases, with prevalence ranging from 1.2 to 4.2 % in persons aged 65 years and older (Hebert and Brayne 1995). The pathophysiology is attributed to interactions between vascular etiologies (coronary vascular disease and vascular risk

factors, such as hypertension, diabetes, smoking), changes in the brain (infarcts, white matter lesions (WMLs), atrophy), and host factors (age, education) (Erkinjuntti 2007). The main subtypes of VaD include cortical VaD or multi-infarct MNCD also referred as post-stroke VaD, subcortical ischemic vascular disease (SIVD) or small-vessel MNCD, strategic-infarct MNCD, and hypoperfusion MNCD resulting from global cerebrovascular insufficiency (Erkinjuntti 2007).

Cortical VaD (multi-infarct MNCD, post-stroke VaD) is characterized by a relatively abrupt onset (days to weeks), a stepwise deterioration (some recovery after worsening) and a fluctuating course of cognitive functions. It is related predominantly to large vessel disease and cardiac embolic events. The frequency of post-stroke MNCD varies from 12 to 32 % within 3 months to 1 year after stroke (Leys et al. 2005). A history of stroke increases the risk of subsequent MNCD by a factor of 5 (Leys et al. 2005).

The presenting symptoms include memory impairment, which may be mild, and such cortical symptoms as aphasia, apraxia, agnosia, and visuospatial or constructional difficulty. In addition, most patients have some degree of dysexecutive syndrome. Moreover, patients often have focal neurological impairments apparent on the exam such as visual field deficits, lower facial weakness, focal motor or sensory deficits, and gait impairment (Leys et al. 2005).

Subcortical Ischemic Vascular Dementia (SIVD) or small-vessel MNCD incorporates two entities, "the lacunar state" and "Binswanger's disease." The onset is variable with 60 % of the patients having a slow onset and only 30 % an acute onset of cognitive symptoms (Erkinjuntti 2007). The course is gradual without (40 %) and with (40 %) acute deficits, and fluctuating in only 20 % (Babikian and Ropper 1987). There is often a preceding clinical history of transient ischemic attacks with only mild focal findings (e.g., drift, reflex asymmetry, gait disturbance). SIVD is attributed to small-vessel disease and is characterized by lacunar infarcts, focal and diffuse ischemic white matter lesions (WMLs), and incomplete ischemic injury. Clinically, it is characterized by the subcortical cognitive syndrome with deficits in executive functioning, slowed information processing, mild memory deficits and behavioral symptoms such as depression and emotional lability (Babikian and Ropper 1987). In addition, neurologic symptoms include motor hemiparesis, bulbar signs and dysarthria, and gait disorder. Imaging reveals multiple lacunes and extensive WMLs.

Strategic-infarct MNCD is characterized by focal, often small, ischemic lesions involving specific sites critical for higher cortical functions, such as the hippocampal formation, angular gyrus and cingulate gyrus, and subcortical sites leading to impairment, including thalamus, fornix, basal forebrain, caudate, globus pallidus, and the genu or anterior limb of the internal capsule (Erkinjuntti 2007).

Moreover, AD and vascular disease coexist in a large proportion of patients, making at times distinguishing primary etiology of MNCD difficult (Erkinjuntti 2007).

13.2.4 Lewy Body Disease

Lewy Body Disease (LBD, DLB) represents up to 20 % of all cases of MNCD cases. It presents late, in 6th through 9th decade and affects both genders equally (Ferman and Boeve 2007). The MNCD is characterized by cortical and subcortical cognitive impairments, with worse visuospatial and executive dysfunction as compared to AD. There is usually relative sparing of memory especially early on. Fifty percent of the cases have mixed presentation with AD. The diagnosis is based on presence of MNCD and additional two out of three features: spontaneous parkinsonism, hallucinations, and daily fluctuation in cognition. Parkinsonian signs must be spontaneous and not attributable to neuroleptics; as compared to Parkinson's Disease (PD) or Parkinson's Disease Dementia (PDD), there is more rigidity and bradykinesia than tremor and parkinsonian symptoms are less severe. Tremor, bradykinesia, and rigidity tend to be more symmetric than asymmetric, and tremor tends to be maximal with posture/action rather than at rest (Ferman and Boeve 2007).

Visual hallucinations (VH) in Dementia with Lewy Bodies (DLB) consist of fully formed, detailed, three-dimensional objects, people, or animals. Auditory hallucinations might happen, but mostly in patients who also have VH. VH have been documented to occur in 59–85 % of autopsy-confirmed DLB samples as compared to 11–28 % of autopsy-confirmed AD sample (Ferman and Boeve 2007). The etiology of DLB hallucinations is likely multifactorial, including severe depletion of acetylcholine, depletion of other neurotransmitters such as dopamine and serotonin, as well as intrusion of dream imagery into wakefulness as a potential mechanism due to the dysregulation of rapid eye movement (REM) sleep in many patients with DLB.

The fluctuations of DLB are characterized by a waxing and waning of cognition, abilities, and arousal. Moreover, patients who have DLB often have daytime drowsiness or somnolence. In addition, these patients often have the parasomnia of REM sleep behavior disorder (RBD) due to the loss of normal muscle atonia during REM. The augmented muscle activity during REM sleep occurs along with dream content and can range from elevated muscle tone to complex behavioral sequences.

Of note, REM sleep behavior disorder can precede the onset of neurodegenerative diseases with alpha-synuclein inclusions (i.e., DLB, PD, or multiple system atrophy [MSA]) by years and even decades and is postulated to be a precursor to the disorders (Iranzo et al. 2013).

In addition, autonomic abnormalities, in particular orthostatic hypotension and carotid sinus sensitivity, are more common in DLB than AD or elderly controls.

To make a diagnosis of DLB, please refer to criteria to make a clinical diagnosis (Table 13.1).

13.2.4.1 Pathology

Neuropathologically, DLB is marked by presence of Lewy bodies in cortical and neocortical brain regions. Lewy bodies, typically present in Parkinson's Disease (PD), are concentric, intracytoplasmic neuronal inclusions within monoaminergic and cholinergic neurons of the substantia nigra, locus ceruleus, and basal nucleus of Meynert with dense eosinophilic core surrounded by a lucent halo, easily seen with routine staining. In contrast to PD, the neocortical Lewy bodies seen in DLB are smaller, lack a halo, and are difficult to see under routine staining conditions. PD and cortical Lewy bodies contain a-synuclein, which is a 140 amino acid protein of unknown function. Abnormal protein processing gives rise to the cytoplasmic collections of a-synuclein, which coalesce to form Lewy bodies. Brains of patients with Lewy bodies demonstrate severe depletion of both cholinergic and dopaminergic markers (Walker et al. 2007).

13.2.5 Posttraumatic Brain Injury

Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease that occurs in association with repetitive traumatic brain injury (McKee et al. 2014). In most instances, the clinical symptoms of the disease begin after a long period of latency ranging from several years to several decades. The initial symptoms are typically insidious, consisting of irritability, impulsivity, aggression, depression, short-term memory loss, and heightened suicidality. The symptoms progress slowly over decades to include cognitive deficits and MNCD. MNCD has been increasingly associated with traumatic brain injuries. Mildcognitive impairment (MCI) after self-reported head trauma with at least momentary loss of consciousness or memory has been found to be associated with greater amyloid deposition, when compared with cognitively intact individuals, suggesting that head trauma may be associated with the development of MNCD (Mielke et al. 2014).

The underlying pathology of CTE is characterized by the accumulation of phosphorylated tau protein in neurons and astrocytes in a pattern that is unique from other tauopathies, including Alzheimer's disease (McKee et al. 2014). The hyper-phosphorylated tau abnormalities begin focally, as perivascular neurofibrillary tangles and neurites at the depths of the cerebral sulci,

and then spread to involve superficial layers of adjacent cortex before becoming a widespread degeneration affecting medial temporal lobe structures, diencephalon and brainstem. Most instances of CTE (>85 % of cases) show abnormal accumulations of phosphorylated 43 kDa TAR DNA binding protein that are partially colocalized with phosphorylated tau protein. In addition CTE is associated with frontal and temporal lobe atrophy, and is increasingly categorized as an acquired Frontotemporal lobar degeneration. Clinically CTE is characterized by behavioral and personality changes, as well as cognitive impairments. As is the case in AD, at present CTE cannot be definitively diagnosed during life, thus its exact incidence and prevalence remain uncertain.

13.2.6 Rapidly Progressive Dementias

Rapidly Progressive Dementias (RPDs) are neurologic conditions that develop subacutely over weeks to months, sometimes even days, not infrequently quickly leading to death (Geschwind et al. 2007). The differential is extensive and is demonstrated along with suggested workup in Table 13.5.

One important category in this class is prion diseases, including Creutzfeldt–Jakob Disease (CJD), characterized by a classic triad of dementia, typical EEG changes, and myoclonus. Most cases are sporadic, with genetic cases comprising 15 % and iatrogenic 2 % (Eggenberger 2007). Prevalence, annual incidence, and yearly mortality of CJD are 0.5–1 per million people. It results from abnormal prion protein form acting in an "auto"-enzymatic fashion, converting normal host prion (prior protein cellular (PrPC)) into the abnormal isoform (protease resistant scrapie form of PrP (PrPSc)) (Eggenberger 2007). The onset of the illness is typically between 50 and 70 years of age with median age of onset at 68 and equal gender distribution. Median survival is 5 months and 85 % of afflicted die within first year of symptom onset. The onset is usually insidious with a nonspecific prodrome in one third, characterized by headache, fatigue, anxiety, changes in sleep, anorexia, weight loss, dizziness, memory difficulties, mood or behavior changes, weakness, and problems with locomotion. These symptoms are followed by progressive aphasia, apraxia, pyramidal signs, myoclonus, and choreiform-athetoid movements. Patients become severely demented within 6 months, with death occurring usually within 12 months of the symptom onset, typically resulting from intercurrent infection. Heidenhain variant is punctuated by visual presentation, most commonly a homonymous visual field defect leading to cerebral blindness early in the course of the disease. EEG can be helpful with the diagnosis, first showing slowing, and later in the course characterized by periodic sharp waves in two thirds of the patients. CSF studies might be remarkable for increased protein 14-3-3, total tau (t-tau), and neuron specific enolase (NSE). Brain MRI demonstrates increased bilateral signal intensity in the basal ganglia, corpus striatum, or thalamus, better visualized on diffusion-weight imaging (DWI) than on fluid-attenuated inversion recovery (FLAIR) sequences (Eggenberger 2007). The definitive diagnosis can be obtained via brain biopsy with tissue pathology demonstrating spongiform degeneration, astrocytic gliosis with neuronal loss, amyloid plaques, lack of inflammatory response, and misfolded prion proteins (PrPs) on immunochemistry (Yung et al. 2010).

13.2.7 Delirium–Dementia Continuum

There seem to be a bidirectional relationship between delirium and dementia. In fact, the presence of baseline cognitive deficits, even those not rising to the level of dementia, significantly increases the risk of developing delirium. The Neuronal Aging Hypothesis (NAH) suggests that the aging process and accompanying physiologic changes constitute an independent risk factor for delirium (Maldonado 2013). The NAH may also explain why the elderly seem to experience a greater chance of developing delirium when challenged by physiological distress that is better tol-

Table 13.5 Differential and suggested workup for rapidly progressive dementias

Category	Differential	Suggested tests
Neurodegenerative	• AD, DLB, FTD • Neurofilament Inclusion Body Disease (NIBD) • Fahr's Disease	• Brain MRI • Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scan
Infectious	• Viral encephalitis, e.g.. HSV • HIV dementia • Progressive Multifocal Leukoencephalopathy (PML) (JC virus) • Opportunistic infections in immunocompromised: Cryptococcus, mycobacteria • Neurosyphilis • Subacute Sclerosing Panencephalitis (SSPE) (measles virus)	• Viral PRCs and cultures • Bacterial, fungal, AFB stains and cultures • RPR • Whipple's PCR
Autoimmune	• Non-vasculitis autoimmune inflammatory meningoencephalopathies: primary angiitis of the CNS (PACNS), polyarteritis nodosa (PAN), sarcoidosis, Systemic Lupus Erythematosus (SLE), Sjögren's syndrome, celiac disease, Behçet's disease, hypereosinophilic syndrome • Cerebral amyloid inflammatory vasculopathy • Hashimoto's encephalopathy • Limbic encephalitis	• ESR, CRP, C3, C4, ANA, rheumatoid factor, anti-SSA, anti-SSB, anti-dsDNA, anti-smith, P-ANCA, C-ANCA, anti-endomysial or anti-gliadin IgA or IgC, SSA, SSB, ACE • TSH, free T4, anti-thyroid peroxidase • Paraneoplastic panel (CSF and serum)
Malignant	• Primary and metastatic solid tumors • Primary CNS lymphoma (PCNSL) • Intravascular lymphoma (i.e., angiotropic lymphoma) • Lymphomatoid granulomatosis	• CT scan body with and without contrast • Whole body PET scan • CSF cytology and flow cytometry • Serum LDH, tumor markers (PSA, CEA, etc.) • Mammogram • Colonoscopy
Vascular	• Strokes • Thrombotic thrombocytopenic purpura (TTP) • Hyperviscosity syndromes: polycythemia vera, gammopathies • CNS vasculitidies	• Brain imaging • Hypercoagulability testing; coagulation profile • Echocardiogram; carotid ultrasound • Cerebral angiogram, meningeal biopsy
Toxic-metabolic	• Vitamin B1, B12, niacin, folate deficiencies • Uremia • Wilson's disease • Portosystemic encephalopathy • Acquired hepatocerebral degeneration • Porphyria • Bismuth, lithium, mercury, arsenic toxicities • Electrolyte abnormalities	• Vitamin B1, B12, niacin, folate • Comprehensive metabolic panel: electrolytes, liver function tests, creatinine/ blood urea nitrogen • Copper and ceruloplasmin; 24 h copper • 24 h urine heavy metal for lead, arsenic, mercury, bismuth, albumin, lithium • Methylmalonic acid levels; thiamine, vitamin E • Exposure history
Prion	• Creutzfeldt–Jakob Disease (CJD)	• EEG • CSF cytology, including protein 14-3-3 • Brain MRI • Brain biopsy

Table 13.6 Mechanisms mediating delirium and cognitive impairment

1. A number of factors and mechanisms leading to delirium, may also directly cause CNS damage and neuronal dysfunction, and thus mediate both the manifestations of delirium and long-term cognitive impairment (e.g., cytokine release and other neuroinflammatory mediators; decrease perfusion and oxygenation leading to decreased cerebral oxidative metabolism; changes in blood–brain barrier permeability; hypercatabolic states; water and electrolyte imbalances; excessive glucocorticoid levels and other HPA axis dysfunctions; melatonin and sleep–wake cycle abnormalities).
2. Pharmacological agents used either to treat the underlying causes of the delirium (e.g., steroids, calcineurin inhibitors, other immunosuppressants, dopamine) or those agents used to treat delirium (e.g., dopamine blocking agents, benzodiazepines) may themselves lead to neuronal damage in a fragile brain.
3. Any of the mechanisms listed above may themselves lead to alterations in neurotransmitter concentration or receptor sensitivity which may underlie the different symptoms and clinical presentations of delirium and/or long-term cognitive dysfunction. Thus, the same mechanisms that cause the substrate for delirium, may mediate the cognitive impairments observed after the acute presentation of delirium has resolved.
4. It is possible that instead of causing cognitive deficits or dementia, delirium (and its underlying causes) only serve as a catabolic agent, leading to an acceleration of normal physiological cerebral aging mechanisms leading to dementia.
5. It is also possible that an episode of delirium simply unmasks subtle cognitive deficits already present, although not yet identified.

Source: (Maldonado 2008a, b, 2013)

erated by younger individuals (Maldonado 2013). Patients with compromised cognitive ability prior to surgery are at greater risk to develop postoperative delirium (Inouye et al. 1998; Litaker et al. 2001; McNicoll et al. 2003; Benoit et al. 2005; Franco et al. 2010; Tognoni et al. 2011). Even subtle deficits in attention or executive function (e.g., problem solving, processing speed, planning, complex sequencing, and reasoning), in the absence of frank cognitive impairment, closely associate with postoperative delirium independent of other risk factors (Rudolph et al. 2006; Lowery et al. 2007; Smith et al. 2009). Similarly, preoperative MMSE scores have been found to be an independent predictor of postoperative delirium (Kalisvaart et al. 2006). A study of elderly subjects undergoing orthopedic surgery demonstrated an increased incidence of postoperative delirium, depending on whether patients suffered from dementia or not (100 % vs. 32 %) (Wacker et al. 2006). Similarly, nearly 70 % of elderly patients admitted to a specialized "delirium ward" carried the diagnosis of "cognitive disorder"—either dementia or mild cognitive impairment (Wahlund and Bjorlin 1999).

Conversely, studies have demonstrated that among elderly surgical patients, delirium is a strong independent predictor of cognitive impairment and the occurrence of severe dependency in activities of daily living. In fact, 38 months after discharge from hospital, 53.8 % of the surviving patients with postoperative delirium continue to experience cognitive impairment, as compared to only 4.4 % of the non-delirious subjects.(Bickel et al. 2008) In some of the studies, the long term outcomes (e.g., mortality, nursing home placement, cognition, function) of patients with persistent delirium were consistently worse than the outcomes of patients who had recovered from delirium (Cole et al. 2009). Similarly, a prospective matched controlled cohort study of elderly hip surgery patients demonstrated that the risk of dementia or mild cognitive impairment (MCI) over a 30-months follow-up almost doubled in inpatients with postoperative delirium compared to those without delirium (Kat et al. 2008). These findings suggest that delirium does not simply persist for a certain time but also predicts a future cognitive decline with an increased risk of dementia.

The relationship between cognitive deficits and dementia seems to be reciprocal, with episodes of delirium causing the development of a new cognitive or accelerated the course of a preexisting dementing process. Data suggests that among the elderly, there is a significant acceleration in the slope of cognitive decline in patients with Alzheimer's disease (AD) following an episode of delirium (Fong, Jones et al. 2009). In fact,

a substantial proportion of delirium survivors are left with post-delirium cognitive impairment (Wacker et al. 2006; Griffiths and Jones 2007; Bickel et al. 2008; Kat et al. 2008; Maldonado 2008a, b; Fong et al. 2009; MacLullich et al. 2009; Girard et al. 2010).

Among medically ill, elderly subjects, those suffering from baseline dementia and developing prevalent or incident delirium during the first week of hospitalization were found to meet persistent delirium criteria at discharge (39 %), 6 (38.5 %) and 12-month (48.9 %) follow-ups, compared to only 11.1, 8.8 and 14.8 % of non-demented subjects (McCusker et al. 2003). Another study found that only 4 % of delirious patients experienced full resolution of all symptoms of delirium before discharge from the hospital; with an additional 20.8 and 17.7 % of subjects experiencing symptom resolution by 3 and 6 months after hospital discharge (Levkoff et al. 1992).

Studies have demonstrated a consistent relationship between delirium and post-delirium cognitive decline (Macdonald 1999; Rockwood et al. 1999; Jackson et al. 2004; MacLullich et al. 2009). A study in an elderly orthopedic population found that among those experiencing postoperative delirium the risk of mild cognitive impairment (MCI) or dementia was almost doubled that of non-delirious subjects (Kat et al. 2008). Another study in the same population showed that up to 53.8 % of patients who developed postoperative delirium continue to experience cognitive impairment 38 months after hospital discharge, compared to only 4.4 % of the non-delirious subjects (Bickel et al. 2008). These studies and others also suggest that delirium duration was also independently associated with long-term cognitive outcome (i.e., the longer the duration of delirium the more significant the cognitive deficits). For example, an increase in the length of delirium from 1 to 5 days was independently associated with nearly a 5-point decline (i.e., a one-half SD decline) in the cognitive testing scores (Girard et al. 2010).

These findings raise questions regarding whether prevention of delirium might ameliorate or delay cognitive decline in patients at risk, particularly those with dementing processes.

13.3 Management of Major Neurocognitive Disorder

13.3.1 Treatment of Behavioral and Psychological Symptoms of MNCD (BPS-MNCD)

Consultation-liaison psychiatrists, especially in inpatient settings, are often consulted for treatment of behavioral symptoms of patients with MNCD, since these symptoms not only contribute to patient suffering, but also place significant burden on caregivers, and are not an uncommon reason for bringing these patients to the emergency rooms.

Aggression and nonaggressive agitation occur in approximately 20 % of people with AD living in community, and in 40–60 % of those who live in care facilities (Ballard and Corbett 2013). Delusions and hallucinations are present in 25 % of people with MNCD in clinical settings, while depression occurs in 20–30 % of people with AD (Ballard et al. 2009; Enache et al. 2011). In patients with Lewy-Body and Parkinson's disease-associated MNCD (PD-MNCD), visual hallucinations, delusions and depression are even more significantly frequent as compared to AD patients, and visual hallucinations are also significantly more intense and persistent (Ballard et al. 2009). Depression is significantly more frequent and persistent in patients with VaD than in AD (Ballard et al. 2009).

While agitation manifests as restlessness, pacing, excessive fidgeting, shouting, and screaming, aggression is usually characterized by verbal insults, hitting, biting and throwing objects, and can be particularly common during personal care (Ballard and Corbett 2013). In almost all individuals, agitation and aggression significantly affect their daily lives, are distressing to individuals themselves and their caregivers, and serve as a significant factor in placement of these patients in institutionalized care facilities (Ballard and Corbett 2013).

When these patients come to the attention of physicians, it is important to (1) identify target symptoms, (2) pursue and address etiology of

behavioral disturbance, (3) employ behavioral approaches, and, if all fails, (4) apply pharmacological interventions. When choosing pharmacological interventions, it is important to identify specific psychiatric symptoms to address in patient's presentation: aggression, psychosis, depression, mania or spontaneous disinhibition. The differential of the etiologies leading to a patient's behavioral dysregulation can be broad and includes medical etiologies leading to delirium (e.g., urinary tract infection, poor oxygenation, pneumonia, encephalitis, meningitis, and dehydration), neurological causes (e.g., seizure, cerebrovascular accident, and tumor), exacerbation of primary psychiatric illness, pain which is often poorly communicated, changes in environment and psychosocial stressors, sensory disturbances (e.g., cataract, hearing loss), and finally Behavioral and Psychiatric Symptoms of Dementia (BPSD). Pain and dehydration are not uncommon contributors to agitation and aggression. While assessment of pain may be difficult in patients with MNCD, a thoughtful approach to its management has been shown to significantly reduce agitation in patients with MNCD (Husebo et al. 2011).

13.3.1.1 Depression in Patients with MNCD

Early and late-life depression has been found to be a risk factor and a prodrome for development of MNCD (Enache et al. 2011). Moreover, approximately 20–30 % of patients with AD have depression (Enache et al. 2011). The proportion seems to be relatively similar across MNCD stages and is higher in patients with vascular depression (VaD) and Lewy Body disease than in Alzheimer's disease (Enache et al. 2011).

The pharmacological treatments for depression in demented patients have not shown consistent benefit. In a Cochrane review (Bains et al. 2002) on the effect of antidepressants for depression in MNCD, only 4 studies with a total of 137 participants reported sufficiently detailed results to enter into meta-analysis. The authors concluded that the evidence offered weak support for the hypothesis that antidepressants are effective for patients with depression and MNCD. They pointed out that the medications are not "necessarily ineffective but rather that there is not much evidence to support their efficacy."

In another meta-analysis based on seven studies with a total of 299 patients, neither response rates (OR 2.12, 95 % CI 0.95–4.70) nor remission rates (OR 1.97, 0.85–4.55) were significant enough between placebo and active treatment (Nelson and Devanand 2011). Thus the authors concluded that the evidence for antidepressant treatment of people with depression and MNCD, although suggestive, did not confirm efficacy. Of note, the studies were underpowered to detect the differences. A recent review of the topic that included in their own analysis 11 randomized placebo-controlled drug trials for depression associated with MNCD, with a total of 1,514 patients, noted that five studies reported that the antidepressant was more effective than placebo (sertraline, clomipramine, maprotiline, moclobemide, citalopram), whereas six were negative (sertraline, mirtazapine, venlafaxine, imipramine, fluoxetine, and estrogen replacement therapy) (Enache et al. 2011). Finally, the largest to date trial on antidepressants in patients with MNCD, Health Technology Assessment Study of the Use of Antidepressants for Depression in Dementia (HTA-SADD) enrolled 326 patients with probable or possible Alzheimer's disease and randomized them to placebo, mirtazapine, or sertraline (Banerjee et al. 2011). The investigators did not find difference in efficacy between three treatment groups as monitored via scores on Cornell scale for depression in dementia (CSDD), but noted more side effects in both treatment groups.

Electroconvulsive therapy (ECT) is the most effective treatment for depression, but few studies have been performed in patients with MNCD. Current evidence suggests that ECT might be an effective treatment for depression in MNCD, although the relatively small number of controlled studies makes the comparison of effectiveness between healthy non-geriatric patients and those with MNCD difficult (Oudman 2012). Of course, there is at least theoretical concern that cognitive side effects of ECT might further worsen cognitive impairment of MNCD. In one study, depressed patients with

mild cognitive impairment or MNCD had a similar improvement of depression as compared to subjects with normal cognition (Hausner et al. 2011). In all three groups, initial non-significant cognitive worsening was followed by cognitive improvement. In patients with mild cognitive impairment, the cognition actually improved 6 months after ECT compared with baseline, and a similar but non-significant improvement was noted in patients with MNCD, with significant improvement among those taking anti-MNCD drugs. Thus, ECT might be considered in patients with MNCD and medication-resistant severe depression.

13.3.1.2 Treatment of Agitation/Psychosis as a Part of Behavioral and Psychiatric Symptoms of Dementia (BPSD)

Agitation, aggression and psychotic symptoms of dementia cause tremendous suffering and place significant burden on caregivers. There have been a variety of non-pharmacological interventions studied to address these symptoms. They have included resource demanding treatments, such as intensive 6–12-month programs educating staff in person-centered care as a first line management to less intensive treatments such as "validation therapy and reminiscence," structured social interaction, personalized bathing and music, and aromatherapy (Ballard et al. 2009). The findings from a large open trial suggested that social interaction confers benefit even when delivered in a simplified form for as little as 10 min per day by a care assistant (Ballard et al. 2009). A recent meta-analysis of 23 studies found that non-pharmacological interventions delivered by family caregivers, consisting of 9–12 sessions tailored to the needs of the person with MNCD and the caregiver in the home using multiple components, have the potential to reduce the frequency and severity of BPSD with effect sizes at least equaling those of pharmacotherapy, as well as to reduce caregivers' adverse reactions (Brodaty and Arasaratnam 2012). In a meta-analysis of 40 studies of non-pharmacological interventions in long-term care facilities, 40 % of included studies reported statistically significant results in favor of non-pharmacological interventions on at least one measure of neuropsychiatric symptoms (NPS), with interventions including staff training in NPS management strategies, mental health consultation and treatment planning, exercise, recreational activities, and music therapy or other forms of sensory stimulation (Seitz et al. 2012). Of course, these interventions often require a lot of resources inside and outside the facilities. Moreover, many of the studies had methodological limitations that placed them at potential risk of bias. Although it is important to know and appreciate non-pharmacological interventions, when psychiatric consultation is requested, it is often a matter of behavioral emergency.

13.3.1.2.1 Antipsychotics

The limitation of the non-pharmacological interventions, lack of appropriate resources, and often the acute need to stabilize the behavior in inpatient setting leads to CL psychiatrists employing pharmacological means to address agitation and psychosis in patients with MNCD. At this time, there are no FDA approved treatments for agitation or psychosis in MNCD. Of interest, in Germany, risperidone does carry the approval for this indication.

Antipsychotics are often thought to be the first-line treatment, but it is important to appreciate their limited effectiveness and significant risks associated with their use.

Conventional antipsychotics have been among first agents used for treatment of agitation and aggression in patients with MNCD. Eleven RCTs, mostly small in size and over 4–12 weeks, have shown a significant but modest improvement compared with placebo, with haloperidol holding the most comprehensive evidence base for treatment of aggression, but not agitation (Ballard and Corbett 2013). Of course, these agents come with significant risks, such as parkinsonism, dystonia, tardive dyskinesia, acceleration of cognitive decline and prolongation of the QTc interval on electrocardiogram (ECG), leading to added risk of cardiac arrhythmias, and thus have been mostly replaced by atypical

antipsychotics which have perceived improved tolerability (Ballard and Corbett 2013).

The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease(CATIE-AD) study was a randomized control trial of 421 patients with Alzheimer's disease and symptoms of psychosis, aggression, or agitation, who were randomized to olanzapine, quetiapine, risperidone, or placebo and followed for up to 36 weeks (Schneider et al. 2006). The trial demonstrated no difference in primary effectiveness outcome of the time to treatment discontinuation for any reason: olanzapine (median, 8.1 weeks), quetiapine (median, 5.3 weeks), risperidone (median, 7.4 weeks), and placebo (median, 8.0 weeks) ($P = 0.52$). Of note, the times to treatment discontinuation due to lack of efficacy were longer in the olanzapine group (22.1 weeks) and risperidone group (26.7 weeks) as compared to the placebo group (9 weeks). On the contrary, the time to discontinuation due to intolerance, adverse effects, or death favored the placebo arm.

In a meta-analysis by Schneider of 15 trials with atypical antipsychotics (olanzapine, risperidone, aripiprazole, quetiapine) of 3,353 patients randomized to drug and 1,757 to placebo, there was a small but significant improvement on rating scales for risperidone and aripiprazole, but not for olanzapine (Schneider et al. 2006). Smaller effects were observed for less severe MNCD, outpatients, and patients selected for psychosis. One third of the patients dropped out across the groups. The side effects included somnolence, urinary tract infections, or incontinence across drugs; extrapyramidal side effects or abnormal gait with risperidone or olanzapine; and importantly worsening of cognitive tests for all drugs. There was significant risk for cerebrovascular accidents (CVAs) (OR 2.13) with 1.9 % of events in the medication group as compared to 0.9 % in the placebo group. Risperidone had the greatest risk for CVA with OR of 3.43, with 3.1 % versus 1.0 % pooled. The authors concluded that "antipsychotics are modestly effective when used judiciously and there are no demonstrated, effective pharmacologic alternatives."

The 2006 Cochrane review that deemed only nine RCTs to have sufficient data to be included in meta-analysis (Ballard and Waite 2006), concluded that risperidone and olanzapine had small, but significant effects on treatment of aggression and risperidone only—for treatment of psychosis. Risperidone- and olanzapine-treated patients had higher rates of cardiovascular events, extra-pyramidal side effects, other adverse outcomes and were associated with significant increase in drop-outs.

In agreement with previous findings, a more recent meta-analysis of 18 placebo-controlled trials, concluded that aripiprazole, olanzapine, and risperidone, but not quetiapine, had small but statistically significant benefits for global behavioral symptom scores associated with MNCD in elderly patients, with aripiprazole and risperidone having significant effects on psychosis and all three agents on agitation (Maher et al. 2011).

The use of antipsychotics for treatment of behavioral symptoms in patients with MNCD has become controversial since an initial 2003 warning by Food and Drug Administration (FDA) regarding increased risk of cerebrovascular adverse events including stroke in MNCD patients treated with risperidone, extending to similar warnings for other antipsychotic medications and culminating with 2005 warning highlighting a significant increase in mortality risk (OR 1.7) for this population, based on 17 placebo-controlled studies of six atypical antipsychotics versus placebo.

Schneider reviewed the evidence on the association of mortality and antipsychotic use in this patient population from 15 of these trials (9 unpublished), generally 10–12 weeks in duration, including 3 trials with aripiprazole, 5 trials with olanzapine, 3 trials with quetiapine, and 5 trials with risperidone with a total of 3,353 patients randomized to study drug and 1,757 randomized to placebo (Schneider et al. 2005). The meta-analysis confirmed a significant increase in mortality (OR 1.54) with the absolute risk difference of 1–2 % between antipsychotic- and placebo-treated patients and with no difference between specific agents.

Studies have also demonstrated that conventional antipsychotics might have even greater risk of death in this patient population. For example in a retrospective cohort study by Wang and colleagues of patients aged 65 years and older with drug insurance benefits in Pennsylvania and first prescribed antipsychotic drug, the mortality was greater for those patients prescribed conventional antipsychotics as compared to atypical (OR 1.27–1.56) (Wang et al. 2005). The greatest increase in risk of death for conventional as compared with atypical antipsychotics occurred with higher doses and during the first 40 days after treatment initiation. The limitations of the study included the fact that these patients were not officially diagnosed with MNCD.

In another population-based cohort study of 75,445 new users of antipsychotic drugs (haloperidol, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone), aged 65 and older and living in nursing homes, 180-day risk of mortality as compared for risperidone was more than doubled for haloperidol (HR 2.07) and slightly lower for quetiapine (HR 0.81) (Huybrechts et al. 2012). The effects were noted to be strongest shortly after the start of treatment and in response to increased dose.

It has also been shown that the mortality risk further increases with continued use of antipsychotics. In the MNCD antipsychotic withdrawal trial (DART-AD), patients from UK care facilities were randomized to continue the antipsychotic ($N=64$) (thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone) for 12 months or be switched to the placebo ($N=64$) (Ballard et al. 2009). There was an impressive reduction in survival in patients who continued to receive antipsychotics compared with those who received placebo: at 12 months, 70 % in the continue treatment group survived as compared to 77 % in the placebo group; at 24 months, the difference was 46 % versus 71 %; and at 36 months, it was 30 % versus 59 %.

However, there is also emerging evidence indicating that it is psychosis and not antipsychotics, either conventional or atypical, leading to increased mortality in this patient population. In fact, in a study of 957 patients with diagnosis of probable AD where 241 patients (25 %) were exposed to antipsychotics (conventional, $N=138$; atypical, $N=95$; both, $N=8$), only conventional antipsychotics were associated with the time to admission to the nursing home and this association was no longer significant after adjustment for the severity of psychiatric symptoms (Lopez et al. 2013). The study found that psychosis was strongly associated with nursing home admission and time to death, but neither conventional nor atypical antipsychotics were associated with time to death.

A recent 2013 Cochrane review on withdrawal of long-term antipsychotics including nine trials with 606 randomized participants indicated that only one of these trials with patients with psychosis or agitation who had responded well to risperidone therapy for 4–8 months, reported that discontinuation led to an increased risk of relapse (Declercq et al. 2013). The only pooled outcome (full NPI score) used in two studies, had no significant difference between people withdrawn from and those continuing on antipsychotics at 3 months. In both studies, there was evidence of significant behavioral deterioration in people with more severe baseline NPS who were withdrawn from antipsychotics.

Of likely importance is that the use of second-generation antipsychotics was also associated with a small but significant effect on caregiver burden (Mohamed et al. 2012) and this is likely to contribute to continued frequent use of the medications.

In conclusion, given that the pharmacological interventions are limited, it is important to consider risks versus benefits of the treatment with antipsychotics for behavioral symptoms of MNCD in each patient and advise of these benefits and risks the patient and their family. If treatment with antipsychotic is warranted, it is imperative to continue treatment short-term and attempt to taper off this medication at most 12 weeks after initiation.

13.3.1.2.2 Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors have also shown promise in decreasing behavioral symptoms, in particular that of agitation, in MNCD. Several

meta-analyses demonstrated a small but significant overall advantage of cholinesterase inhibitors (ChEIs) over placebo with regard to the treatment of behavioral and psychiatric symptoms (BPSD) in AD (Trinh et al. 2003; Rodda et al. 2009). Moreover, in a randomized withdrawal study, cessation of donepezil was associated with a significant worsening of the total Neuropsychiatric Inventory (NPI) score within 6 weeks (Holmes et al. 2004). In addition, while there was no short-term benefit for treatment of clinically significant agitation with donepezil over 12 weeks in a large RCT (Howard et al. 2007), an ad hoc analysis of 978 patients randomized to galantamine or placebo demonstrated that patients with behavioral symptoms at baseline had significant reduction (29–48 %) in aberrant motor behavior, agitation, and anxiety (Cummings et al. 2004). In addition, it demonstrated concomitant decrease in caregiver-reported distress.

Trials of rivastigmine in Lewy Body disease and Parkinson's disease dementia (McKeith et al. 2000; Emre et al. 2004) also indicate a significant improvement in BPSD over 6 months in treated individuals. Since there is significant cholinergic deficiency in Lewy Body disease which might even mediate hallucinations, acetylcholinesterase inhibitors might be especially helpful in treatment of psychotic symptoms in this patient population. On the contrary, in frontotemporal dementia (FTD), the cholinergic system is likely intact and so far, the evidence for use of acetylcholinesterase inhibitors for treatment of behavioral symptoms in FTD is questionable (Manoochehri and Huey 2012).

13.3.1.2.3 NMDA Antagonists

Memantine, a NMDA-antagonist has some encouraging evidence for its ability to treat agitation and aggression in MNCD, supported by findings from individual studies, meta-analyses, and pooled analyses (Gauthier et al. 2005, 2008; McShane et al. 2006), but little RCT evidence. While a recent RCT did not show benefit of memantine in controlling agitation in moderate to severe MNCD over 12 weeks (Fox et al. 2012), a post hoc analysis (Wilcock et al. 2008) and a recent RCT (Howard et al. 2012) have suggested that memantine may be of value in reducing the emergence of overall behavioral and psychiatric symptoms.

Thus, the current evidence indicates that memantine may confer benefit in the prevention and treatment of mild-to-moderate agitation and aggression in longer-term use.

13.3.1.2.4 Antidepressants

Evidence for the use of antidepressants is promising and growing. A Cochrane review on the subject including nine trials with a total of 692 individuals with five studies comparing selective serotonin inhibitors (SSRIs) to placebo, found overall significant difference between antidepressants and placebo on measures of agitation on Cohen-Mansfield Agitation Inventory (CMAI) total score and good tolerability (Seitz et al. 2011). It concluded that although there are "relatively few studies …, the SSRIs sertraline and citalopram were associated with a reduction in symptoms of agitation compared to placebo in two studies. Both SSRIs and trazodone appear to be tolerated well when compared to placebo, typical and atypical antipsychotics." In particular, a 12-week RCT of 103 non-depressed patients with MNCD hospitalized secondary due to behavioral symptoms, including aggression, agitation, hostility, suspiciousness, hallucinations, and delusions, and randomized to citalopram versus risperidone, demonstrated similar improvement in symptoms of agitation and psychosis with both medications much better tolerability of citalopram (Pollock et al. 2007). The results from the recent "Citalopram for Agitation in Alzheimer Disease Study" (CitAD) support the usefulness of SSRIs in the long-term management of agitation in dementia (Porsteinsson et al. 2014). In this randomized, double-blind, placebo-controlled study, patients with probable AD ($N = 186$) were randomized to receive either citalopram (up to 30 mg) or placebo for 9 weeks. Patients in the citalopram group showed significant improvement (compared to placebo) on both primary outcome measures: the Neurobehavioral Rating Scale agitation subscale (NBRS-A) and the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change

(mADCS-CGIC). In fact, using mADCS-CGIC, 40 % of citalopram participants had moderate or marked improvement from baseline compared with only 26 % of those on placebo(odds ratio [OR] 2.13 (95 % CI, 1.23–3.69), $P=0.01$). Moreover, caregivers of patients in the citalopram group reported less distress. Unfortunately, the use of citalopram was associated with worsening of cognition (−1.05 points Mini Mental Status Examination (MMSE); 95 % CI, −1.97 to −0.13; $P=0.03$) and QT interval prolongation (18.1 ms; 95 % CI, 6.1–30.1; $P=0.01$). Similarly, trazodone has been shown to be effective in decreasing agitation in patients with FTD (Lebert et al. 2004).

Both acetylcholinesterase inhibitors and SSRIs might be reasonable medications for long-term treatment of agitation and possibly psychotic symptoms in patients with MNCD. It might be reasonable to use an antipsychotic agent initially to control acute symptoms, while initiating and optimizing long-term agents, such as acetylcholinesterase inhibitors and/or SSRI's. Our clinical experience suggests that having optimal doses of both an acetylcholinesterase inhibitor and an SSRI facilitates the tapering off antipsychotic agents, maximizes control of behavioral symptoms, and minimizes side effects.

13.3.1.2.5 Anticonvulsants

There have been two studies of showing effectiveness of carbamazepine in reduction of aggression and one study of oxcarbazepine. The use of these agents, especially the former, is associated with significant side effects and drug–drug interactions. Although valproic acid (VPA) seemed to be promising (Konovalov et al. 2008), as of yet there is no evidence that it is effective. The latest Cochrane review does not support the use of VPA for agitation in demented patients (Lonergan and Luxenberg 2009). However, there are certainly individual patients who can benefit from the thoughtful use of this medication, especially when other agents are not effective or contraindicated.

There is emerging, but still limited, evidence, supporting use of low-dose gabapentin in the management of agitation in patients with MNCD (Kim et al. 2008; Cooney et al. 2013). The benefits of gabapentin include absence of hepatic metabolism, although sedation may be a significant side effect, and thus its use has to very cautious.

13.3.1.2.6 Melatonin

Since there seems to be a relationship between decline in melatonin function and behavioral symptoms in MNCD (Jansen et al. 2011), various studies have investigated melatonin's effects on neurobehavioral symptoms. While some trials have supported melatonin's usefulness (Asayama et al. 2003), others have not (Gehrman et al. 2009). A Cochrane review analyzed five clinical trials and concluded that while there was no evidence to support the effectiveness of melatonin for cognitive impairment, it demonstrated significant improvements in psychopathologic behavior and mood (Jansen et al. 2011).

13.4 Conclusion

MNCD is common and has profound effects on the quality of life of those affected and their families. Psychiatrists are often consulted in the management of behavioral and psychological symptoms of MNCD and thus it is imperative that they are familiar with the literature behind the effectiveness and risks associated with so far limited treatments.

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Anxiety and Anxiety Disorders

14

Hoyle Leigh

Contents

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14.1 Vignettes

1. An emergency psychiatric consultation was requested for a 48-year-old man who was admitted to the coronary care unit (CCU) with massive myocardial infarction (MI). He was reported to be acutely agitated, and he wanted to sign out against medical advice. The reason for consultation was to determine the patient's competence to sign out. When the consultant arrived in the CCU, a number of staff members were surrounding the patient as he attempted to exit the cubicle. He shouted, "I want to get out! You cannot hold me here!"

   The consultant told him, "I am a psychiatrist, and I am here to help you. I think it might be possible for you to leave if you wish, but I need to speak with you first."

   "Not here, not in this room!" replied the patient.

   "OK, would it be OK if we talked in the waiting room?"

   The patient agreed. He was placed in a gurney and wheeled to the waiting room.

   The consultant said, "Since you became quite anxious and flushed, I would like the nurse to give you a sedative to help you relax as we talk." Lorazepam 1 mg IV was administered, which calmed the patient considerably. In the interview, the consultant learned that the patient became panicky when he was rushed into the particular cubicle in the CCU, as it was the same cubicle in which his father

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had died of an MI some 4 months prior to the patient's own admission. The patient was convinced that he would die in that cubicle just as his father did. When the patient was offered another cubicle, he gladly accepted it without any hesitation. He recovered uneventfully.

2. A 73-year-old woman was admitted for pain in the lumbar area associated with a mass found on a computed tomography (CT) scan. She had a history of major depression in the past but was currently on no medications. A psychiatric consultation was requested as the staff thought the patient was depressed. The patient denied current depression, but admitted to having insomnia and panicky feelings. She was a retired executive, who had "always been on top of things." The patient felt quite apprehensive and out of control as she did not know what was happening to her physically. She stated that the doctors did not explain anything to her, saying only that they needed to do more tests. She was afraid to ask questions because she felt that the doctors were withholding information from her so as to not upset her. When the consultant asked her if she would like the doctors to explain to her exactly what they found and what they were planning to do, she agreed. It turned out that the doctors had not yet found the time to have an in-depth conversation with the patient simply because they had been busy with other patients, not because they were afraid of upsetting her. In fact, the mass turned out to be benign and the patient was discharged without any antidepressant or antianxiety medications.
3. Psychiatric consultation was requested for a 34-year-old man who had undergone a magnetic resonance imaging (MRI) scan and panicked while he was positioned in the narrow confines of the imaging apparatus. On examination, the patient turned out to have claustrophobia. As the MRI was a medical necessity, lorazepam 2 mg po was administered 30 min prior to the next scheduled MRI. Though apprehensive, he was able to complete the MRI scan.

14.2 Anxiety: General Considerations

14.2.1 The Function of Anxiety

The most prominent subjective features of anxiety are *fear, a sense of dread,* and *apprehension*. This fearful feeling is usually vague and diffuse, but it may also focus on a specific idea, such as fear of dying, or of cardiac arrest, or of having a serious disease such as cancer. It may also arise under specific situations, such as being in closed spaces, as in the final vignette cited above. Physiological changes are part of anxiety. They are mediated by activation of the sympathetic outflow and of the hypothalamic-pituitary-adrenal (HPA) system. Thus, the manifestations may include rapid pulse, increased blood pressure, excessive sweating, changes in bowel function, changes in appetite, trouble sleeping, and difficulty breathing. Subjective feelings of dread and fear accompanied by symptoms and signs of appropriate physiologic changes indicate the presence of anxiety. The brain structures associated with anxiety include the sensory and association cortices for processing the anxiety signal, the limbic system, particularly the amygdala and the anterior cingulate gyrus, the reticular activating system, and locus ceruleus (see Chap. 7).

Anxiety clearly has adaptive value both for the individual and in an evolutionary sense. Fear is essential in learning to avoid dangerous situations. Fear with associated physiologic arousal, when followed by resolution through mastery, such as successfully avoiding or overcoming the feared object, can also be associated with pleasure and euphoria, explaining thrill-seeking behavior. Genes coding for a low threshold for anxiety and fear, like a sensitive smoke detector, might have conferred survival advantage for our ancestors who needed to be fleet on their feet to avoid predators (see Chap. 7). In the modern age, individuals endowed with such genes might be diagnosed with a generalized anxiety disorder (Nesse 2001). Certain genetic polymorphisms, such as the serotonin transporter promoter gene

(5HTTLPR) short allele may code for a constitutional proneness for anxiety (Caspi et al. 2010; Ernst et al. 2013; Uher et al. 2011) (see Chap. 7).

Anxiety has an inverted U relationship with task performance. Too little anxiety results in little motivation and a lackluster performance, whereas too much anxiety leads to paralysis. Mild and transient, barely perceptible anxiety may arise when a stimulus has the potential to reactivate a long-standing psychological conflict that may result in overwhelming anxiety. Such anxiety, called *signal anxiety*, activates automatic psychological defense mechanisms (somewhat akin to a thermostat), such as denial, repression, projection, rationalization, and sublimation, that ward off the perception of the stimulus or its connections to the conflict.

14.2.2 Dysregulation of Anxiety

Anxiety is considered pathologic if it is uncontrollably excessive or persistent so as to affect one's functioning. Such dysregulation of anxiety may occur at several levels: genes, gene x environment interaction in childhood, and recent and current stress, both psychosocial and biological. The final common pathway brain dysfunction in the anxiety circuits underlies the anxiety syndrome (see Chap. 7).

14.3 Anxiety Syndromes

Anxiety disorders are the most common psychiatric condition. The 12-month prevalence estimate of anxiety disorders ranges from 4 to 17 %, and the lifetime prevalence ranges from 9 to 29 % (Somers et al. 2006). Anxiety disorders are more common in females than males (2:1 ratio). People seeking treatment for physical conditions have a higher than expected rate of anxiety disorders. A World Health Organization (WHO) study of 14 countries found a mean 1-month prevalence rate of 7.9 % of generalized anxiety disorder for patients presenting at a primary care clinic (Maier et al. 2000). Another recent WHO study of 17 countries found a positive linear relationship between the number of pain conditions and the rate of combined anxiety disorder (Gureje et al. 2008; Jordan and Okifuji 2011)

A childhood diagnosis of separation anxiety disorder significantly increases the risk of any later anxiety disorder (Kossowsky et al. 2013).

14.3.1 Secondary Anxiety Symptoms and Syndromes

In the consultation-liaison (CL) setting, secondary anxiety syndromes are quite common and should be considered first in diagnosing the anxious patient. Anxiety may be secondary to the stress of hospitalization itself, to the apprehension associated with a serious diagnosis or with procedure such as surgery, or to the biochemical changes secondary to the biochemical changes caused by the medical disease or by the drugs to treat the disease. Patients' lack of information concerning the illness and proposed treatment is another very common cause of anxiety. See Table 7.1 in Chap. 7 for a list of medical diseases that may underlie psychiatric syndromes.

Anxiety symptoms are particularly common in endocrine/metabolic disorders, such as hyperthyroidism, Cushing's syndrome, hypoglycemia, and hypocalcemia. They may also occur in certain neoplasms, particularly pheochromocytoma and carcinoid tumors as well as tumors of the CNS. Delirium and drug withdrawal states are almost always associated with anxiety. Pain is also an important concomitant of anxiety.

The stress of a serious medical disease or of hospitalization tends to heighten the underlying personality traits of an individual. Thus, a patient who has an anxious personality will experience even greater anxiety and may develop general anxiety or phobic symptoms, and an obsessive-compulsive personality may develop heightened obsessive-compulsive symptoms.

Differential Diagnosis of Anxiety Syndromes

1. Secondary Contributing Factors
   (a) Substances (adverse effects, intoxication, withdrawal)
      - Prescribed Drugs
      - Recreational Substances
   (b) Medical Diseases
2. Primary Anxiety Disorders

14.3.2 Primary Anxiety Disorders

Once secondary anxiety has been either ruled out or considered as a contributing but not primary factor, the presence of primary anxiety syndrome should be considered. Primary anxiety syndrome usually antedates the illness for which the patient is being treated, though it may be exacerbated by the illness or the stress of hospitalization.

DSM-5 classifies anxiety disorders as below:

Separation Anxiety Disorder
Selective Mutism
Specific Phobia
  Animal
  Natural environment
  Blood–injection–injury
  Fear of blood
    Fear of injections and transfusions
    Fear of other medical care
    Fear of injury
  Situational
  Other
Social Anxiety Disorder (Social Phobia)
Panic Disorder
Agoraphobia
Generalized Anxiety disorder
Substance/Medication-Induced Anxiety Disorder
Anxiety Disorder Due to Another Medical Condition
Other Specified Anxiety Disorder
Unspecified Anxiety Disorder

14.3.2.1 Separation Anxiety Disorder (SAD)

Predominantly a disorder of childhood and adolescence, this is characterized by developmentally inappropriate and excessive fear or anxiety concerning separation from the person(s) to whom the patient is attached. There is often recurrent excessive distress in anticipation of separation, persistent and excessive worry about losing the attachment figure, persistent and excessive worry about an untoward event (e.g., accident, abduction) that may cause a loss or separation, persistent reluctance to go out away from home for fear of separation, persistent or excessive fear of being alone, repeated nightmares involving the theme of separation, and repeated physical symptoms when separation from an attachment figure occurs or is anticipated. According to DSM-5, at least three of the above, and a duration of 4 weeks for children and adolescents and of 6 months for adults as well as clinically significant distress or impairment in social, academic, occupational, or other important functioning is required for the diagnosis.

According to DSM-5, the 12-month prevalence for adults is 0.9–1.9 %; in children, 4 %, and in adolescents, 1.6 %. Separation anxiety disorder is the most prevalent anxiety disorder in children under 12 years of age.

Separation anxiety disorder has high comorbidity with other anxiety disorders, obsessive-compulsive disorder, as well as depression and bipolar disorder.

Twin and family studies show a genetic contribution to SAD. Behavioral inhibition, which is a heritable temperamental characteristic, seems to be predictive of anxiety disorders in later childhood. (Hanna et al. 2006) Genetic influences may be greater for girls while shared environmental influences may be greater for boys. SAD seems more common in the siblings of children who have SAD and in the offspring of women who have anxiety or depressive disorders. Offspring of parents who have panic disorder have been shown to have a threefold increased risk of SAD, while offspring of parents who have panic disorder plus major depressive disorder have more than a tenfold increased risk.

Childhood anxiety disorders, particularly SAD, exhibit many of the respiratory abnormalities characteristic of adult panic disorder (Battaglia et al. 2009). These and other findings suggest that certain childhood anxiety disorders may share pathophysiologic features with adult panic disorder and that parents who have panic disorder may transmit a diathesis for some forms of anxiety that is observable in the respiratory system (Aschenbrand et al. 2003). In addition to genetic factors, developmental factors such as insufficient habituation, and the lack of safe environment and parental coping mechanisms of avoidance may contribute to the development of SAD.

14.3.2.2 Selective Mutism

Children with selective mutism do not initiate speech or respond to others when spoken to. Such children will speak with immediate family members at home but often not even in front of close friends or relatives (DSM-5). Children with selective mutism often refuse to speak in school, resulting in academic impairment. This condition may be accompanied with excessive shyness.

Selective mutism is a relatively rare condition, with prevalence of less than 1 %.

The onset is usually before age 5, and the course is variable, with most "outgrowing" the condition but many with social anxiety may continue to experience it.

Comorbidities include other anxiety disorders, especially social anxiety. Others include enuresis, encopresis, obsessive-compulsive disorder, depression, premorbid speech and language abnormalities, developmental delay, and Asperger's disorders (Wong 2010).

14.3.2.3 Specific Phobia

Specific phobias consist of marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation such as particular animals, heights, thunder, darkness, flying, being in closed spaces, urinating or defecating in public toilets, eating certain foods, undergoing dental work, the sight of blood or injury, and the fear of exposure to specific diseases. The onset is usually in childhood or early adulthood. The seriousness of the condition depends on how easy it is for the patient to avoid the phobic situation. Disease phobias (e.g., HIV/AIDS, radiation sickness) and needle phobias are common in CL settings. The phobic object may be a conditioned stimulus to fear.

Specific phobias are relatively common, up to 10 % of general population. Functional neuroimaging using symptom provocation paradigms show abnormal activations in brain areas involved in emotional perception and early amplification, mainly the amygdala, anterior cingulate cortex, thalamus, and insula. The insula, thalamus, and other limbic/paralimbic structures are particularly involved in specific phobias with prominent autonomic arousal. Emotional modulation is also impaired after exposure to phobic stimuli, with abnormal activations reported for the prefrontal, orbitofrontal, and visual cortices. Other cortices and the cerebellum also appear to be involved in the pathophysiology of this disorder (Del Casale et al. 2012).

DSM-5 lists the following specific phobias.

Animal (e.g., ailurophobia—cats, arthrophobia—insects, arachnophobia—spiders, ophidiophobia—snakes, misophobia—germs)
Natural environment (e.g., acrophobia—height, aquaphobia—water)
Blood-injection-injury
  Fear of blood
  Fear of injections and transfusions
  Fear of other medical care
  Fear of injury
Situational (e.g., claustrophobia—closed space, aviophobia—flying)
Other

14.3.2.4 Social Anxiety Disorder (Social Phobia)

Social phobia is characterized by marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. In children, the anxiety must occur in peer settings and not just in interaction with adults. Individuals with social phobia fear that they will act in a way that will be humiliating or embarrassing, and consequently they avoid such social situations. The social situations must almost always provoke fear or anxiety to be diagnosed with this condition.

The phobia may be restricted to eating in public, to public speaking, or to encounters with the opposite sex, or it may be generalized, that is, involving almost all social situations outside the family circle. The onset is usually in childhood or adolescence, and it is more common in females.

About 7 % of the population have full social phobia, while up to 24 % have symptoms of social phobia. In a recent survey, about 9 % of adolescents in the USA had social phobia. There are more females with diagnosed social phobia, though the symptoms may be equally distributed between the sexes (Burstein et al. 2011; Merikangas et al. 2002).

The prevalence decreases with age, reaching in adults 2–5 % (DSM-5). However, those afflicted with the condition develop increasing impairment if left untreated (Hidalgo et al. 2001).

DSM-5 describes the syndrome of *taijin kyofushoI* (in Japan and Korea) as a culture-related diagnostic issue. This syndrome is characterized by the fear that the individual makes *other* people uncomfortable, e.g., "My gaze upsets people so they look away and avoid me" In societies with high collectivistic orientation, there may be higher social anxiety but lower prevalence of social anxiety disorder.

Behavioral inhibition and fear of negative evaluation are underlying traits of social anxiety disorder. Childhood abuse and maltreatment increases the risk of social anxiety disorder. First degree relatives of social anxiety disorder are two to six times at greater risk of developing the disorder (Hidalgo et al. 2001) (DSM-5).

14.3.2.5 Panic Disorder

In panic disorder, there are recurrent attacks of intense anxiety under unpredictable circumstances. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes (DSM-5). There is often a sudden onset of palpitations, sweating, chest pain, choking sensations, dizziness, nausea, chills, chest pain or discomfort, and feelings of unreality (depersonalization or derealization). There is also a secondary fear of dying, losing control, or going mad. These attacks usually peak within 10 min and usually result in the patient's hurried exit from the place in which the attack occurs. A panic attack is often followed by a persistent fear of having another attack. Frequent and unpredictable panic attacks produce fear of being alone or going into public places where escape may be difficult (panic disorder with agoraphobia).

There is a remarkable similarity between the physiological and behavioral response to a conditioned fear stimulus and a panic attack which are mediated by a "fear network" in the brain that is centered in the amygdala and its interaction with the hippocampus and medial prefrontal cortex (Dresler et al. 2013; Gorman et al. 1989, 2000). There is evidence of decreased 5-hydroxytryptamine 1A (5-HT_{1A}) receptors in anterior cingulate, posterior cingulate, and raphe nuclei in panic disorder patients (Neumeister et al. 2004).

The onset of panic disorder is usually in early to middle childhood, affecting about 1–3 % of the population but as high as 7 % in an urban population (Goodwin et al. 2001; Pilowsky et al. 2006; Weissman et al. 1997). It occurs more commonly among females and is often associated with depression and increased suicidal ideation (Goodwin et al. 2001). Both heritable factors and stressful life events, particularly in early childhood, may be responsible for the onset of panic disorder.

Cardiac symptoms such as chest pain and palpitations, as well as mitral valve prolapse, hypertension, and cardiomyopathy, share significant comorbidity with panic disorder. In the respiratory subtype, there is often increased sensitivity to carbon dioxide (Amaral et al., 2013; Freire et al., 2010). There is also significant comorbidity between panic disorder and chronic obstructive pulmonary disease, irritable bowel syndrome, and migraine headache. There may be common pathophysiological mechanisms that may explain the association between panic disorder and comorbid medical illnesses, such as autonomic dysregulation of cardiac activity and smooth muscle tone and dynamic abnormalities of the coronary microvasculature (Zaubler and Katon 1996).

14.3.2.6 Agoraphobia

Agoraphobia is intense fear or anxiety triggered by real or anticipated exposure to a wide range of situations including at least two of (a) using public transportation, e.g., buses, planes, (b) being in open spaces e.g., parking lots, marketplaces ("agora" in Greek means "market"), (c) standing in line or being in a crowd, (d) being outside of home alone. Patients typically have thoughts of something terrible happening and that it would be difficult to get out, and panic-like symptoms may develop. The fear, anxiety, or avoidance must be out of proportion to the actual danger posed by the situation.

Approximately 1.7 % of adolescents are diagnosed with agoraphobia every year and females

are twice likely to have agoraphobia according to DSM-5. Prevalence in people over 65 years of age is 0.4 %. A high percentage of agoraphobic patients (30–50 %) also have panic attacks. The onset is before 35 years in 60 % of cases, and the course is chronic and persistent, and there is a high rate of comorbidity with other psychiatric disorders.

14.3.2.7 Generalized Anxiety Disorder (GAD)

In this syndrome, there is excessive anxiety and worry or apprehensive expectation about many events and activities. The symptoms may include nervousness, shakiness, muscular tension, sweating, light-headedness, palpitations, and stomach discomfort. There may be vague apprehension and forebodings of dreadful accidents or illness happening to them or to loved ones. Generalized anxiety disorder affects about 2.9 % of the adult population, is more common in women, and is often associated with chronic stress. Up to 10 % of the primary care population may have GAD (Lieb et al. 2005). In a recent study, 12 % of a large veteran population had GAD, and 40 % of patients with PTSD had comorbid GAD (Parmentier et al. 2013). GAD is associated with significant disability.

In GAD, there is evidence of dysregulation of central fear circuitry that includes components of the anterior limbic network (ALN) and involves connections between the amygdala and the ventromedial prefrontal cortex, ventrolateral prefrontal cortex, along with the rostral insula and subgenual and rostral anterior cingulate cortex. The ALN is innervated by multiple systems whose neurochemistry has been implicated in anxiety disorders. Serotonergic neurons, which originate from the median raphe nuclei innervate many of the individual components of the ALN and these structures (e.g., amygdala, ACC) contain numerous serotonin receptors. Similarly, structures such as the amygdala and hippocampus are densely coated with receptors for the inhibitory neurotransmitter γ-amino-butyric acid (GABA). In adolescents with GAD, viewing fearful faces caused increased activation of the amygdala, ventral prefrontal cortex, and ACC compared to healthy subjects. There was also less "negative coupling" between the VLPFC and amygdala, suggesting a failure of either modulatory or compensatory functions of the VLPFC (Strawn et al. 2012).

14.3.2.8 Anxiety-Related Physical Symptoms/Psychophysiologic Syndromes

This does not translate into a specific DSM-5 anxiety disorder diagnosis, but some patients manifest more prominent physical symptoms than the subjective feelings of anxiety. Only by careful questioning does one discern that the symptoms are associated with stress or stressful situations. Common such physical symptoms are palpitations, choking sensation, sweating, frequency of urination, nausea, vomiting, and constipation. Less common but more serious conditions include hyperventilation syndrome, irritable bowel syndrome, neurodermatitis, asthma, and fainting (Culpepper 2009). Any physical symptom associated with a physical disease may become exaggerated or exacerbated by anxiety, for example, tremors, seizures, COPD, migraine, and back pain. There is a bidirectional relationship between anxiety, hypertension, and coronary disease (Player and Peterson 2011).

Under DSM-5, many anxiety-related somatic symptoms would qualify for the diagnosis of somatic symptom disorder.

14.4 Management and Treatment of Anxiety Syndromes

In general, anxiety, regardless of cause, may be reduced by the use of antianxiety drugs, cognitive behavioral techniques, and environmental means. In secondary anxiety syndrome, the underlying cause should be identified and treated in conjunction with management of anxiety per se.

General pharmacologic treatment for anxiety involves the use of γ-aminobutyric acid (GABA) agonists such as benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), and antipsychotic drugs. Benzodiazepines are useful for immediate relief of anxiety, especially situational anxiety. SSRIs are useful for treatment and attenuation of anxiety on a long term basis, as their

antianxiety effects are manifest weeks after beginning treatment. For severe anxiety, especially when associated with dissociative or psychotic symptoms, antipsychotic drugs such as perphenazine or quetiapine may be useful. Beta-blockers such as propranolol may be used for physiologic symptoms such as palpitation, and especially for performance anxiety. For performance anxiety, such as public speaking, propranolol 10 mg po 30 min prior to the performance may be quite effective. Antihistaminics, such as hydroxyzine, may be used for the sedative effect in anxiety disorders. Tricyclic antidepressants, for example imipramine and amitriptyline, and monoamine oxidase inhibitors (MAOIs) may also be used in place of SSRIs.

General nonpharmacologic treatments include cognitive-behavioral therapy (CBT), reassurance, supportive psychotherapy, relaxation training, mindfulness training, and self-hypnosis.

14.4.1 Separation Anxiety Disorder

Cognitive-behavioral therapy and psychoeducation of family is the treatment of choice for SAD (Bogels et al. 2013; Schneider et al. 2011, 2013). SSRIs, clomipramine, and tricyclics may also be useful (Lehman 2002; Seksel and Lindeman 2001). Benzodiazepines may be used judiciously, especially short-acting ones in the morning to allow the child to go to school (Hanna et al. 2006).

14.4.2 Selective Mutism

Treatment includes individual cognitive-behavioral therapy, family therapy, and psychotherapy with antidepressants (e.g., SSRIs) and antianxiety medications. Integrated behavior therapy for selective mutism has also been developed (Bergman et al. 2013).

14.4.3 Specific Phobias

Most phobias respond robustly to in vivo exposure, but it is associated with high dropout rates and low treatment acceptance. Response to systematic desensitization is more moderate. Virtual reality may be effective in flying and height phobia. Cognitive therapy is most helpful in claustrophobia. D-Cycloserine has been used effectively in conjunction with psychotherapy for specific phobias (Choy et al. 2007). Other psychotherapeutic techniques include relaxation training, flooding, and exploratory psychotherapy.

14.4.4 Social Anxiety Disorder

The drugs of choice are selective serotonin-reuptake inhibitors (SSRIs) including fluvoxamine, sertraline, paroxetine, citalopram, escitalopram, and fluoxetine, and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine and duloxetine. Benzodiazepines, such as clonazepam and alprazolam, also are used frequently to treat anxiety disorders. Clonazepam is an efficacious treatment for social phobia. These drugs may interfere with exposure to feared situations that often is a part of cognitive behavioral therapy (CBT) for social phobia.

Monoamine oxidase inhibitors (MAOIs), such as phenelzine sulfate, are among the most efficacious treatments for social phobia. MAOIs, however, may have pressure responses to tyramine containing food and sympathomimetic drugs. Gabapentin seems to be effective only at higher doses. β-Adrenergic blockers do not seem to be efficacious for social phobia when administered on a regular dosing schedule, but they may have a role in the management of anxiety experienced occasionally in performance situations (Jorstad-Stein and Heimberg 2009). Propranolol 10 mg po 30 min prior to performance, such as public speaking, may be particularly effective.

Behavioral therapy, guided exposure, CBT with social skills training, and group therapy have been shown to be effective (Hofmann 2010).

CBT package (ie, psychoeducation, cognitive restructuring, and exposure) with an additional social skills training module may be particularly efficacious (Halaby et al. 2013; Hidalgo et al. 2001). CBT group therapy for social anxiety is also well established (Jorstad-Stein and Heimberg 2009).

Interpersonal therapy and psychodynamic psychotherapy may also be utilized. A recent study showed that both CBT and psychodynamic therapy were effective, but CBT had a higher remission rate (36 % vs. 26 %). The response rates were 60 % and 52 % respectively, and were comparable to those with pharmacotherapy (Leichsenring et al. 2013).

More recently, psychotherapeutic techniques such as motivational interviewing, mindfulness training, and acceptance and commitment therapy (ACT) have been utilized. In ACT, attempt is made to reduce experiential avoidance of fearful situations by helping socially anxious patients to accept and endure the negative experiences (i.e., develop greater "psychological flexibility"), rather than resort to avoidance and escape strategies (Eifert and Forsyth 2005; Mahaffey et al. 2013).

D-Cycloserine (DCS), a partial agonist of the NMDA receptor, has been shown to augment learning and memory, and doses of DCS received shortly after exposure facilitate extinction to feared stimuli in animals. Short-term dosing of DCS in social anxiety patients was found to be more effective than placebo in enhancing the effect of exposures. Patients who received DCS before exposures reported less social anxiety than patients who received placebo Patients who received DCS also reported improvement in their perception of their speech (Guastella et al. 2008; Hofmann et al. 2013a, b; Otto et al. 2007; Smits et al. 2013; Yaka et al. 2007).

14.4.5 Panic Disorder

Antidepressant drugs (SSRIs, tricyclics, and MAOIs) and high-potency benzodiazepines have been shown to be effective for panic disorder with or without agoraphobia. Commonly used SSRIs include fluoxetine, paroxetine, and sertraline, and high-potency benzodiazepines include alprazolam and clonazepam. Alprazolam is effective in treating the acute panic attack, but has a high potential for tolerance and abuse. Venlafaxine and mirtazapine have also been found to be effective in reducing anxiety in panic disorder (Andrisano et al. 2013).

Panic disorder has been subtyped into two subtypes based on differential responses to CO_2 challenge. Patients who showed prominent respiratory symptoms (respiratory subtype) were more sensitive to CO_2 challenge, had a significantly longer illness duration, had more severe panic and phobic symptoms, and were more likely to be heavy smokers than were patients without respiratory symptoms (Biber and Alkin 1999). Clonazepam may be especially useful in treating patients with the respiratory subtype of panic disorder (Nardi et al. 2013).

Cognitive-behavioral therapy is effective, particularly in combination with pharmacotherapy (de Carvalho et al. 2010; McHugh et al. 2009; Schmidt and Keough 2010). The cognitive component may include, for example, reevaluating the symptoms as being due to anxiety and not due to a heart attack, and the behavioral component may include *exposure and response prevention;* that is, the patient is exposed to a panic-producing situation and the patient learns to "ride out" the panic until it passes.

14.4.6 Generalized Anxiety Disorder

Generalized anxiety disorder is a chronic illness, and a realistic goal of treatment is to reduce anxiety symptoms sufficiently for functioning, not total elimination. In general, a combination of pharmacotherapy and cognitive behavioral therapy is effective in GAD (Wetherell et al. 2011, 2013).

Evidence suggests the efficacy of the SSRIs (e.g., sertraline, fluvoxamine, fluoxetine, paroxetine) and the SNRIs, venlafaxine and duloxetine in treating GAD. Buspirone, a 5-HT1A partial agonist, seems less effective (Mavranezouli et al. 2013; Strawn et al. 2012). Imipramine, hydroxyzine, valproate, and pregabalin are also effective, and the antipsychotic mood stabilizers, risperidone, olanzapine, ziprasidone, and aripiprazole may also reduce symptoms (Huh et al. 2011).

Psychoeducation, CBT, supportive psychotherapy, relaxation training, meditation, and self-hypnosis may be useful in GAD. All forms of CBT, including individual, group, and family/parental formats of CBT have been shown to be

effective for GAD. Interpersonal therapy, motivational interviewing, and acceptance-based behavioral therapy (ABBT) may also be effective (Garfinkle and Behar 2012)

14.4.7 Anxiety-Related Physical Symptoms and Psychophysiologic Syndromes

Treatment of the physical symptoms associated with anxiety should be geared to both the physical symptoms and the underlying anxiety. Thus, paper-bag rebreathing to reduce the hypocapnea is an effective treatment for *hyperventilation syndrome*, and anticholinergic drugs may be effective for *irritable bowel syndrome*. The effective use of non-deceptive placebo for irritable bowel syndrome has been reported (Kaptchuk et al. 2010).

Benzodiazepines or antidepressants may be used to control/reduce anxiety. In psychophysiologic syndromes, there may be excessive physiologic arousal in the presence of only moderate anxiety, and such arousal may be treated with antianxiety agents. There is no evidence that prolonged use of moderate to large doses of benzodiazepines to control such physical symptoms results in tolerance and the need for more benzodiazepines. The pharmacologic and psychotherapeutic measures described for GAD are also applicable for psychophysiologic syndromes (Dekel et al. 2013).

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Affect, Mood, Emotions: Depressive Disorders and Bipolar and Related Disorders

15

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Contents

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15.1 Vignette

A 34-year-old Hispanic woman was admitted to the hospital with altered mental status and fever. The patient had been suffering from systemic lupus erythematosus for a number of years, with several small strokes that left her partially paralyzed on the left side. A urinary tract infection was diagnosed, and she was treated with antibiotics and steroids with good results until she aspirated, developed pneumonia, and became comatose. After an intensive care unit stay of several weeks, she emerged from her coma. She was noted to have frequent crying spells. A psychiatric consultation was requested.

The consultant diagnosed a depressive syndrome based on her mood, hopelessness, and a wish to die. She had some equivocal family history of depression, but no previous episodes of depression. The consultant concluded that her depression was a result of several factors—her prolonged hospitalization, the illness and its complications, and the steroids that she was taking. She was prescribed fluoxetine 20 mg per day. She was able to be transferred from the intensive care unit to the general medical service, and she showed some improvement over the next 2 weeks.

But after 2 weeks she refused to take any of her medications, she refused to participate in physical therapy, and she expressed a desire to die. The consultant was called urgently to assess whether she had the capacity to refuse treatment.

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The patient told the consultant that she was very discouraged, felt abandoned by her family, and felt defeated, as she did not have the energy to cooperate with physical therapy. She just wanted to go home and die. The consultant asked her if she would cooperate with therapy and take medications if she had a bit more energy, so that she could successfully complete a course of physical therapy that will make her strong enough to go home, to which she replied in the affirmative, provided she could sign an advance directive. The consultant decided that the patient did have the capacity to sign an advance directive, and that she should be given a trial of stimulants, which she agreed. She was given methylphenidate 10 mg in the a.m. The next day, she showed remarkable improvement in mood and energy level and was eager to participate in physical therapy. In fact, she was smiling for the first time, and wanted to use the wheelchair. In a week, methylphenidate was discontinued, but she maintained her normalized mood and energy level. She was discharged in 2 weeks, still on fluoxetine, to be followed by an outpatient psychiatrist.

15.2 Affect, Mood, and Emotions

15.2.1 Definitions

The emotional feeling tone of an individual, such as sadness, joy, depression, or elation, is called an affect. When the affect is prolonged and colors the whole emotional life of the person, it is called a mood. Thus, a person may be in a blue mood, an elated mood, or a depressed mood. These terms are somewhat confusing, as the term affect is also used for the emotional expression observed, especially in the context of a mental status examination, while the term mood may be used to denote the subjective emotion that the patient experiences. In this sense, affect is usually described in terms of the form of expression, for example, full, blunted, flat, stable vs. labile, or appropriate vs. inappropriate. Mood is a continuum, with one end representing feeling down, blue, sad, miserable, depressed, or down in the dumps; the middle representing euthymia; and the other end representing feeling happy, high, joyous, euphoric, elated, exulted, ecstatic, or manic. The term emotion usually denotes both the subjective and physiological aspects of affect.

15.2.2 The Functions of Mood and Affect

All of us experience varying gradations of moods, and they are necessary and adaptive experiences for survival and emotional maturation. Sadness is usually experienced after suffering a failure, or the loss of a loved one, a prized possession, or prestige. The loss may be purely imaginary, and even the anticipation of a loss may cause sadness.

There is a close relationship between anxiety and sadness. When one anticipates an event which may result in a loss of a valuable object (e.g., a loved person, prized possession, prestige, bodily part), he/she experiences anxiety. If the loss actually occurs, sadness or even depression ensues. Experiencing sadness *motivates* the individual to anticipate and prevent it by protecting one's bonds both with loved ones and with one's possessions. It also allows for empathy, which is critical in social bonding, and the likelihood for procreation.

Pleasure is clearly the motivating force behind all endeavors and achievements, both at the individual and social levels. Affective or emotional expression is important in communication and social interaction.

15.2.3 Dysregulation of Mood

The extremes of moods, the depressive syndrome and the manic syndrome, are final common pathway brain dysfunctions (see Chap. 7).

Unlike sadness or normal grief, the final common pathway pathological state of the depressive syndrome is characterized by a period of depressive mood and/ or a pervasive loss of interest or pleasure. The patients often feel sad, hopeless, helpless, and empty. Guilt feelings are prominent, and there is a loss of self esteem. Feeling discouraged and "down in the dumps" is common. The patients typically withdraw from family and

friends, and activities and hobbies that used to give them pleasure no longer interest them. There is usually some sleep disturbance, usually early-morning awakening, but middle-of-the-night awakening and difficulty in falling asleep are not uncommon, especially if anxiety is also prominent. In bipolar patients, there may be hypersomnia. Loss of appetite is quite common, with concomitant weight loss, although in some patients, particularly those with bipolar illness, there may be an increase in eating, resulting in a weight gain. The patients often show psychomotor agitation or retardation. In agitation, pulling out hair, pacing, wringing hands, inability to sit still, incessant talking, and shaking of hands and feet often occur. Psychomotor retardation is characterized by slowing of speech, slowed body movements, or even muteness.

In the *depressive syndrome*, patients often manifest cognitive disturbances, including the inability to concentrate, indecisiveness, and generally slowed thinking processes. Often, patients feel they do not have enough energy to think about a simple problem. They feel tired, fatigued, and exhausted in the absence of physical exhaustion. They may experience vague pains, aches, and discomfort, without any physical basis; headaches, toothaches, backaches, and muscle aches are especially common.

Patients often suffer from feelings of inadequacy, worthlessness, and sometimes completely unrealistic low self-esteem. The smallest task may appear impossible or monumental. There may be excessive guilt feelings concerning current or past failings, most of them minor, or even delusional conviction of sinfulness or responsibility for some untoward tragic event.

Suicidal ideas are frequent and may take the form of fears of dying, the belief that the person himself or herself or others would be better off if the person were dead, or suicidal desires or plans. (See Chap. 4 for further discussion of suicide and suicide attempt.)

Depression increases the risk of suicide. The lifetime risk of suicide in bipolar disorder is considered to be at least 15 times that of general population, and bipolar disorder may account for 1/4 of all completed suicides (APA 2013).

Often, there is a diurnal variation in that the symptoms are worse on waking in the morning and improve slightly as the day progresses, which may be more prominent in bipolar patients (Forty et al. 2008; Morris et al. 2007).

When the symptoms are mild, temporary improvement often occurs in the presence of positive environmental stimuli.

In severe cases, the syndrome is not affected by environmental change to any extent.

15.3 Major Depressive Episode

DSM-5 definition includes five or more of Criteria A symptoms during the same 2 week period, which represent a change from previous functioning, and must include either depressed mood or loss of interest or pleasure. They are: depressed mood most of the day, markedly diminished interest or pleasure in activities nearly every day, change in appetite and/or weight, persistent insomnia/hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy nearly every day, feelings of worthlessness or inappropriate or excessive guilt, difficulty with concentration or indecisiveness nearly every day, recurrent thoughts of death or suicidal ideation, plan, or attempt. In addition, Criterion B requires that the symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Criterion C specifies that the episode is not attributable to substances or other medical condition.

15.4 Euphoria, Hypomania, Manic Episode

Just as sadness and grief are experienced by most people from time to time, the opposite, pleasurable moods of euphoria and elation, short of mania or hypomania, fall within the normal range of mood. In euphoria, there is a positive feeling of emotional and physical well-being. In elation, there is a definite feeling of joy with increase in self-confidence, motor activity, and energy level.

These states can be induced by drugs such as alcohol, narcotics, and amphetamines.

Mania and hypomania, like the depressive syndrome, form a syndrome with definite features and signs. The characteristic feature of the manic syndrome is a distinct period when the predominant mood is elevated, expansive, or irritable and is associated with other symptoms of the manic syndrome. They include hyperactivity, excessive involvement in indiscreet and foolish activities without recognition of the high potential for painful consequences, pressure of speech, flight of ideas, inflated self-esteem, decreased need for sleep, and distractibility. The patient may describe the elevated mood as being euphoric, unusually good, or high. The good mood may have an infectious quality, so that the physician and others in contact with the patient may find themselves feeling expansive and elated. The patient may show indiscriminate enthusiasm in relating to people or in planning things, so that they may start a dozen projects at once, call up distant relatives and acquaintances all over the globe, and go on a buying spree.

On the other hand, the mood may be characterized by irritability rather than joyfulness, especially when the patient's expansiveness is thwarted. The patient then becomes touchy and domineering. The hyperactivity is often generalized, including participation in multiple activities that may be sexual, occupational, political, or religious. The patients often have poor judgment, and the activities are disorganized, flamboyant, and bizarre. Manic speech is usually loud, rapid, and difficult to understand. It is often full of jokes and puns and is theatrical, with singing and rhetorical mannerisms. In the irritable mood, there may be hostile comments and angry outbursts. Abrupt changes from topic to topic based on understandable associations and distracting stimuli often occur (flight of ideas). When severe, the speech may be incoherent. Distractibility is usually present.

Self-esteem is usually inflated, with unrealistic and uncritical self-confidence and grandiosity. For example, the patient may give advice on matters about which he or she has no knowledge whatsoever, such as how to perform a surgical procedure or how to run the federal government. Grandiose delusions may occur, such as, "I have a special hot line to God."

Hypomania refers to elevated mood with many of the symptoms of the manic syndrome but not severe enough to interfere with function significantly. If there are psychotic features, the episode is by definition manic (APA 2013).

15.4.1 Manic Episode

DSM-5 definition includes, in Criterion A, a distinct period of at least 1 week (or any duration if hospitalization is necessary) of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy nearly every day. During the period described above, three or more of the Criterion B symptoms are present to a significant degree and they represent a noticeable change from usual behavior. Criterion B symptoms include inflated self-esteem or grandiosity, decreased need for sleep, pressured speech or talkativeness, flight of ideas or racing thoughts, distractibility, increase in goal-directed activity or psychomotor agitation, excessive involvement in risky activities (e.g., shopping sprees, sexually risky activity, risky business ventures). Criterion C provides that the disturbance is severe enough to cause marked impairment in social or occupational functioning, or there are psychotic features, or hospitalization is necessary. Further, Criterion D stipulates that the condition is not attributable to substances or a medical condition. Criteria A–D constitute a manic episode, and at least one lifetime manic episode is required for the diagnosis of Bipolar I disorder.

15.4.2 Hypomanic Episode

DSM-5 definition of the hypomanic episode includes Criteria A and B of Manic Episode above, but stipulates, in Criterion C, that the episode is associated with an unequivocal change in functioning uncharacteristic of the individual when not symptomatic, and that the change is observable by others (Criterion D), and Criterion E, the episode is not severe enough to cause

marked impairment in social or occupational functioning or necessitate hospitalization, and F, the episode is not attributable to medications or a medical condition.

15.5 Diagnosis of Mood Syndromes

Evaluation of depression is probably the most common reason for requesting psychiatric consultation (the second most common reason is likely to be delirium).

The depressive syndrome and manic syndrome are final common pathway syndromes with varying degrees of contribution by genetics, early experiences, developmental factors, prescription and recreational drugs, physical illness, and recent and current stresses including hospitalization (see Chap. 7). Once a phenomenological diagnosis of depression or mania/hypomania is made, a differential diagnostic process should be undertaken to determine whether there is prominent contribution by an identifiable physical illness or prescription and recreational drugs, that is, a secondary mood syndrome (see Chap. 4; also see Table 7.1 in Chap. 7).

Depression is commonly comorbid with many medical conditions including heart disease, stroke, seizure disorder, lung diseases such as asthma and COPD, cancer, HIV, liver disease, kidney disease, as well as in peripartum states, etc. Specific discussions of depression in these conditions are found in chapters dealing with these conditions.

15.5.1 Differential Diagnosis

15.5.1.1 Secondary Mood Syndromes

Mood syndromes are quite commonly the result of physical illness or prescription and recreational drugs. It is useful to classify secondary mood syndromes as follows:

(A) Substance-induced
   1. Prescription Drugs, e.g., exogenous steroids, sedatives, opioid analgesics
   2. Recreational Drugs, e.g., alcohol, methamphetamine, heroin

(B) Secondary to General Medical Condition
   1. Metabolic/Endocrine disorders, e.g., diabetes mellitus, hypoglycemia, hypothyroidism and hyperthyroidism, Cushing's syndrome
   2. Infections, e.g., HIV, syphilis, encephalitis, post-viral syndrome
   3. Neoplasms, e.g., pheochromocytoma, paraneoplastic syndromes, e.g., ca of pancreas
   4. Neurologic disorders, e.g., Parkinsonism, Epilepsy, Migraine
   5. Other conditions, e.g., anemia, heavy metal poisoning

Depression is commonly associated with hypothyroidism, hypopituitarism, Cushing's disease, viral infections, pancreatic cancer (for which it may be the presenting symptom), Parkinsonism, and many other medical conditions (see Chap. 7). Various drugs may cause depression as a side effect or a withdrawal effect (e.g., cocaine crash). See Table 7.1 in Chap. 7 for a comprehensive listing of medical causes of psychiatric syndromes.

According to DSM-5, secondary mood syndromes consist of

Substance/Medication-Induced Depressive or Bipolar disorder

Depressive or Bipolar disorder secondary to Another Medical Condition

15.5.1.2 Primary Mood Syndromes

Once physical illness or prescription and recreational drugs have been ruled out as the primary cause of a mood syndrome or are considered to be contributing to a preexisting primary mood disorder, a primary mood disorder may be diagnosed. DSM-5 separates bipolar disorder from depressive disorder but in CL practice, it is more convenient to first ascertain that the mood syndrome does or does not have contribution from secondary factors (substances and/or other medical condition), then determine which syndrome best fits the patient's symptoms.

It is important to note that the differential diagnosis of primary mood disorders includes major psychiatric syndromes that are not usually classified as mood disorders but are often accompanied with mood symptoms—i.e., schizoaffective disorder, schizophrenia, and PTSD.

15.5.1.2.1 Major Depressive Disorder

Major depression (unipolar depression) may be diagnosed in the presence of the depressive syndrome if the criteria for Major Depressive Episode are met (see above).

According to DSM-5, the 12-month prevalence of major depressive disorder is about 7 % in the USA; in 18–29-year-old groups, it is three times higher than in persons 60 years or older. Female to male ratio is 1.5–3:1 beginning in early adolescence (APA 2013).

The onset of major depressive disorder is variable, but peaks around age 20, but late onset is not uncommon.

According to DSM-5, the heritability is approximately 40 %, and the personality trait of neuroticism accounts for a major portion. Childhood adverse experiences are risk factors as well as recent stressors (see Chap. 7 for further discussion).

15.5.1.2.2 Bipolar and Related Disorders

DSM-5 states that bipolar and related disorders are separated from the depressive disorders and placed between the chapters on schizophrenia spectrum and other psychotic disorders and depressive disorders *in recognition of their place as a bridge between the two diagnostic classes* in terms of symptomatology, family history, and genetics (APA 2013). DSM-5 includes under this heading bipolar I disorder, bipolar II disorder, cyclothymic disorder, and substance/medication-induced bipolar disorder, and bipolar disorder secondary to a medical condition, as well as other specified and unspecified bipolar and related disorders.

Bipolar I disorder is little changed from the classic Kraepelinian description of manic-depressive illness (Kraepelin and Defendorf 1902; Kraepelin 1976) except that neither psychosis nor a lifetime experience of major depression is a requirement (only a manic episode is).

When a person has at least one manic episode, bipolar I disorder is diagnosed.

If a person meets the criteria for at least one major depressive episode and one hypomanic episode without the extreme of the manic syndrome, *bipolar II disorder* is diagnosed. If the patient with a bipolar disorder or depressive disorder also has psychotic symptoms, then a mood disorder with mood-congruent or mood-incongruent psychotic features is diagnosed.

If episodic prominent mood symptoms are superimposed on psychotic symptoms that persist even when the mood symptoms are not present, schizoaffective disorder is diagnosed.

The prevalence of bipolar I disorder in the USA is 0.6 % and male to female ratio is 1.1:1. Bipolar disorder is more common among higher income countries. Family history of bipolar disorder is a very strong risk factor. It is believed that bipolar disorder and schizophrenia share a genetic contribution as there is familial co-aggregation of schizophrenia and bipolar disorder.

The onset of bipolar disorder is usually in the teens or early adulthood, and more than 90 % of patients with a single manic episode have recurrent episodes. Approximately 60 % of manic episodes are followed immediately by a depressive episode (DSM-5).

15.5.1.2.3 Subthreshold Mood Syndromes

Many persons suffer from mild to moderate depression that does not quite meet the threshold for the depressive syndrome. Such depression may have prominent affective (feeling sad, crying spells) or cognitive (feeling hopeless and helpless) components without the neurovegetative component (insomnia, hypersomnia, anorexia, anhedonia), or vice versa. Subthreshold depressive symptoms are particularly common in the medical setting, and may be caused by any of the factors for secondary depression, or may be an *adjustment disorder* with depressed mood, associated with the stress of hospitalization or of the medical illness.

Persistent Depressive Disorder (*Dysthymia*) refers to chronic or neurotic depression, low-grade depression of long, perhaps lifelong, duration. Such patients are at higher risk of developing major depression (double depression), and even when the major depression is successfully treated, are likely to revert back to dysthymia. *Cyclothymia* is a trait characterized by ups and downs in mood but not quite reaching the degree seen in bipolar illness.

15.5.1.2.3.1 Demoralization Syndrome

Although not a Diagnostic and Statistical Manual of Mental Disorders (APA 2013) diagnosis, demoralization syndrome is a useful concept in consultation-liaison (CL) settings. Seen mostly in patients with chronic illness, especially in palliative care settings, this syndrome is characterized by helplessness, hopelessness, fatigue, and anhedonia (Clarke et al. 2003; Kissane et al. 2001). See Chap. 27 and 29 for further discussion of demoralization syndrome.

15.5.1.2.3.2 Disruptive Mood Dysregulation Disorder

This is a new diagnosis in DSM-5, which is meant to "address concerns about the potential for the overdiagnosis of and treatment for bipolar disorders in children." It refers to children up to 12 years of age with persistent irritability and frequent episodes of extreme behavioral dyscontrol. This is placed in the category of depressive disorders because children with these symptoms typically develop unipolar depressive or anxiety disorders when they mature (APA 2013). The prevalence is considered to be 2–5 %.

Premenstrual Dysphoric Disorder is classified under depressive disorders in DSM-5. This is discussed in Chap. 31.

15.6 Management and Treatment of Mood Syndromes

15.6.1 Depression

The management and treatment of depression in the CL setting depends on several factors including the nature of the medical condition for which the patient is being treated, the severity and cause of the depression, and the comorbid conditions such as delirium. Treatment of delirium takes precedence over the treatment of depression. If the depressive syndrome is severe, pharmacotherapy or electroconvulsive therapy should be considered regardless of whether the depression is secondary or primary. For mild to moderate depression, supportive psychotherapy, providing reassurances and explanations, and encouraging supportive visitors may be most helpful. If the patient is actively suicidal, they should be placed on constant observation and promptly transferred to a psychiatric inpatient service when medically stabilized.

15.6.1.1 Pharmacotherapy

Pharmacotherapy of depression should be reserved for the depressive syndrome rather than for subthreshold adjustment syndromes, for which psychotherapy and social support may be more effective.

If drug therapy is indicated, it usually involves selective serotonin reuptake inhibitors (SSRI) or third-generation antidepressants such as mirtazapine (a serotonergic and noradrenergic agonist through adrenergic α_1-agonism and α_2-antagonism on serotonergic and adrenergic neurons), serotonin and norepinephrine reuptake inhibitors (SNRI) such as duloxetine, and bupropion, which is a norepinephrine–dopamine reuptake inhibitor and nicotinic acetylcholine receptor antagonist. In the medically ill population, antidepressants should be used cautiously and doses modified, as many medically prescribed drugs interact with them. In general, however, drugs used for medical purposes do not need dose adjustment because of the antidepressant. Serotonin syndrome is a rare but serious potential adverse reaction of antidepressants, especially when used in combination (see Sect. 7.2.3.1 in Chap. 7).

The choice of antidepressants depends on which side effect might be beneficial or detrimental for a patient. For example, a patient with insomnia may benefit from mirtazapine, which in small doses tends to induce sleep, while fluoxetine might be the drug of choice for an obese patient for its appetite suppressing effect. For patients who are psychomotor retarded, bupropion may be helpful because it is a mild stimulant. Bupropion also does not have sexual side effects often seen in other antidepressants. However, bupropion lowers the seizure threshold and should be used with caution in patient with a history or family history of seizure disorder.

Unfortunately, extant antidepressants are not very effective in treating depression.

*Star*D* (Sequenced Treatment Alternatives to Relieve Depression) was a large scale, multicenter

randomized outpatient study in which patients received citalopram first, then for non-responsive patients, various switch or augmentation options were provided including sertraline, bupropion, buspirone, venlafaxine, mirtazapine, nortriptyline, lithium, and tranylcypromine, as well as cognitive behavioral therapy (Rush et al. 2004). The depression remission rate for the first phase involving citalopram (average 40 mg or more) was only 27 % and the response rate (some improvement but not full remission) was 47%. About 40% of patients who had remission required 8 weeks or more to achieve it. With the addition of switching, augmentation, etc., the remission rate could be brought up to about 60% in those who completed treatment (Gaynes et al. 2009). Except in seriously depressed patients, there is little difference between placebo, antidepressants, and psychotherapies in alleviating depression. Combining pharmacotherapy with psychotherapy may have some advantage over one modality alone (Fournier et al. 2010; Kirsch 2009).

Some promising newer treatment modalities are being developed for treatment-resistant depression which may revolutionize treatment for depression. *Ketamine* is a glutamatergic *N*-methyl-D-aspartate (NMDA) receptor antagonist which produces a rapid antidepressant response within hours in about two thirds of patients with treatment-resistant depression, with effects lasting up to 2 weeks (Salvadore and Singh 2013). Ketamine is an intravenous anesthetic drug that has psychotomimetic effects and is a drug of abuse. The antidepressant effect occurs in subanesthetic doses and seems to occur as a result of NMDA receptor antagonism resulting in an increase in brain derived neurotrophic factor (*BDNF*), contributing to an increase in synaptic plasticity (Duman et al. 2012; Kavalali and Monteggia 2012; Liu et al. 2012; Salvadore and Singh 2013).

In fact, an increase in BDNF activity may be the common downstream effect of almost all effective psychotropic drugs (Bath et al. 2012; Budhdeo and Deluca 2012; Kerman 2012; Li et al. 2012; Lindholm et al. 2012; Park et al. 2011; Rantamaki et al. 2011), and epigenetic changes in the BDNF gene may play an important role in the susceptibility to various psychiatric disorders (Boulle et al. 2012).

Another promising development is *deep brain stimulation* (Lujan et al. 2013; Mayberg et al. 2005; Neimat et al. 2008; Riva-Posse et al. 2012). Mayberg and her colleagues have shown that deep brain stimulation of subcallosal anterior cingulate (Area 25), which is often hyperactive in depression, resulted in rapid amelioration of depressive symptoms in about 40–60 % of treatment-resistant patients. Chronic stimulation of the area up to 2 years in treatment-resistant patients with unipolar and bipolar depression resulted in remission rate of 50 % in major depression and 90 % in bipolar depression, with no relapse reported (Holtzheimer et al. 2012).

15.6.1.2 Electroconvulsive Therapy (ECT)

ECT is the most effective treatment for severe depressive syndrome, and, if available, is particularly useful in the CL setting (Klapheke 1997; Pandya et al. 2007). The remission rate with ECT is about 60 % even in treatment resistant depression (Holtzheimer and Mayberg 2012). The main side effects are postictal confusion and usually transient anterograde and retrograde amnesia.

Other neuromodulatory treatments for depression include transcranial magnetic stimulation, with a remission rate of 20–40 % of major depression and 10–20 % of treatment resistant depression, and vagus nerve stimulation which has a response rate of approximately 30–40 % and remission rate of 15 % in treatment resistant depression patients (Holtzheimer and Mayberg 2012).

In the future, pharmacogenomics may play an important role in the choice of an antidepressant. For example, patients who have the short-allele polymorphism of the serotonin transporter gene linked polymorphic region (5-HTTLPR), a drug that has both noradrenergic and serotonergic action, such as mirtazapine, may be preferable to a pure SSRI (Murphy 2004a, b). When the depressive syndrome is accompanied with psychotic symptoms such as hallucinations, delusions, or paranoia, the addition of an antipsychotic medication is indicated. If the patient is acutely

agitated, the agitation should be managed immediately, before antidepressant therapy can begin (see Sect. 4.3.4 in Chap. 4).

For demoralization syndrome, a stimulant such as methylphenidate (5–10 mg in the a.m.) or dextroamphetamine (2.5–5 mg in the a.m.) may be particularly effective.

When antidepressant therapy is instituted, it is critical that outpatient follow-up is provided.

15.6.2 Hypomania, Mania, Mood Stabilizers

Isolated hypomania may not need treatment. A bipolar patient who is already on mood stabilizers should be continued on them in the general hospital. If the symptoms increase due to the stress of hospitalization, one or more of the following may be done: the mood stabilizer could be increased, another mood stabilizer added, or an antipsychotic medication added.

If a patient who is not currently on a mood stabilizer develops a manic syndrome, with or without psychotic features, or if schizoaffective syndrome is suspected or diagnosed, an antipsychotic/mood stabilizer drug such as quetiapine or aripiprazole should be used. Haloperidol IV or IM, chlorpromazine IM, olanzapine IM, and/or lorazepam IV or IM may be used for immediate sedation if indicated (see Sect. 4.3.4 in Chap. 4).

Anticonvulsant mood stabilizers, such as valproic acid, carbamazepine, and lamotrigine may also be used as well as lithium carbonate. With valproic acid, liver function should be closely monitored. Carbamazepine may cause agranulocytosis. Carbamazepine may cause Stevens–Johnson syndrome and toxic epidermal necrolysis especially in Asians—FDA recommends testing for *HLA allele B*1502* in all Asians prior to carbamazepine therapy (Ferrell and McLeod 2008). Carbamazepine is an enzyme inducer and affects drug levels and efficacy of many drugs metabolized by liver enzymes. Lamotrigine should be titrated up very gradually watching carefully for the occurrence of rashes as it is also associated with a risk of Stevens–Johnson syndrome. As with clozapine, if maintenance lamotrigine was stopped for more than 48 h, it should be restarted at the low starting dose of 25 mg/day and follow the initial escalation schedule. The dose has to be lowered in patients taking valproic acid.

15.6.3 Psychotherapy for Depression and Mood Syndromes

15.6.3.1 Supportive Psychotherapy and Psychoeducation

In the CL setting, supportive psychotherapy is essential in helping patients with depression and demoralization. Supportive psychotherapy includes listening to the patient, showing empathy for the patient, responding to questions, and offering help in problem solving. It also involves allowing patients to express feelings of hopelessness and helplessness about their medical illness and the procedures they are undergoing, and providing explanations and reassurances when indicated. It may also involve facilitating communication between the patient and the responsible physician or nursing staff. Psychoeducation and supportive psychotherapy are also the major psychotherapeutic tools for major depression, bipolar syndrome, and schizoaffective disorder. Psychoeducation involves educating the patient and family about the nature, symptoms, course, and the indications and potential side effects of medications. Recognizing the first symptoms of depression and seeking help may be lifesaving for patients with major and bipolar depression.

15.6.3.2 Formal Psychotherapies

Cognitive-behavioral therapy (CBT) and interpersonal psychotherapy (IPT) have been shown to be effective in the treatment of depression. Both are brief psychotherapies for which manuals are available.

Cognitive-behavioral therapy postulates that the cognitive distortions in depression such as pessimism, low self-esteem, and consequent behaviors such as self-criticism and social isolation are fundamental to depression. Thus, CBT attempts to correct such cognitive distortions through careful examinations of such faulty beliefs and overcome them through behavioral

exercises and homework (Beck 1995). Cognitive-behavioral therapy seems effective for mild to moderate depression.

Interpersonal psychotherapy recognizes that depression has biological roots but is often triggered by interpersonal factors. Such factors may include grief from the loss of a loved one or grief from having a chronic illness; interpersonal disputes with family, friends, or coworkers; role transitions, such as changing jobs or disability; and interpersonal deficits, such as social isolation and substance abuse. Interpersonal psychotherapy examines such triggers and attempts to work through and potentially prevent recurrence of triggers through problem-solving techniques. Interpersonal psychotherapy is often used in combination with antidepressant drugs and thus is effective even in severe depressions (Klerman et al. 1994).

Psychotherapy does not necessarily involve face-to-face contact. Remote psychotherapies, such as through telephone or Internet, have been effectively performed for depression (Applebaum et al. 2012; Furukawa et al. 2012; Ketterer 1999; Shore 2013).

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Trauma and Stressor-Related Disorders 1: Acute Stress Disorder, Posttraumatic Stress Disorder

16

Hoyle Leigh

Contents

16.1 Vignettes

1. An 18-year-old man was admitted to the intensive care unit following an automobile accident. He was a passenger in the car whose driver was killed in the crash. The patient had suffered 30 % second degree burn. On the fourth day of admission, a psychiatric consultation was requested for suspected depression. The patient admitted to some feelings of sadness, flashbacks, and interrupted sleep due to nightmares in spite of significant opiate analgesics. An acute stress disorder was diagnosed, and a regimen of Olanzapine 2.5 mg p.o. at bedtime for 2 weeks was initiated. The patient's nightmares and flashbacks subsided within 24 h. He was subsequently discharged without any psychotropic medications.
2. A 32-year-old woman with a history of repeated suicide attempts was referred to the Psychiatric Consultation Service following another acetaminophen overdose for evaluation of "suicidal gesture." On interview, the patient admitted to feeling depressed, paranoid, and abusing methamphetamines. History revealed that the patient had repeated traumatic rapes when she was involved with a motorcycle gang in her teens, and she had severe flashbacks, startle reactions, and almost daily nightmares. The patient was diagnosed with major depression, posttraumatic stress disorder, and methamphetamine abuse. Prazosin 1 mg h.s. was prescribed for the

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nightmare as well as sertraline 50 mg per day for depression and PTSD once the liver function returned to normal, and she was referred for outpatient treatment.

16.2 Introduction: Stress, Trauma, Reactions, and Results

Stress is an adaptational demand on an entity, be it an organism, an organ, a tissue, or a molecule, and conversely, a family, a nation, or a planet. It may be in the form of matter-energy, as in excessive or insufficient ambient heat, environmental toxins, or in the form of information, as in an unwelcome (or welcome) news, an approaching exam, or an inundation by internet connection demands.

Stress is obviously necessary for any change to take place, and optimal physical, intellectual, and emotional development is contingent on a steady dose of optimal stress.

When an organism encounters an excessive amount of stress, then homeostasis may fail, and the initial distortion exerted by the stress on the organism, called strain, may remain as the new baseline and the organism may have to carry on further adaptation with the preexisting load (*allostatic load*). This results in a distorted developmental path, which, if combined with a constitutional/genetic vulnerability, may lead to the development of disease. (For further discussion on this topic, see Chap. 7.)

What constitutes excessive stress? The answer must always be an equation of the interaction: gene × meme × stressor × environment as discussed in Chap. 7. Thus, the same stress (e.g., rape) may have different outcome just as the same genes (i.e., monozygous twins) may fare very differently depending on experience (of trauma or nurturance).

In Trauma and Stressor-Related Disorders, there is a presumption that a person experiences a very strong stressor, and the outcome is classified in DSM-5 on the basis of age of the individual and the type and severity of symptoms. The disorders in children are Reactive Attachment Disorder and Disinhibited Social Engagement Disorder, which are discussed in this chapter. The disorders that are not exclusively seen in children are: Posttraumatic Stress Disorder (PTSD), Acute Stress Disorder (ASD), Adjustment Disorders (AD), Other Specified Trauma- and Stressor-Related Disorders, and Unspecified Trauma- and Stressor-Related disorders. The latter three disorders are discussed in Chap. 17.

16.3 Posttraumatic Stress Disorder (PTSD) and Acute Stress Disorder (ASD)

Though classified as a primary psychiatric disorder, this syndrome is secondary to or the sequelae of major identifiable stresses. In fact, until the term, PTSD, was introduced in 1970s and formalized in DSM III in 1980, combat neurosis, combat fatigue, and shell shock were the terms used to denote the psychiatric sequelae of exposure to the extreme stress of combat (1916; Crocq and Crocq 2000; Earlam 1998; Hayman 1946; Milligan 1916; Wadsworth et al. 1946).

Now it is recognized that posttraumatic stress disorder is not confined to combats or wars, but *any major trauma*, either directly experienced or witnessing such trauma to others, as well as learning about trauma to family or close friend, or experiencing repeated or extreme exposure to details of traumatic events, may cause PTSD (DSM-5).

About 8–9 % of the general population will have PTSD during their lifetime (Hidalgo and Davidson 2000; Yule 2001). In the CL setting, PTSD is often found in trauma, burn, and rape victims. Patients with acute coronary syndrome, and patients admitted to the intensive care unit, often develop PTSD-like symptoms (see Chap. 26.)

Others may have an existing posttraumatic stress disorder diagnosis from combat experience and may be hospitalized for an unrelated medical condition. The prevalence of PTSD in combat veterans is considered to be about 25 %, and in other traumatized groups, 3–60 %.

PTSD is characterized by three classes of symptoms and signs: (1) intrusion symptoms, including intrusive thoughts, nightmares, and

dissociative symptoms such as flashbacks; (2) arousal symptoms, including hypervigilance, hyperarousal, and startle reactions; (3) avoidance of situations and stimuli that may remind the person of the trauma, and (4) negative alterations in cognitions and mood associated with the traumatic event, such as inability to remember aspects of the trauma, persistent negative belief or expectations, persistent negative emotional state, inability to experience positive emotions, markedly diminished interest, feelings of detachment and estrangement. In addition to these symptoms, any number of psychiatric symptoms may be associated with PTSD, including brief psychotic episodes with hallucinations and delusions, depression, panic, substance abuse, and suicidal behavior. Memory impairment and learning disability may be prominent. In fact, PTSD may be called the SLE (systemic lupus erythematosus) of psychiatry in the protean symptomatology. A traumatic childhood may predispose an individual to adult stress disorders.

Therefore, PTSD should be included in the differential diagnosis of any psychiatric symptom.

16.4 Pathophysiology

The pathophysiology of PTSD involves the limbic system, particularly the amygdala, hippocampus, the locus ceruleus, and the prefrontal cortex. A reduced volume of the hippocampus has been consistently reported in PTSD (Bremner et al. 1995; Karl et al. 2006). Hypercortisolemia associated with acute stress has been postulated to underlie the learning disability and memory impairment associated with PTSD (Munhoz et al. 2010; Rodrigues et al. 2009; Sapolsky 1996). In addition to dysfunctions of the limbic system and hippocampus, there is dysfunction of contextualization by medial prefrontal cortex in PTSD (Liberzon and Sripada 2008; Zovkic and Sweatt 2013).

Charney and colleagues postulated that the primary symptoms of PTSD, the persistent reexperiencing of the traumatic event, avoidance of stimuli associated with the trauma, and the symptoms of increased arousal, are related to the neural mechanisms involved in fear conditioning, experimental extinction, and behavioral sensitization as well as the altered function of specific brain regions and neurochemical systems (Charney et al. 1993; Southwick et al. 1994).

In addition to stress inducing the secretion of norepinephrine, dopamine, and opioids, long term potentiation through NMDA receptors in the amygdala may be involved in the encoding of traumatic memories vividly in PTSD (Ledoux et al. 1989).

An intriguing area of research is the role of the protein, Stathmin, which is known to be involved in fear memory formation. In one study, adult male rats were exposed to repetitive blast injury while under anesthesia. Blast exposure induced a variety of PTSD-related behavioral traits that were present many months after the blast exposure, including increased anxiety, enhanced contextual fear conditioning, and an altered response in a predator scent assay. The authors also found elevation in the amygdala of the protein stathmin 1. Because the blast overpressure injuries occurred while animals were under general anesthesia, their results suggest that a blast-related traumatic brain exposure can, in the absence of any psychological stressor, induce PTSD-related traits that are chronic and persistent (Elder et al. 2012).

There is evidence that the balance between neuronal activities of the amygdala and prefrontal cortex defines an impairment or facilitation of extinction to the cue while the hippocampus is involved in the context-specificity of extinction (Martel et al. 2012).

In memetic terms, PTSD results from an overwhelming infusion or activation of stress memes that take over the function of the brain (Leigh 2010, 2012). The stress reaction involves the activation of the hypothalamo-pituitary-adrenocortical axis and massive production of glucocorticoids which are neurotoxic to the hippocampus, and may result in a smaller volume and difficulty in processing memory. With PTSD, there may be a permanent damage to the meme-processing ability of the brain, setting the stage for a labile equilibrium among conflicting memes and susceptibility to be overwhelmed with new incoming memes or an inability to process new and useful memes. The stress memes that

overwhelmed the brain are likely to reside in the brain and proliferate at every opportunity. Note that strong emotions may enhance long-term potentiation and thus memory formation through dopaminergic and serotonergic mechanisms ("flashbulb memory"). Persons who have no memory of a traumatic event in 24 h were shown to be less likely to develop PTSD in 6 months than those who had memories of the trauma (Gil et al. 2005). This finding supports the notion that the ability to inhibit the traumatic meme proliferation (memory) prevents PTSD.

Once PTSD has been established, reservoirs of traumatic memes may proliferate unpredictably and uncontrollably as in flashbacks and nightmares.

16.5 Treatment

16.5.1 Psychotherapy

Remembering the traumatic event within 24 h after it occurred has been shown to be a predictor of future PTSD, whereas amnesia concerning the event is a predictor of not developing PTSD (Gil et al. 2006). Thus, when a patient who suffered an acute stress, such as a motor vehicle accident or assault, has no memory of the incident, it is prudent for the medical staff not to encourage the patient to remember it. Psychological debriefing and critical incident debriefing, in which the individual relives in detail the traumatic experience in a group situation, have been shown to be ineffective or even detrimental and more likely to result in PTSD (Mayor 2005). In contrast to this type of acute reliving of trauma in group situations, individualized, planned psychotherapy seems to be the most effective treatment for PTSD.

Among the various modalities of psychotherapy, *Cognitive behavioral therapy* (*CBT*) and *Prolonged exposure therapy* (*PE*) have strongest evidence base for PTSD, and are probably far more effective than extant pharmacotherapy (Cukor et al. 2010).

PE is based on the learning theory model, and views PTSD as a disorder of extinction, whereby the individual's response to crisis does not diminish sufficiently, and the association between the memory of the event and a message of danger has not been extinguished even when the danger has passed. The main components of PE, imaginal exposure and in vivo exposure, entail the revisiting of trauma memories and triggers to extinguish this response, by facilitating habituation to the memory, decreasing avoidance, and eliminating associations with danger by providing corrective information about safety (Foa et al. 2007). During imaginal exposure, patients are instructed to relate their trauma experience in detail with their eyes closed, while trying to engage emotionally in the memory. The patient retells his/her trauma experience repeatedly over the course of a number of sessions, thereby allowing the processing of the trauma experience. In vivo exposure entails approaching activities, people, and/or places the patient may have been avoiding to allow habituation to the environment, and the assimilation of the corrective information regarding safety.

Within CBT for PTSD, prolonged imaginal exposure may be used as a specific therapeutic technique in various populations including sexual assault and motor vehicle accidents (Cukor et al. 2010).

Cognitive processing therapy (CPT) is another exposure-based protocol with a strong emphasis on increasing the cognitive components and decreasing the amount of exposure necessary for treatment, which some believe will be more palatable to individuals with PTSD. CPT consists of a 12-session protocol comprising of two integrated elements. The cognitive therapy component focuses on deconstructing assimilated distorted beliefs, such as guilt, and more global beliefs about the world and self, and generating more balanced statements. The exposure component entails having the patient write the trauma memory and read it to their therapist and to themselves and then examine the writing for "stuck points"(Resick et al. 2002; Rizvi et al. 2009).

Initial case studies and clinical trials were promising and led to a randomized controlled trial comparing CPT to PE and a minimal attention waitlist control for the treatment of PTSD in a sample of chronically distressed rape victims.

Results found that both PE and CPT were highly successful in treating PTSD and comorbid depressive symptomatology.

Stress management and relaxation therapy, may be effective.

Couples and family therapy may also be helpful in treating PTSD patients.

16.5.2 Pharmacotherapy

The SSRIs are considered to be the first line of treatment. For many patients who experience insomnia, nightmares, flashbacks, and hypervigilance shortly after severe trauma, antipsychotic mood stabilizers such as olanzapine in small doses (e.g., 2.5–5 mg) hs for 2 weeks to 1 month may be particularly helpful (Labbate and Douglas 2000; Stein et al. 2002). For nightmares associated with PTSD, the α-adrenergic blocker prazosin (1 mg h.s. po gradually increased up to 6 mg) has been shown to be useful. Benzodiazepines may also be used for reducing anxiety. For PTSD, the treatment is always symptomatic, as the symptoms may range from depression, to impulsivity, to psychotic symptoms, to panic. Thus, in addition to SSRIs and antipsychotics, mood stabilizers such as valproic acid and lithium may be indicated. Beta-blockers such as propranolol and alpha-2 agonists like clonidine, as well as drugs that act on NMDA and MDMA receptors may be helpful in modifying the fear conditioning process in PTSD (Kerbage and Richa 2013).

Only two pharmacologic agents are FDA approved for the treatment of PTSD: sertraline and paroxetine. These selective serotonin reuptake inhibitors (SSRIs) have response rates rarely over 60 % with less than 30 % achieving full remission (Berger et al. 2009). Overall, less than 50 % of PTSD patients improve on SSRIs. Nevertheless, practice guidelines endorse SSRIs as first line pharmacotherapy for PTSD (Ipser and Stein 2012). Antipsychotics such as risperidone or olanzapine may be useful for some symptoms such as insomnia, and anticonvulsants seem helpful when used as an augmentation to other therapeutic regimens (Berger et al. 2009). Benzodiazepines are generally not recommended in PTSD because of its potentially addictive nature and the question of whether it may contribute to the development of PTSD, but in practice, it is frequently used to target more isolated symptoms such as insomnia and anxiety (Cukor et al. 2010).

Prazosin is an alpha-1 adrenergic receptor blocker which is efficacious in treating sleep-related PTSD symptoms. These symptoms are believed to be moderated by increased central nervous system adrenergic activity, resulting in greater release of norepinephrine and increased sensitivity to norepinephrine at receptor sites. Prazosin's effectiveness for the treating nightmares has been reported in various studies, with reports of 50 % decrease in nightmares after 8 weeks of treatment at 1–6 mg h.s. dosing (Ipser and Stein 2012).

D-*Cycloserine* (*DCS*, *Seromycin*) is a cognitive enhancer that shows promise among pharmacologic agents for PTSD for its potential to facilitate extinction learning. Originally developed as an antituberculosis antibiotic, DCS is a partial agonist for the *N*-methyl-D-aspartate (NMDA) glutamate receptor, which has a crucial role in learning and memory functions. DCS has been shown to facilitate extinction learning in animal models of conditioned fear and in some human trials of other types of learning including social phobia and shows a potential role of DCS in facilitating fear extinction and reducing post-treatment relapse (Cukor et al. 2010)

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Trauma and Stressor-Related Disorders 2: Adjustment Disorders

17

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Contents

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17.1 Introduction: DSM-5 Classification

"Trauma and stressor-related disorders include disorders in which exposure to a traumatic or stressful event is listed specifically as a diagnostic criterion. These include reactive attachment disorder, disinhibited social engagement disorder, posttraumatic stress disorder (PTSD), acute stress disorder, adjustment disorder, and other stress and trauma related disorders." (American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders 5th Edition p. 265) (DSM-5). This chapter focuses on the seminal changes made in the last four of these disorders from the DSM-IV-TR to the recently published DSM-5 (American Psychiatric Association: Diagnostic and Statistical Manual for Mental Disorders 4th Edition). Furthermore, there is a greater focus on the adjustment disorders (AD) for this handbook.

It was decided that this group of disorders should be combined because of the commonality of their being precipitated by a stressor (*traumatic* or *non-traumatic*), i.e., etiology rather than common symptoms, i.e., phenomenology. It was considered whether PTSD should be considered an anxiety disorder, a stress induced fear circuitry disorder, an internalizing disorder or a trauma and stressor-related disorder (Friedman et al 2011). As a result of literature reviews, examination of recent research studies and consultant discussions it was decided that PTSD and acute

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stress disorder (ASD) should be removed from the anxiety group and that the AD were to be removed from a free standing, residual solitary position and join other diagnoses in the stress related chapter. PTSD and ASD had many patients who did not have a fear based syndrome but the "most prominent features of anhedonic and dysphoric symptoms, externalizing angry and aggressive symptoms or dissociative symptoms." (DSM-5 p. 265). This supported moving them to a more cohesive trauma and stress related diagnostic grouping. There was both heuristic value and clinical utility in grouping specific diagnosis within broad diagnostic categories. AD are a heterogeneous group of responses after exposure to a stressor (traumatic or non-traumatic) and therefore are placed in the Trauma and Stress Related Disorder chapter rather than a residual category. Dissociative disorders (DD) do not require a specified stressor as a criterion and consequently were put in a separate chapter, despite the fact that they commonly occur following adverse occurrences. That is stressors are not identified as etiological or *precipitating* agents for the DD, but rather *predisposing* elements (Friedman et al. 2011).

PTSD criteria are significantly different in DSM-5. Most importantly the stressor criterion A has much greater specificity with regard to issues that qualify for "*traumatic*." Criterion A2 from DSM-IV-TR—subjective reaction—has been eliminated. There are now four major symptom clusters—reexperiencing, arousal, avoidance, and persistent negative alterations in cognitions and mood. The final cluster—alterations in arousal and reactivity—now also includes "irritable behavior or angry out-bursts and reckless or self destructive behavior" (DSM-5 p. 812).

ASD was first employed in DSM-IV to demarcate acute stress reactions that occur in the initial month after exposure to a "*traumatic*" event and before the possibility of diagnosing PTSD (which requires 1 month after the stress event) and to identify trauma survivors in the acute phase who were thought to be at high risk for PTSD. The evidence suggests that ASD does not adequately identify most patients who develop PTSD (Bryant et al. 2011). ASD should be reserved for acute stress disorders 3–30 days after the occurrence of the *traumatic* stressor. The nature of the traumatic stressor has been specified in criterion A. Criteria B—presence of nine or more symptoms from five categories: intrusion, negative mood, dissociation, avoidance, and arousal—is required for this diagnosis and clearly differentiate ASD from the AD which are precipitated by a traumatic or non-traumatic stressor, and do not have the Criterion B symptom profile. Also AD have both an acute and chronic form so that they are not affected by the 3 or 30 day limitation of the ASD.

The ICD-10 in contrast to the DSM-IV describes acute stress reactions (ASR) (rather than using the nomenclature ASD) as a transient reaction that can be evident immediately after the traumatic event and usually resolves within 2–3 days thereafter (International Classification of Disease 10 (1994)). Therefore, ASR begins before ASD can begin (3–30 days). It may be that those patients whose symptoms beginning 3 days later rather than immediately are a different cohort.

17.2 Other Specified Trauma and Stressor-Related Disorder (309.89)

A new category in DSM-5 states: "This category applies to presentations in which symptoms characteristic of a trauma and stressor-related disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any other disorders in this {genre}…." (DSM-5 p. 289). Such a diagnosis could accommodate AD that occur more than 3 months after the stressor or have a prolonged duration of more than 6 months without prolonged duration of the stressor; *Ataque de nervios*; other cultural syndromes; and persistent complex bereavement disorder. For example, this category could accommodate PTSD, ASD like symptoms but where all the required criteria are not met so that an official PTSD, ASD diagnosis cannot be rendered.

1. Adjustment-like disorders with delayed onset of symptoms that occur more than 3 months after the stressor.
2. Adjustment-like disorders with prolonged duration of more than 6 months without prolonged duration of the stressor.
3. Ataque de nervios.
4. Other cultural syndromes
5. Persistent complex bereavement disorder.

17.3 Adjustment Disorders (AD)

The AD are a common psychiatric diagnosis in the military, children, and in consultation-liaison psychiatry patient populations. The DSM-5AD diagnostic criteria are shown in Table 17.1. Originally they were thought to be transitory diagnoses that should not exceed 6 months (DSM-III), but this was expanded in DSM-IV to include both an *acute* and a *chronic* form which could continue beyond 6 months if the stressor continued, e.g., rheumatoid arthritis, or the effects of the stressor continued, loss of a spouse, loss of income, loss of dwelling, loss of support for children, which could go on for many months or years. In this chapter we view AD as a Trauma and Stress Related Disorder in agreement with Maercker et al. (2006).

Table 17.1 Diagnostic criterion for adjustment disorders—DSM-5

A. The development of emotional behavioral symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s).
B. Marked distress that is in excess of what would be proportionate to the stressor or Significant impairment in social, occupational or other areas of functioning.
C. Does not meet criteria for another Axis I disorder and is not merely an exacerbation of a preexisting Axis I or II disorder.
D. Does not include normal bereavement
E. Symptoms do not persist more than 6 months after removal of stressor (or its consequences).
Specify if: Acute: If disturbance lasts <6 months Chronic: If disturbance lasts >6 months Subtypes: With Depressed Mood With Anxiety With Mixed Anxiety and Depression With Disturbance of Conduct With Mixed Disturbance of Emotions and Conduct

17.3.1 Specificity vs. Nonspecificity

AD was deliberately designed to be phenomenologically nonspecific (Strain and Friedman 2011). Only alterations in mood, anxiety, or conduct (or combinations of these) which are associated with distress *and/or* dysfunction in work, or school, or relationships in excess of what would be culturally acceptable for the stressor involved are required. And, these are subjective assessments with no severity guidelines as to when they can be counted as criteria. Furthermore, the AD can be characterized by type: depressive, anxious, conduct disorder, mixed moods and behavior. This is in marked contrast to the current proposal by Maercker for AD in the ICD-11 which requires *both* distress *and* dysfunction and *three* specific symptoms: failure to adapt, intrusions, and avoidance behavior (Maercker 2012). These workers have reconceptualized AD as a stress response syndrome so that it fits into a theoretical context that places AD at one end of the spectrum and PTSD and ASD at the other. Furthermore, persons who do not fulfill all the criteria for PTSD and ASD should be placed in the Other Specified Trauma and Stressor-Related Disorder category (309.89) since the primary diagnoses do not have a partial/subsyndromal PTSD or ASD option within DSM-5.

This nonspecificity has had great clinical utility since it offers a diagnosis for those patients with significantly clinical distress and dysfunction—who qualify for a psychiatric disorder—but who do not meet the criteria for other diagnoses in the DSM-5. This also allows for prodromal expressions of more discreet disorders that are in early stages and could benefit from clinical intervention (Strain and Friedman 2011). However, the down side to this lack of specificity signals the issue of reliability and validity of the diagnosis which may account for the difficulty in crafting a measure for its assessment, and the lack of research for this diagnostic entity (Baumeister and Kufner 2009; Linden et al.

2004; Casey et al. 2006). To our knowledge Einsle et al. are the only group of investigators who attempted to develop and validate a schedule for screening AD (Einsle et al. 2010). Such an instrument is essential if there is to be an evidence base that might inform future revisions of the AD criteria. However, employing the current Einsle instrument would eliminate many of the patients diagnosed as AD using the DSM-IV-TR and now the DSM-5 criteria. The trained clinician remains the "*gold standard*" with the current DSM-5 taxonomy.

One significant change in the DSM-5AD D criterion was adding "*normal*" to the bereavement exclusion. If bereavement is not normal, i.e., lasting more than 12 months for adults, and 6 months for children than it enters into the new category: Other Specified Trauma and Stressor-Related Disorder category (309.89) sub type "*persistent complex bereavement disorder*."

> I am almost sure I am dying, and I hope I have a few more months to enjoy my young sons. They are only 4 and 6. I am concerned what other people may have said to them, When I leave the hospital will they be afraid to hug me, touch me, tell me how they feel. I hope they do not think I am a "Typhoid Mary." I have always managed unpleasant events before but having terminal cancer with maybe 4–6 months to live is distressing. I hope I can function as their mother, and do my routine up to the end. That is what is scary and makes me so sad; can I function as their mom. My sister is going to care for them when I am gone. They like her and she will be great with them, but what pain to know I won't be here for them. The C-L, psychiatrist assured the patient it was important to share her feelings and her worries, and that she should share with her sister that she hoped they would remember her birthday, keep a picture of their mother in their room, and that she would share stories about their mother. The care team would do all they could to make her pain free, be ambulatory as long as possible and be happy to talk with her when the worries and sadness became over-whelming. She should also talk to her husband about helping the children remember her. She would not be forgotten.

Table 17.2 DSM Classifications

DSM-I (1952): Transient situational personality disorder
Gross stress reaction
Adult situational reaction
Adjustment reaction of infancy
Adjustment reaction of childhood
Adjustment reaction of Adolescence
Adjustment reaction of late life
Other transient situational personality disturbance
DSM-II (1968): Transient situational disturbance
Adjustment reaction of infancy
Adjustment reaction of childhood
Adjustment reaction of adolescence
Adjustment reaction of late life
DSM-III (1980): Adjustment disorder
Adjustment disorder with depressed mood
Adjustment disorder with anxious mood
Adjustment disorder with mixed emotional features
Adjustment disorder with disturbance of conduct
Adjustment disorder with mixed disturbance of emotions and conduct
Adjustment disorder with work (or acADemic) inhibition
Adjustment disorder with withdrawal
Adjustment disorder with atypical features
DSM-III-R (1987): Adjustment disorder
Adjustment disorder with depressed mood
Adjustment disorder with anxious mood
Adjustment disorder with mixed emotional features
Adjustment disorder with disturbance of conduct
Adjustment disorder with mixed disturbance of emotions and conduct
Adjustment disorder with work (or academic) inhibition
Adjustment disorder with withdrawal
Adjustment disorder with physical complaints
Adjustment disorder not otherwise specified
DSM-IV (1994) and DSM-IV-TR (2000): Adjustment disorder
Adjustment disorder with depressed mood
Adjustment disorder with anxiety
Adjustment disorder with mixed anxiety and depressed mood
Adjustment disorder with disturbance of conduct
Adjustment disorder with mixed disturbance of emotions and conduct
Adjustment disorder unspecified

17.3.2 History of the Adjustment Disorders

The diagnosis of AD has undergone a major evolution since DSM-1 in which it was considered a "transient situational personality disorder" (Table 17.2) (American Psychiatric Association: Diagnostic and Statistical Manual: Mental. American Psychiatric Association 1952; American Psychiatric Association: Diagnostic and Statistical Manual of Mental

Disorders, 2nd Edition. American Psychiatric Association 1980; American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised. American Psychiatric Association 1987; American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. American Psychiatric Association 2000).

Furthermore with regard to the AD in the DSM-IV-TR the term *psychosocial stressor* was changed to the broader concept of *stressor*. (Note the extension to the new Trauma and Stress Related Disorders chapter in DSM-5.) What is a stressor, and what is a traumatic stressor? Psychosocial is too restrictive when one considers the Chernobyl reactor incident (Havenaar et al 1996) or cardiac surgery (Oxman et al. 1994). Critics of the AD diagnosis state that the symptom complex is too subjective or "depends structurally on clinical judgment" in contrast to sound operational criteria (Casey et al. 2001a, b). First the definition of the stressor, and secondly how to determine when a situation is clinically significant for distress and/or dysfunction cause uncertainty. And, the definition of both must take into account age (child), culture, and personality factors (e.g., degree of neuroticism). Powell and McCone (2004) raise the question in their treatment of a patient with an AD secondary to the September 11th terrorist attacks: "What is a normal response to a terrorist attack in the US from a foreign adversary?" Finally, the complex interplay between external events and internal resources (e.g., resilience) varies considerably from one individual to the next so that one person's threat is another's challenge (Charney 2004).

The AD diagnosis has clinical appeal to both doctors and patients: The idea of temporary emotional symptoms resulting directly from a stressful life event is viewed as a more normal human reaction than an idiopathic pathological psychiatric state and is therefore regarded as less stigmatizing. Additionally, the disorder's more benign course (especially in adults) encourages a clinician to be more prognostically optimistic (Slavney 1999). This optimism is shared by medical insurance carriers, who do not consider the diagnosis to be a preexisting condition.

AD may be associated with suicide attempts, completed suicide, substance abuse, somatic complaints, other mental disorders, and with a general or medical surgical illness. An AD may complicate the course of illness by impairing compliance with the medical regimen or increasing the length of hospital stay.

The AD diagnosis can be employed with a second psychiatric diagnosis if the symptoms of that diagnosis meet criteria for another disorder. The AD diagnosis cannot be employed if the symptoms are secondary to the physiological effects of a general medical illness or its treatment. Nor is it to be utilized for normal bereavement. Finally, demoralization should be distinguished from AD (Slavney 1999; Diagnostic and Statistical Manual Fifth Edition 2013).

17.3.3 Etiology

Stress is the etiological agent for AD. However, diverse variables, modifiers, and features of resilience are involved regarding who will experience an AD following stress. Cohen argued that (1) acute stresses are different from chronic ones in both psychological and physiological terms; (2) the meaning of the stress is affected by "modifiers" (e.g., ego strengths, support systems, prior mastery, resilience, genetic predisposition); and (3) the manifest and latent meanings of the stressor(s) must be differentiated (e.g., loss of job may be a relief or a catastrophe) (Cohen 1981). AD with maladaptive denial of pregnancy, for example, can be a consequence of a stressor such as separation from a partner (Brezinka et al. 1994). An objectively overwhelming stressor may have little effect on one individual, whereas a minor one could be regarded as cataclysmic by another. A recent minor stress superimposed on a previous underlying (major) stress that had no observable effect on its own may have a significant additive effect and foster the outbreak of symptoms (i.e., concatenation of events; B. Hamburg, personal communication, April 1990).

Andreasen and Wasek described the differences between the chronicity of stressors found in adolescents and those observed in adults: 59 % and 35 %, respectively, of the stressors had been present for 1 year or more and 9 and 39 % for 3 months or less (Andreasen and Wasek 1980). Popkin et al. (1990) stated that in 68.6 % of the cases in their Consultation-Liaison (CL) cohort, the medical illness itself was judged to be the primary stressor. Snyder and Strain (1989) observed that stressors as assessed on Axis IV were significantly higher ($P=0.0001$) for CL patients with AD than for patients with other diagnostic disorders supporting the construct that a stressor was the mechanism of the AD disorder.

Although more attention has been directed toward the current precipitating stressor in the diagnosis of AD, recent investigations highlight the role of childhood experiences in the later development of these disorders. Several recent studies of young male soldiers with AD secondary to conscription revealed that stress at a young age, such as abusive and overprotective parenting or adverse early family events, are risk factors for the later development of AD (For-Wey et al. 2002; Giotakos and Konstantakopoulos 2002). In a similar cohort, a history of childhood separation anxiety was found to be correlated with the later development of AD.

17.3.4 Prevalence of the Adjustment Disorders

AD occur in children, adolescents, and the elderly (2–8 % in community samples): In acute care general hospital inpatients (12 %), in mental health outpatient settings (10–30 %), and in special settings, e.g., following cardiac surgery (up to 50 %) (Oxman et al. 1994). Women are given the diagnosis of AD twice as often as men, but in adolescents and children there is no gender difference.

Andreasen and Wasek (1980) observed that 5 % of inpatient and outpatient cohorts were diagnosed with AD. Fabrega et al. (1987) noted that 2.3 % of walk-in clinic (a diagnostic and evaluation center) patients met criteria for AD, with no other psychiatric diagnoses. When patients with other psychiatric diagnoses were included, 20 % had the diagnosis of AD. In general hospital psychiatric consultation populations, AD were diagnosed in separate studies 21.5 % (Popkin et al. 1990), 18.5 % (Foster and Oxman 1994), and 11.5 % (Snyder and Strain 1989).

Strain et al. (1998b) examined the consultation-liaison (CL) psychiatric data from seven university teaching hospitals in the USA, Canada, and Australia. All hospitals employed a common computerized clinical database to examine 1,039 consecutive psychiatric referrals—the MICRO-CARES software system. AD was diagnosed in 125 patients (12.0 %): It was the sole diagnosis in 81 (7.8 %) and comorbid with other psychiatric diagnoses in 44 (4.2 %). It was considered a "rule-out" diagnosis in an additional 110 (10.6 %). AD with depressed mood, anxious mood, or mixed emotions were the most common subtypes. AD was diagnosed comorbidly most frequently with personality disorder and organic mental disorder. AD patients were referred for problems of anxiety, coping, and depression; had less past psychiatric illness; and were rated as previously functioning better than those patients with major mental disorders—all of which is consistent with the construct of AD as a contemporary maladaptation to a stressor.

Psychiatric interventions were similar to those utilized for other psychiatric diagnoses, in particular, the prescription of antidepressant medications. (This finding was in contrast to the consensus that the treatment of choice for AD is psychotherapy and/or counseling, at least initially.) Patients with AD required a similar amount of clinical treatment time and resident supervision time when compared with other psychiatric disorders. Thus, AD were not performing like a subthreshold—less serious mental disorder—in the psychiatric consultation with medically and surgically ill inpatients.

Oxman et al. (1994) reported that 50.7 % of elderly patients (age 55 years or older) receiving elective surgery for coronary artery disease developed AD from the stress of surgery. Thirty percent had symptomatic and functional impairment 6 months after surgery. Kellermann et al.

(1999) reported that 27 % of elderly patients examined 5–9 days after a cerebrovascular accident fulfilled the criteria for AD. Spiegel (1996) describes that half of all cancer patients he studied have a psychiatric disorder, usually an AD with depression. AD are frequently diagnosed in patients with head and neck surgery 16.8 %; (Kugaya et al. 2000), with HIV (dementia and AD), 73 %; (Pozzi et al 1999); cancer (from a multicenter survey of CL psychiatry in oncology) (27 %): (Grassi et al 2000); dermatology (29 % of the 9 % who had psychiatric diagnoses); (Pulimood et al 1996), and suicide attempters examined in an emergency department 22 % (Schnyder and Valach 1997). Other studies include the diagnosis of AD in more than 60 % of burn inpatients, (Perez-Jimenez et al 1994); 20 % of patients in early stages of multiple sclerosis (Sullivan et al. 1995); and 40 % of post-stroke patients (Shima et al 1994). Faulstich et al. (1986) reported the prevalence 12.5 % of DSM-III AD and conduct issues for adolescent psychiatric inpatients.

17.3.5 Course and Prognosis of Adjustment Disorder

DSM-IV-TR criterion E for AD implies a good long-term outcome by stating "once the stressor (or its consequences) has terminated, the symptoms do not persist for more than an additional 6 months." American Psychiatric Association (1994); Andreasen and Hoenk's (1982) landmark study demonstrated this by showing that prognosis was favorable for adults, but that in adolescents, many major psychiatric illnesses eventually occur as they age. At a 5-year follow-up, 71 % of the adults were completely well, 8 % had an intervening problem, and 21 % had developed a major depressive disorder or alcoholism. In adolescents at 5-year follow-up, only 44 % were without a psychiatric diagnosis, 13 % had an intervening psychiatric illness, and 43 % had developed major psychiatric morbidity (e.g., schizophrenia, schizoaffective disorder, major depression, bipolar disorder, substance abuse, personality disorders). In contrast to the predictors for major pathology in adults, the chronicity of the illness and the presence of behavioral symptoms in the adolescents were the strongest predictors for major pathology at the 5-year follow-up. The number and type of symptoms were less useful as predictors of future outcome than the length of treatment and chronicity of symptoms.

AD with disturbance of conduct, regardless of age, has a more guarded outcome. Just as Andreasen and Wasek (1980) observed, Chess and Thomas (1984) underscored that a significant number of AD patients either do not improve or grow worse in adolescence and early adult life. Kovacs et al. (1994) also examined children and youth (ages 8–13 years) for up to 8 years and observed that, controlling for the effects of comorbidity, AD does not predict later dysfunction. Jones et al. (2002) described 10 years of readmission data for various psychiatric diagnoses, including the AD and observed that AD had the lowest readmission rates. Initial psychological recovery from an AD may be attributable to removal of the stressor or recovery from the effects of the stressor. This was the case in prisoners who developed AD after being placed in solitary confinement and whose symptoms resolved shortly after their release (Andersen et al. 2000).

17.3.6 Suicide and Adjustment Disorder

As an example of the clinical significance of AD, Runeson et al. (1996) found that a lesser interval (1 month) between the diagnosis of AD and suicidal behavior than for depression (3 months), borderline personality disorder (30 months), and schizophrenia (47 months). Portzky et al. (2005) conducted psychological autopsies on adolescents with AD who had committed suicide and found that suicidal thinking in these patients was brief and evolved rapidly and without warning, complicating an attempt at timely intervention. Suicide—a most serious behavioral symptom—has been associated with the diagnosis of AD which may be the only indicator of this life threatening behavior.

A slightly different profile was found in two other studies that looked at suicide attempters

with a diagnosis of AD. These patients were more likely to have poor overall psychosocial functioning, prior psychiatric treatment, comorbid personality disorders, substance abuse histories, and a current "mixed" symptom profile of depressed mood and behavioral disturbances (Kryzhanovskaya and Canterbury 2001; Pelkonen et al 2005).

A study of the neurochemical variables of AD patients of all ages who had attempted suicide revealed biological correlates consistent with the more major psychiatric disorders. Attempters exhibited lower platelet monoamine oxidase activity, higher 3-methoxy-4-hydroxyphenylglycol (MHPG) activity, and higher cortisol levels than control subjects. Although these findings differ from the lower MHPG and cortisol levels found in patients with major depression and suicidality, they are similar to the observations in other major stress-related conditions.

Despland et al. (1997) observed 52 patients with AD at the end of or after 3 years of treatment: Results showed the occurrence of psychiatric comorbidity (31 %), suicide attempts (14 %), development of a more serious psychiatric disorder (29 %), and an unfavorable clinical state (23 %). Spalletta et al. (1996) stated that suicidal behavior and deliberate self-harm are important predictors in the diagnosis of AD. Suicide attempts and self mutilation may be included in psychiatric diagnosis as an F code (other conditions that may be a focus of clinical attention). Thus, with self-harm, there would be two psychiatric diagnoses: the primary disorder and the suicide attempt.

17.3.7 Treatment

17.3.7.1 Psychotherapy

Treatment of AD relies primarily on psychotherapeutic measures that enable reduction of the stressor or its consequences, enhanced coping with stressors that cannot be reduced or removed, and establishment of a support system to maximize adaptation.

The first goal is to note significant dysfunction secondary to a stressor and to help the patient moderate this imbalance. Many stressors may be avoided or minimized (e.g., taking on more responsibility than can be managed by the individual or putting oneself at risk by having unprotected sex with an unknown partner). Other stressors may elicit an overreaction (e.g., abandonment by a lover): The patient may attempt suicide or become reclusive, or damage the source of income. The therapist assists the patient to minimize distress and other feelings by placing them into words rather than into destructive actions; more optimal adaptation and mastery of the trauma or stressor are sought.

The role of verbalization cannot be overestimated as an effective approach for reducing the impact of the stressor and enhance coping—in essence conflict resolution. The therapist needs to clarify and interpret the meaning of the stressor for the patient. For example, a mastectomy may have devastated a patient's feelings about her body and herself. It is necessary to clarify that the patient is still a woman, capable of having a fulfilling relationship, including a sexual one, and that the patient can have the cancer removed or treated and not necessarily have a recurrence. Otherwise, the patient's pernicious fantasies—"all is lost"—may take over in response to the stressor (i.e., the mastectomy) and make her dysfunctional in work and/or sex, in relationships, and precipitate a painful disturbance of mood that is incapacitating.

> A 48 year old enterprising executive has experienced his first myocardial infarction. He is now in the Coronary Care Unit on bed rest and without a telephone. He is anxious, worried what is happening at his office and with all his accounts that are currently being reviewed for renewal. He wonders if he will be the man he was, running three times a week, sex a couple of times a week and sometimes more, playing ball with his teen age son, and being able to pull the "all nighters" upon occasion when the demands are brisk. "Will I be the man I was. Can you give me something for my anxiety so I can manage the stress I am under? I have never felt so lost or incompetent before. I was always the guy who could and was expected to get through."
>
> The CL psychiatrist reassured the patient, that it took quite a man to stay in bed when he had been so active, and that the most manly thing he could do was to stay in bed, stay off the phone and let his heart have a chance to heal. It may be one of the most difficult things he ever had to do since he was always so active. And then the psychiatrist said: "I know you can be passive and give up all

those activities for a few days to let your heart have a chance to recover." This supported the concept that passivity and following directions was one of the most manly things he could do.

17.3.7.1.1 Counseling, Cognitive Behavioral Therapy (CBT), Supportive Group Treatment, Family Therapy

Counseling, cognitive behavioral therapy (CBT), interpersonal therapy, medical crisis counseling, crisis intervention, family therapy, and supportive group treatment may be employed to encourage the verbalization of fears, anxiety, rage, helplessness, and hopelessness related to the stressors imposed (or self imposed) on a patient. The goals of treatment in each case are to expose the concerns and conflicts that the patient is experiencing, identify strategies to reduce the stressors, enhance the patient's coping skills, help the patient gain perspective on the adversity and establish relationships (e.g., a support network) to assist in the management of the stressors and the self. CBT was successfully used in young military recruits (Nardi et al. 1994).

17.3.7.1.2 Brief Psychotherapy

AD diagnosed by DSM III-R criteria has been reported to profit most from brief psychotherapy (Sifneos 1989). The psychotherapy should attempt to reframe the meaning of the stressor(s). Although brief therapeutic interventions are often sufficient, ongoing stressors or enduring character pathology that may make a patient vulnerable to stress intolerance may signal the need for lengthier treatments.

Many types of therapeutic modalities have a place in the treatment of AD. Wise (1988), drawing from military psychiatry, emphasized the treatment variables of Brevity, Immediacy, Centrality, Expectance, Proximity, and Simplicity (BICEPS principles) (Wise 1988). The treatment approach is brief, usually no more than 72 h and focuses on the immediate stressors (True and Benway 1992).

17.3.7.1.3 Interpersonal Psychotherapy

Interpersonal psychotherapy was applied to depressed HIV-positive outpatients and found to be effective (Markowitz et al. 1992).The mechanisms of interpersonal psychotherapy are important in understanding psychotherapeutic approaches to the AD: (1) psychoeducation about the sick role, (2) a here-and-now framework, (3) formulation of the problems from an interpersonal perspective, (4) exploration of options for changing dysfunctional behavior patterns, (5) identification of focused interpersonal problem areas, and (6) the confidence that therapists gain from a systematic approach to problem formulation and treatment.

17.3.7.1.4 The Elderly

Elderly patients are particularly vulnerable to the development of AD as the stress of interpersonal losses, medical illness, and multiple medications abound. Life transitions such as relocating to a nursing home or losing one's driving privileges are commonly experienced as stressors in the elderly. A treatment that strengthens a patient's ego functions by acknowledgement of the stressor and by promoting effective coping strategies is useful in this population. An active therapeutic stance and the use of life review foster a sense of mastery over the stressor (Frankel 2001).

17.3.7.1.5 Support Groups

Support groups are employed in patients with AD to adjust and enhance their coping mechanisms (Fawzy et al. 2003; Spiegel et al 1989). Studies of the survival benefits of psychosocial group interventions have mixed results. Cancer patients who attended support groups have shown increased survival time by some researchers and not by others, improvements in mood, reduced distress level, and enhanced quality of life (Akechi et al 2008; Spiegel et al 2007; Newell et al. 2002; Spiegel 2011). Are other stress-related disorders improved by such systematic and carefully defined behavioral interventions?

Akechi et al. (2004) investigated associated and predictive factors in cancer patients with AD and major depression. Findings revealed that psychological distress in these patients was associated with a variety of factors, including reduced social support, impaired physical functioning, and existential concerns. This highlights the

necessity of a multidimensional care plan for the treatment of AD that includes physical, psychosocial, and existential components. Studies have yet to evaluate the potential role of family and couples therapy as well as treatments from complementary and alternative medicine (CAM) such as acupuncture and yoga.

17.3.7.1.6 Mirror Therapy

The Cochrane Database revealed only two randomized, controlled trials of specific psychotherapeutic treatment of AD. Gonzalez-Jaimes and Turnbull-Plaza (2003) observed that "mirror psychotherapy" for AD patients with depressed mood secondary to a myocardial infarction was both an efficient and effective treatment. Mirror therapy is described as comprising psycho-corporal, cognitive, and neurolinguistic components with a holistic focus. As part of the treatment, a mirror is used to encourage patient acceptance of his/her physical limitations that resulted from the lack of past self-care behaviors. Mirror therapy was compared with two other treatments: Gestalt psychotherapy or medical conversation, and a control group. Depressive symptoms improved in all treatment groups compared with the control sample, but mirror therapy was significantly more effective than other treatments in decreasing symptoms of AD at posttest evaluation.

17.3.7.1.7 Occupational Intervention–Cognitive-Behavioral Approach–Problem Solving Treatment

In another RCT, an "activating intervention" for AD was employed for occupational dysfunction (van der Klink and van Dijk 2003; van der Klink et al. 2003). One hundred ninety-two employees were randomized to receive either the intervention or usual care. The intervention consisted of an individual cognitive-behavioral approach to a graded activity, similar to stress inoculation training. The worker was asked to do more demanding and complicated activities as treatment progressed. Goals of treatment emphasized the acquisition of coping skills and the regaining of control.

The treatment proved to be effective in decreasing sick leave duration and shortening long-term absenteeism when compared with the control cohort. Both intervention and control groups, however, showed similar amounts of symptom reduction. This study formed the basis for the "Dutch Practice Guidelines for the Treatment of AD in Primary and Occupational Health Care": guidelines were prepared by 21 occupational health physicians and one psychologist and subsequently reviewed and tested by 15 experts, including several psychiatrists and psychologists. Nine other RCTs with interventions involving the work place have been accomplished using CBT and Problem Solving Treatment (PST). Of the 59 published studies, only 9 were considered scientifically adequate to be included in the Cochrane meta-analysis. Even the nine studies selected had the major problem of heterogeneity of psychiatric diagnosis. "Burn out," "stress," "neurasthenia," "work related stress," and "minor mental disorder," were considered as diagnoses of AD in several studies which further dilutes the definition of this already problematically defined psychiatric disorder. Some studies were included if as few as 30 % of the diagnoses were "pure" AD. Finally, AD was diagnosed using varied criteria, screening instruments, and diagnosticians.

17.3.7.1.8 Brief Dynamic Therapy–Brief Supportive Therapy

Although no other RCTs involving the psychotherapeutic treatment of pure cohorts of patients with AD could be found, many exist that studied an array of depressive and anxiety disorders and included AD in their cohorts. A recent trial comparing brief dynamic therapy with brief supportive therapy in patients with minor depressive disorders, including AD, (therefore a mixed diagnostic sample) was reported in the Cochrane Database. Although both therapies proved efficacious in reducing symptoms, brief dynamic therapy was more effective at 6-month follow-up (Maina et al. 2005).

17.3.7.1.9 Consultation-Liaison Psychiatry Interventions

A 35-year-old man suffered acute spinal cord trauma resulting in paraplegia. In the hospital the nurses became very irritated at him because he

would press the call button constantly, usually asking for what they considered trivial needs. A psychiatric consultation was requested. The consultant evaluated the patient as having an adjustment disorder. The patient was very anxious and fearful of being unable to take care of his needs. The nurses often delayed coming to his room for a long time after he would press the call button. This reinforced his fears and led him to pressing the call button more often. In addition to providing supportive psychotherapy to the patient, the consultant talked to the nurses. He let them ventilate about their frustrations with this patient, and then he recommended that they go into the patient's room once or twice every hour when he had not been pressing the call button and ask him if he needed anything. This changed a vicious cycle into a virtuous cycle. The patient perceived that the nurses were anticipating his needs and he did not need to press the call button very often. As he pressed it less often, the nurses became increasingly comfortable at going into the room and checking on him. His anxiety greatly diminished and the nurses came to like this patient.

17.3.7.2 Pharmacotherapy

Although psychotherapy is the mainstay of treatment for the AD, psychopharmacological intervention can be especially helpful in the treatment of minor depression. (Stewart et al. 1992) There is a significant difference in criteria between minor depression and the AD with depressed mood. The minor depressions require dysphoria and or anhedonia plus two other ideational or vegetative symptoms, e.g., lack of energy, suicidality. They can be from any of the eight systems listed for major depressive disorder in the DSM-5. These authors argued that pharmacotherapy is generally recommended, but data do not support this contention. Despite the lack of rigorous scientific evidence, Stewart and colleagues advocated successive trials with antidepressants in any depressed patient (major or minor disorders), particularly if he/she has not benefited from psychotherapy or other supportive measures for 3 months. The authors do not mention the AD with depressed mood in particular. In an RCT in the treatment of minor depressive disorder, fluoxetine proved superior to placebo in reducing depressive symptoms, improving overall psychosocial functioning, and alleviating suffering (Judd 2000). The question remains, does this also apply to AD with depressed mood?

RCTs of pharmacotherapy in patients with AD are rare. Formal psychotherapy appears to be the current treatment of choice (Uhlenhuth et al 1995), although psychotherapy combined with benzodiazepines also is used, especially for patients with severe life stress(or) and a significant anxious component (Uhlenhuth et al 1995; Shaner 2000). Tricyclic antidepressants or buspirone have been recommended in place of benzodiazepines for patients with current or past heavy alcohol use because of the greater risk of dependence (Uhlenhuth et al. 1995). Treatment with benzodiazepines beyond the short term is generally not recommended because the risks may exceed the benefits (see Chap. 20). In a 25-week multicenter RCT WS 1490 (a special extract from kava-kava) was reported to be effective in AD with anxiety in comparison with placebo and did not produce side effects, as is the case with tricyclics and benzodiazepines (Volz and Kieser 1997).

In a RCT (Bourin et al. 1997) assigned patients to receive either Euphytose—a preparation containing a combination of plant extracts (*Crataegus, Ballota, Passiflora,* and *Valeriana,* which have mild sedative effects, and *Cola* and *Paullinia,* which mainly act as mild stimulants)—or placebo. Patients taking the experimental drugs improved significantly more than those taking placebo. In another study, tianeptine, alprazolam, and mianserin were found to be equally effective in symptom improvement in patients with AD with anxiety (Ansseau et al. 1996). In a RCT, trazodone was more effective than clorazepate in cancer patients for the relief of anxious and depressed symptoms (Razavi et al. 1999). Similar findings were observed in HIV-positive patients with AD (DeWit et al. 1999).

There are no RCTs employing selective serotonin reuptake inhibitors (SSRIs), other antidepressants or anxiolytics (e.g., nefazodone, venlafaxine, buspirone, or mirtazapine). These medications may offer symptom relief of dysphoric or anxious moods. The difficulty in obtaining an AD study cohort with reliable and valid diagnoses may impede the conduct of an RCT comparing these agents against placebo and psychotherapy.

Clinical trials regarding AD are also compromised by not having specific symptoms to monitor when examining the outcome of an intervention. In the case of the AD, should this be when the stressors have stabilized, when the stressors have abated, or after an agreed-on time (e.g., 3 months) has elapsed? The stressor attributes add a further confound to obtaining a homogeneous sample because of the differences in the stressors, including nature (quality), severity (quantity), and acuteness (less than 6 months) or chronicity (more than 6 months). Psychotropic medication is used in medically ill patients, terminally ill patients, and patients with illness refractory to verbal therapies. Many of these patients had AD, but it cannot be ascertained if some had minor depression

Rosenberg et al. (1991) reported that 16 of 29 patients (55 %) improved within 2 days of treatment with the maximal dosage of amphetamine derivatives. The presence of delirium was associated with a decreased response. Whether methylphenidate would be useful in AD with depressed mood remains to be investigated, but it has the problem of potential for addiction and cardiovascular stimulation, e.g., heart rate, blood pressure, etc.

Reynolds 1992, reviewing RCTs stated that bereavement-related syndromal depression also appears to respond to antidepressant medication. If medication is prescribed for minor disorders (including subthreshold disorders), the predominant mood that accompanies the (adjustment) disorder is an important consideration. Schatzberg 1990 recommended that therapists consider both psychotherapy and pharmacotherapy in AD with anxious mood and that anxiolytics should be part of the psychiatrists' armamentarium. Nguyen et al. (2006), using an RCT compared the efficacies of etifoxine, a nonbenzodiazepine anxiolytic drug, and lorazepam, a benzodiazepine, in the treatment of AD with anxiety in a primary care setting. Efficacy was evaluated on days 7 and 28 using the Hamilton Rating Scale for Anxiety. The two drugs were found to be equivalent in anxiolytic efficacy on day 28. However, more etifoxine recipients responded to the treatment. One week after stopping treatment, fewer patients taking etifoxine experienced rebound anxiety compared with those on lorazepam.

A new Cochrane meta-analysis is underway examining the psychopharmacological treatment of AD. This is an important investigation as few RCTSs of psychopharmacological treatment in the disorder of AD exist. However, as with the Cochrane meta-analysis of RCTs in the work place, there are many concerns about the diagnostic integrity of the patient cohorts to be examined. In this proposed review the researchers state that the terms "situational disturbance," "reactive," "mild, minor, situational," "subthreshold subsyndromal" or "subclinical depression" will be used interchangeably with the diagnosis of AD. This heterogeneity of diagnosis would impair the Cochrane meta-analyses as the gold standard for producing data that enhances validated evidence based interventions.

Understanding the etiology of depression and its treatment has advanced with the discoveries of neurobiology of affective disorders and the utilization of animal models. The neurobiology of major disorders, including the anxiety disorders may offer new pathways for the minor, subsyndromal diagnoses as well. Duman and Aghajanian (2012) present a Perspective of Synaptic Dysfunction in Depression: Potential Therapeutic Targets. Ketamine a *N*-methyl-D-aspirate receptor antagonist produces rapid antidepressant responses, induces synaptogenesis and reverses the synaptic deficits caused by chronic stress. This would include neuronal atrophy and decreases in synaptic density (synaptic loss). Would this mechanism of therapeutic action have any effect on AD with depressed mood, especially the chronic form? It has been asked: is neurogenesis a pathway to recovery from a mood disorder? "The neurogenic hypothesis of mood disorders remains promising for conceptualizing depression mechanisms, which may lead to novel avenues for treatments." (Dunman and Aghajanian 2012). This emphasizes the need to know the relationship if any between subsyndromal symptoms and fully developed symptom profiles of the major syndromes. And, this would enhance our understanding of the treatment regimens that may be utilized with the AD.

17.3.7.3 Resilience

In the "Science of Resilience: Implications for the Prevention and treatment of Depression," Southwick and Charney (2012) expound on the need to better understand the psychobiology of resilience as an important component of effective treatment for stress induced dysfunction and distress. They emphasize that persons react remarkably differently to stress: how individuals respond to stress depends on numerous genetic, developmental, cognitive, psychological, and neurobiological risk and protective factors. The authors state: "resilience is generally understood as the ability to bounce back from hardship and trauma." The American Psychological Association states resilience as "the process of adapting well in the face of adversity, trauma, tragedy, threats or even significant sources of threat." (Dunman and Aghajanian 2012). Overwhelming stressors in childhood may lead to "giving in and giving up" to later stressors, whereas manageable stressors in childhood may actually strengthen the individual's capacity to cope with stress later on. Southwick and Charney (2012) have schematized stressors and genetic predisposition. This is an entirely different conceptual framework of systematizing the etiology of distress and dysfunction in the AD, and also offers an alternative route to treatment. The authors adumbrate neurobiological interventions: developing therapeutic agents to contain stress-induced overdrive of corticotrophin releasing hormone (CRF), which controls and integrates the body's response to stress, would likely reduce rates of trauma-related (stress related) psychopathology.

17.3.8 Clinical and Theoretical Considerations for the Trauma and Trauma Related Disorders

The key role of the hypothalamic-pituitary-adrenocortical (HPA) system in the human stress response was proposed by Hans Selye (1956). Our current more sophisticated understanding of neurocircuitry and psychobiological systems has amended his original formulations. HPA mechanisms are now accepted in depression, PTSD, and other anxiety disorders (Arborelius et al. 1999; Kim and Gorman 2005; Southwick et al 2007). Following Maercker's suggestion that AD should be considered a stress activated syndrome it would be important to know the operation of the HPA system in the AD. Furthermore, are the AD subtypes different with regard to HPA functioning. Friedman and McEwen (2004) and others examining PTSD proposed overarching constructs such as allostatic load which could apply to the AD. Would psychobiological findings in depression and anxiety disorders also be applicable to AD with depression, and AD with anxiety? (Would there be a difference in the psychobiological findings with PTSD and those patients that have all the ingredients except say one criteria and are therefore placed in the other stressors and specific trauma disorder because they fail to qualify for the full blown diagnosis)?

Another question is: does the same genetic difference determine vulnerability versus resilience in depression, anxiety PTSD, ASD, and AD? "Does AD exhibit shared neural substrates, familiarity, shared genetic risk factors, shared environmental risk factors, shared biomarkers, shared temperamental antecedents, and/or shared abnormalities with depression, PTSD, ASD, or other anxiety disorders? Finally, will treatments that effectively produce clinical remission in depression, anxiety disorders, PTSD, ASD also be effective for the subtypes of AD?" (Strain and Friedman 2011). Important studies are necessary to answer these questions and permit a better biological, clinical, and treatment approach to the AD.

17.4 Conclusion

The AD are common diagnosis in the military, in children, and in psychosomatic medicine—consultation-liaison psychiatry. And, yet so little is known because their diagnoses have questionable reliability and validity. No specific screening instrument can authenticate their presence, and there are few outcome studies from the current interventions. How many AD have spontaneous recovery, how many go on to major disorder symptomatology, and how many retain a chronic

form of the subsyndromal AD? It is essential to learn not only more about diagnosing this most common mental disorder, but also the interventions most likely to have a salutatory response and in what setting, e.g., integrated primary care health settings. With the excitement of current and future neuroscience breakthroughs there is a pathway to a more rigorous understanding of these ubiquitous disorders.

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Dissociative Disorders

18

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Contents

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18.1 Vignettes

1. A patient complained that she was feeling numb, and felt as it her surroundings were unreal, and that she was in a dream. These feelings occurred since 2 days ago. On careful history, the physician found that the patient had discontinued paroxetine 40 mg per day 3 days prior as she ran out of the medication. Depersonalization/derealization associated with SSRI withdrawal was diagnosed, and the drug was resumed. The symptoms disappeared within a day. Then paroxetine was gradually tapered over 2 weeks to successfully avoid any discontinuation syndrome
2. Agatha Christie, the British mystery writer who invented Hercule Poirot and Miss Marple, disappeared on 3 December 1926 only to reappear 11 days later in a hotel in Harrogate, apparently with no memory of the events which happened during that time span (http://www.straightdope.com/columns/read/361/why-did-mystery-writer-agatha-christie-mysteriously-disappear)
3. Jeff Ingram, appeared in Denver in 2006 with no memory of his name or where he was from. After appearing on national television to appeal for help identifying himself, his fiancée Penny called Denver police identifying him. The episode was diagnosed as dissociative fugue. Jeff has experienced three incidents of amnesia: in 1994, 2006, and 2007.

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(http:/www.npr.org/2012/12/14/167187734/for-man-with-amnesia-love-repeats-itself) (from fugue state cases, Wikipedia)

18.2 Introduction

Dissociation is a phenomenon in which there is a lack of connection in a person's thoughts, memories, feelings, actions, or sense of identity. During the period of dissociation, certain information is split off from other information with which it is normally connected. Dissociative experience is probably a continuum, from complete absorption in a task with total unawareness of surroundings, to fugue states, to total amnesia.

Dissociation can be interpreted as an "emergency defense," or a "shut off mechanism."

It may be an evolutionarily adaptive mechanism designed to prevent overwhelming flooding of consciousness at the time of trauma. Once the individual has learned to dissociate in the context of trauma, he or she may subsequently transfer this response to other situations and it may be repeated thereafter arbitrarily in a wide variety of circumstances. The dissociation therefore may destabilize adaptation and becomes pathological (Allen and Smith 1993).

Patients who receive treatment interventions that address their trauma-based dissociative symptoms show improved functioning and reduced symptoms (Gentile et al. 2013).

Dissociation is closely related to conversion syndrome (hysteria, hysterical dissociation), and some consider the latter to be a subset of dissociation syndrome. Hypnosis is a widely used technique to induce dissociation. There is evidence that identical functional brain changes occur in conversion paralysis and hypnotically induced paralysis of the lower limb (Halligan et al. 2000). Dissociation is an important symptom in posttraumatic stress disorder (PTSD), as well as in the borderline personality (see Chap. 25). Conversion, PTSD, and borderline personality disorder, however, are not classified under the rubric of dissociative disorders in DSM-5. Syndromes included in the DSM-5 as dissociative disorders are dissociative identity disorder (multiple personality), dissociative amnesia, dissociative amnesia with dissociative fugue, depersonalization/depersonalization disorder, and other specified or unspecified dissociative disorder.

18.3 Depersonalization and Derealization

Depersonalization refers to a psychological state in which the perception or experience of the self feels detached or unreal. One feels as if one is an outside observer of one's mental processes or body, as if in a dream. Depersonalization is accompanied by feelings of disembodiment and subjective emotional numbing. It has been proposed that depersonalization is caused by a fronto-limbic (particularly anterior insula) suppressive mechanism—presumably mediated via attention—which manifests subjectively as emotional numbing, and disables the process by which perception and cognition normally become emotionally colored, giving rise to a subjective feeling of 'unreality'. Depersonalization syndrome patients show increased prefrontal activation as well as reduced activation in insula/limbic-related areas to aversive, arousing emotional stimuli. Parietal mechanisms may underlie feelings of disembodiment (Reutens et al. 2010; Sierra and David 2011)

Derealization is an alteration in the perception or experience of the external world so that it seems strange or unreal. In depersonalization, there is increased alertness that may be associated with an activation of prefrontal attentional systems (right dorsolateral prefrontal cortex) and reciprocal inhibition of the anterior cingulate, leading to the experiences of "mind emptiness" and indifference to pain that are often seen in depersonalization. In derealization, there may be a left-sided prefrontal inhibition of the amygdala resulting in dampened autonomic output, hypoemotionality, and lack of emotional coloring, resulting in feelings of unreality or detachment. Derealization and depersonalization may be

conceptualized as a syndrome of corticolimbic disconnection (Sierra and Berrios 1998). Depersonalization and derealization may serve an evolutionarily adaptive function of intensifying alertness and dampening potentially disorganizing emotion (Stein and Simeon 2009).

Depersonalization and derealization experiences often occur in normal people in situations of severe anxiety, as in medical settings where a serious diagnosis or medical procedures may be discussed. Furthermore, many drugs, particularly analgesics and sedatives, as well as mild delirium that may be associated with a medical condition, may predispose patients to depersonalization/derealization. Specific neurological conditions such as partial complex seizures as well as encephalopathies and strokes may be associated with these phenomena. In the CL setting, psychological support and reassurance may alleviate the frightening aspect of these experiences. Reduction or change in a medication that might be associated with the condition, as well as treatment of delirium and the underlying medical condition may be therapeutic.

When there is functional impairment due to depersonalization or derealization, depersonalization or derealization *disorder* may be diagnosed. According to DSM-5, the lifetime prevalence of depersonalization/derealization disorder is 3 %, equally in males and females.

Depersonalization and derealization are common features of other psychiatric conditions, particularly borderline personality and posttraumatic stress disorder (PTSD).

18.3.1 Treatment of Depersonalization/ Derealization Disorder

Cognitive-behavioral therapy, mindfulness training, and repeated exposure are the psychotherapeutic techniques that have been reported useful in depersonalization/derealization disorder (Hunter et al. 2005; Michal et al. 2007; Stein and Simeon 2009; Weiner and McKay 2013).

SSRIs, clonazepam, naltrexone, methylphenidate, and lamotrigine, in monotherapy or in combination, have been used effectively in treatment of depersonalization/derealization syndrome (Aliyev and Aliyev 2011; Foguet et al. 2011; Rosagro-Escamez et al. 2011; Sierra 2008).

18.4 Dissociative (Psychogenic) Amnesia and Fugue

18.4.1 Vignette

A 25-year-old man was hospitalized with no memory of who he was, where he was from and with no identification. When tested however he could do serial 7's and remember new things he was told. Under hypnosis he revealed that he lived in another state. He came home late one night intoxicated, tried to make popcorn and accidentally set the house on fire. His parents died in the fire. After the funeral, he disappeared, apparently traveling to a distant state. After the hypnosis session, his memory gradually returned and he was helped to grieve.

18.4.2 Definition and Subtypes

Dissociative amnesia is characterized by a pervasive loss of memory of significant personal information, such as name, occupation, and residence. Aspects of dissociative amnesia may be present in dissociative identity disorder (multiple personality), factitious syndromes, psychosis, and the borderline syndrome. Dissociative amnesia is diagnosed when the amnesia cannot be directly attributed to a neurological cause such as trauma or to another major psychiatric condition, and is extensive enough to impair function. In head trauma, there may be localized amnesia that may be retrograde or anterograde. According to DSM-5, the 12 month prevalence for dissociative amnesia is 1.8 % (1 % for males, 2.6 % for females). Dissociative amnesia has been linked to overwhelming stress, such as abuse, accidents, disasters, or war that the patient has experienced or witnessed. It is more common in women, and tends to be more prevalent in stressful periods

such as wars and natural disasters. Dissociative amnesia following general anesthesia has been reported (Chang et al. 2002).

Dissociative amnesia has a variable course, with some resolving rapidly while others may persist for decades or longer. Dissociative amnesia often recurs. Dissociative capacity may decline with age.

The subtypes of dissociative amnesia include the following:

Selective amnesia: The patient can recall only small parts of events that happened during a defined period of time. For example, a victim of abuse may have only fragmentary memory of her abuse.

Generalized amnesia: The amnesia encompasses the person's entire life.

Continuous amnesia: The patient has no memory for events beginning from a certain point in the past continuing up to the present.

Systematized amnesia: A loss of memory for a specific category of information.

For example, a person may have no memories about one particular family member.

With Dissociative Fugue

In a dissociative fugue, the person leaves home suddenly and unexpectedly and goes off on a journey, often to distant places (see Vignettes 2–3). The journey may last hours, days, months, or even years. A person in a fugue state is unaware of or confused about his/her identity, and in some cases will assume a new identity.

18.4.3 Differential Diagnosis

18.4.3.1 Vignette

A young man was hospitalized unable to identify himself or answer questions other than by responding "OK." He was given food that included a hard-boiled egg. He was observed to attempt to bite ito it shell and all. The consultant was suspicious and ordered an EEG. It showed A continuous epileptiform pattern. His mental status normalized with anticonvulsant medication. He then was able to reveal that he had been on vacation and ran out of his epilepsy medication.

18.4.3.2 General Considerations

In the CL setting, patients who manifest a global amnesia are likely to be referred for a psychiatric consultation. Major differential diagnostic considerations in such cases include memory disturbance associated with neurocognitive disorders including delirium and dementia, ictal and postictal states, head trauma, as well as transient global amnesia discussed below. Amnestic syndromes associated with alcohol abuse (e.g., Korsakoff's psychosis) should also be considered. Comorbidity with other psychiatric disorders is common with dissociative amnesia, and depression and other major psychiatric syndromes may emerge as the amnesia clears.

18.4.3.3 Transient global amnesia (TGA)

Transient global amnesia (TGA) is a neurologic condition that usually occurs in persons over the age of 50, and is characterized by abrupt anterograde memory loss with repeated questioning ("Where am I?" "What's my name?"). The duration is usually 1–8 h with full recovery, though durations of 15 min and of 24 h have been reported.

Emotional and physical stress may precipitate these attacks, and in younger patients, migraine headaches appear to be a risk factor. In females, anxiety, depression, and emotional instability may be risk factors (Quinette et al. 2006a, b).

MRI data suggest that a transient perturbation of hippocampal function may underlie transient global amnesia. Various factors such as migraine, focal ischemia, venous flow abnormalities, and epileptic phenomena may contribute to the risk. The vulnerability of hippocampal neurons to metabolic stress may play a pivotal part in the pathogenesis of TGA (Bartsch and Deuschl 2010).

18.4.3.4 Treatment of Dissociative Amnesia

Various psychotherapeutic modalities may be used to treat dissociative amnesia including cognitive behavioral therapy (CBT), exploratory psychotherapy, creative therapies (art therapy, music therapy), and hypnotherapy. Intravenous sedative interview has been reported to be effective

(Lee et al. 2011). There are no specific medications for dissociative amnesia, but antidepressants and anxiolytics may be used for symptomatic indications.

18.5 Dissociative Identity Disorder (Multiple Personality)

In this condition, two or more identities or personalities alternatively take over the person's behavior. One or more of the personalities may be aware of the other identities, while others may be totally unaware of the existence of other personalities. Patients with this condition often have amnestic periods during which another identity had taken over.

Many patients, in addition, have symptoms of anxiety, depression, derealization, and depersonalization. Substance abuse is common, as well as suicide attempts.

This condition is relatively common in acute psychiatric settings (3–4 %), or very rare depending on the observer's orientation, and may cause serious functional impairment. The risk of suicide is high in patients suffering from dissociative identity disorder.

More than 90 % of patients with dissociative identity disorder report experiencing childhood physical or sexual abuse. Dissociative identity disorder has been conceptualized as a neurodevelopmental disorder caused by traumatic childhood that prevented an integration of the child's experiences and interactions (Forrest 2001).

Reinders et al. (2003) demonstrated specific changes in localized brain activity on PET scan, consistent with their ability to generate at least two distinct mental states of self-awareness, each with its own access to autobiographical trauma-related memory. The findings revealed the existence of different regional cerebral blood flow patterns for different senses of self.

Thus, specific brain functional differences in the medial prefrontal cortex and posterior association areas may be associated with different personalities in dissociative identity disorder (Reinders et al. 2003). Smaller hippocampal and amygdala volume has also been associated with dissociative identity disorder, as well as in PTSD and borderline syndrome with a history of childhood abuse and depression (Vermetten et al. 2006).

18.5.1 Diagnosis and Treatment

In the CL setting, psychiatric consultation may be requested on patients who have a known diagnosis of dissociative identity disorder (multiple personality), or in the course of an evaluation concerning amnesia, depersonalization, anxiety, depression, or unexplained physical symptoms.

Interviewing patients after placing them under hypnosis or after administering an intravenous sedative (see Chap. 34) may facilitate the diagnosis. The diagnosis is established when an alternate personality is demonstrated, either spontaneously or in an altered state. Great care must be taken not to subtly reinforce the development of altered states by expressing great interest in them.

The treatment of choice is psychotherapy (individual, couples, group) on an outpatient basis. Antidepressants (SSRIs, SNRIs, tricyclics, etc.), antipsychotic mood stabilizers (aripiprazole, quetiapine, etc.), antianxiety agents, beta-blockers, anticonvulsant mood stabilizers (carbamazepine, valproate, etc.), and naltrexone (for self-injurious behaviour), and other drugs are sometimes helpful in conjunction with psychotherapy (Burton and Lane 2001; Fine 1999; Kluft 1996).

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Psychosis (Schizophrenia Spectrum and Other Psychotic Disorders)

19

Hoyle Leigh

Contents

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19.1 Vignette

A consultation was requested for a 25-year-old Caucasian man on the medical service. He was brought to the hospital by the police after he barricaded himself in a motel room, not allowing the housekeeping personnel to come in for days. The patient was found to be agitated and mute. In the emergency department, he was found to have a fever of 40 °C, an elevated creatine phosphokinase (CPK), and increased serum osmolality. He was admitted to the general medical floor, and intravenous fluids were given.

To treat agitation, the psychiatric consultant might consider an antipsychotic or a benzodiazepine. In view of the patient's fever and elevated CPK and unknown history, neuroleptic malignant syndrome, a contraindication for an antipsychotic, could not be ruled out. Thus, intravenous lorazepam 2 mg q 2 h was recommended for agitation. The patient fell asleep after receiving 6 mg of lorazepam. The next morning, the patient started speaking, initially incoherently. He had a flat affect, and his responses to questions were often incoherent and tangential; he seemed to be responding to internal stimuli. He was placed on a regimen of lorazepam 1 mg t.i.d. po as his agitation subsided considerably.

Later that afternoon, he became somewhat more coherent, and stated that he was hearing accusatory voices. He denied visual hallucinations, and admitted to the feeling that there were people trying to do harm to him, perhaps drug

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dealers. He had barricaded himself in the motel room because he was afraid that the drug dealers would "come get me" if he stayed at home. He denied any drug use except for one occasion when he smoked marijuana. The patient's mother was located, who provided the history that the patient had been an excellent student until about age 16, when his grades started to plummet, and he would isolate himself in his room, staying awake most of the night. The patient became hyper-religious, constantly quoting the Bible, but did not attend church. The parents tried to bring him to a psychiatrist, but he resisted. The age and the insidiousness of onset, the persecutory delusions, the auditory hallucinations, the flatness of affect, and the absence of substance abuse history pointed to the diagnosis of schizophrenia. As the CPK was now normalized, and there was no history of antipsychotic drug use that might have caused neuroleptic malignant syndrome, lorazepam was discontinued and a regimen of aripiprazole 10 mg po in AM was instituted. Within 24 h, the patient's auditory hallucinations were significantly attenuated, and his loosening of associations abated. His affect remained flat. He was referred for outpatient therapy when discharged.

19.2 The Recognition of Psychosis

The symptoms and signs of psychosis are perceptual, cognitive, and behavioral abnormalities that suggest an involuntary break with reality. Cardinal symptoms include hallucinations, delusions, illusions, and bizarre behavior. Loose associations, tangentiality, flight of ideas, and illogical or incoherent speech may be present. Anxiety, agitation, insomnia, depression, euphoria, and suicidal or homicidal behavior may occur, often secondary to the delusions or hallucinations.

In the consultation-liaison (CL) setting, the nursing staff may report the patient's unusual behavior or speech, or blunted or inappropriate affect, resulting in a psychiatric consultation. When patients with an existing diagnosis of psychosis or schizophrenia are admitted to a general hospital, psychiatric consultation is usually generated even when they are psychiatrically stable. This is appropriate, as collaboration between medicine and psychiatry may be essential in considering adjustments of medications as well as meeting the patient's psychotherapeutic needs.

If the patient is severely psychotic, it may be impossible to obtain coherent history from the patient or perform a structured mental status examination. Under those conditions, it is imperative that collateral information from family or friends be obtained. Acute and severe psychotic symptoms in a patient with abnormal physical or laboratory findings should be considered to be delirium unless proven otherwise, and a workup for delirium should be initiated (see Chap. 12). Antipsychotic treatment may be necessary before a history can be obtained.

19.2.1 The Psychotic Mode of Experiencing and Its Function

Though patients with psychosis may seem bizarre, all normal people have at times experiences such as hallucinations and delusions, for example, during dreaming. Most normal people are capable of having psychotic experiences while awake, under the influence of psychotomimetic drugs such as D-lysergic acid (LSD) or under sensory deprivation conditions. In fact, delirium due to any cause is often associated with psychotic symptoms. Primary process, which involves a nonlinear-picture mode (rather than word-based mode) of cognition that may involve the nondominant hemisphere of the brain, is the language of the unconscious mind, of dreams, and of the creative process (Brakel and Shevrin 2005; Burns 2006; Mohler et al. 2008; Roiser et al. 2012).

The psychotic mode of being may also be adaptive at times of overwhelming stress, where a disconnection from reality may be advantageous for survival. We all possess the capacity for the psychotic mode of experiencing reality-the difference between this and psychosis as a syndrome is

the lack of control over the experience in the latter. The lack of control seen in psychosis may be due to endogenous or exogenous toxins, extreme stress, or neurodevelopmental abnormality (Devylder et al. 2013; Holtzman et al. 2013). Regardless of the cause, this lack of control is invariably frightening to the newly psychotic patient, and recognizing this frightened state is essential in approaching such a patient.

19.2.2 Psychotic Syndrome as a Final Common Pathway

Like mood syndromes and anxiety syndromes, psychosis is a final common pathway syndrome that can be contributed by many factors. Regardless of the contributing factors, a common neurobiologic pathway to the psychotic syndrome seems to be a functional hyperactivity of the dopaminergic (particularly D_2) neurons in the mesolimbic system. Dopamine agonists, such as LSD and amphetamines, can induce psychosis, and dopamine receptor blockers, such as haloperidol, are effective for psychotic symptoms regardless of the underlying etiologies.

One may conceptualize two broad categories of the psychotic syndrome—secondary and primary—based on the prominent contributing factors. Secondary psychoses comprise psychotic syndromes that are associated with diagnosable nonpsychiatric medical conditions, prescription and recreational drugs, or identifiable environmental factors such as sensory deprivation.

Primary psychoses consist of syndromes classified as psychiatric disorders, including schizophrenia, schizoaffective disorder, bipolar disorder, psychotic depression, delusional disorder, brief psychotic episode, and psychotic symptoms accompanying posttraumatic stress disorder (PTSD) and borderline personality disorder. Primary psychoses may be exacerbated or precipitated by the factors that contribute to secondary psychoses (e.g., LSD or delirium) and are the results of interaction among genes, early development, early, recent, and current stresses, and psychosocial support.

19.3 Diagnosis of Psychotic Syndromes

19.3.1 Secondary Psychosis

The most common underlying condition for secondary psychosis is delirium (see Chap. 12). In addition, many medical conditions and prescription and recreational drugs may cause psychotic symptoms (see Table 7.1 in Chap. 7).

19.3.2 Primary Psychosis

Psychotic syndrome manifested in a patient in whom the medical condition or prescription and recreational drugs are not sufficient explanations may be considered to be due to a primary psychosis. It is important to recognize, however, that primary and secondary psychoses are not mutually exclusive, but may be syncretic. For example, a patient with chronic schizophrenia with prominent auditory hallucinations may become delirious due to uremia, and develop visual hallucinations and agitation. Included in this category are schizophrenia, schizoaffective disorder, bipolar disorder, psychotic depression, delusional disorder, brief psychotic episode, and psychotic symptoms accompanying PTSD and borderline personality disorder. Stress may play a predominant role in inducing PTSD and a brief psychotic episode, while genetic factors may play greater roles in schizophrenia and mood disorders. There is some evidence that there may be a common genetic contribution to the psychotic symptoms of schizophrenia, schizoaffective disorder, and bipolar disorder (Green et al. 2010; Green et al. 2005; Hamshere et al. 2006).

19.3.2.1 Schizophrenia

Schizophrenia is the classic, representative psychosis, but it is important to note that it is a subset of psychotic syndromes. Schizophrenia is a final common pathway syndrome with multiple contributing factors, many of which are shared with other psychiatric syndromes.

History

The French psychiatrist Morel coined the term *demence precoce* in 1860 to describe an adolescent patient who became gradually withdrawn, gloomy, and silent. Emil Kraepelin, the German psychiatrist known as the father of descriptive psychiatry, systematically described the signs and symptoms of a psychiatric illness that was characterized by a progressive deterioration in mental functioning under the rubric of dementia praecox, which means premature dementia. Eugen Bleuler, a Swiss psychiatrist, radically changed the concept of schizophrenia by pointing out that not all patients who had the symptoms that Kraepelin described actually had an unremitting deteriorating course. He coined the term, schizophrenia, meaning "splitting of the mind" in his book, Dementia Praecox or the Group of Schizophrenias.

Clinical Manifestations

Bleuler proposed that there are four fundamental symptoms of schizophrenia, the "four A's"—disturbances in association and affect, and the presence of autism and ambivalence.

Disturbances in association include loosening of associations, tangentiality, derailment, clang associations, and neologisms. Affect may be flattened or inappropriate. Autism, or dereistic thinking, means that the patient lives in a world of his or her own, with a very tenuous relationship with external reality, which often leads to social withdrawal. Hallucinations, delusions, and illogical thinking may be part of autism.

Kurt Schneider described the most characteristic symptoms of schizophrenia that he called the "first-rank symptoms," the presence of even one of which merits serious consideration for the diagnosis of schizophrenia. They are complete auditory hallucinations (such as hearing two voices conversing with each other, voices commenting on one's own behavior, hearing one's thoughts spoken aloud), thought withdrawal (feeling that one's thoughts are taken away), thought insertion (others are putting thoughts in one's head), thought broadcasting, and delusions of control (e.g., one is controlled by radio waves from spaceships).

Positive and Negative Symptoms

It is useful to classify the symptoms of schizophrenia as positive or florid symptoms and negative or deficit symptoms as they may reflect underlying central nervous system (CNS) changes. The positive symptoms include hallucinations, delusions, and loose associations, which are present in all psychotic syndromes. The positive symptoms generally respond well to dopamine receptor blockers such as haloperidol and most antipsychotic medications.

The negative symptoms include flat affect, paucity of thought, anhedonia, and motor retardation, and they may be associated with cerebral cortical abnormalities and enlarged ventricles and sulci often associated with schizophrenia. The negative symptoms are resistant to treatment with antipsychotics in general, though the second-generation antipsychotics such as clozapine have some beneficial effect.

Types

In DSM-5, schizophrenia types have been eliminated from the formal diagnostic scheme. Nevertheless, based on predominant symptoms, schizophrenia has been typed as follows:

Paranoid type: delusions and paranoid ideations predominate

Disorganized (hebephrenic) type: bizarre behavior, hallucinations, and posturing

Catatonic type: catatonia, mutism, sometimes alternating with agitation

Undifferentiated type: mixtures of various psychotic symptoms

Residual type: usually occurs after a long course of illness; most positive symptoms have been under control or "burned out," with mostly negative symptoms persisting

19.3.2.2 Prevalence and Incidence

The lifetime prevalence is considered to be 0.3–0.7 %, with an incidence rate of approximately 15 per 100,000 per year (Brown 2011); (APA 2013).

In a general hospital population that is consulted by psychiatry, the prevalence rate of the diagnosis of schizophrenia in some 2,500 psychiatric consultations with a major psychiatric diagnosis was approximately 5 %. Among some 300

patients with psychotic symptoms, about 37 % were eventually diagnosed with schizophrenia (based on analysis of data at Community Regional Medical Center, Fresno, CA, USA).

19.3.2.3 Onset

The age of onset is in the teens to the mid-20s for men and late 20s for women. The onset is often insidious, with prodromal symptoms of social withdrawal, poor personal hygiene, deterioration in school or work performance, and day-night reversal. In general, the prognosis is poorer the earlier the onset.

19.3.2.4 Etiology and Pathogenesis

According to the neurodevelopmental hypothesis, the etiology of schizophrenia may involve pathologic processes, caused by both genetic, epigenetic, and environmental factors, that begin before the brain approaches its adult anatomical state in adolescence. These neurodevelopmental abnormalities, developing in utero as early as late first or early second trimester for some and thereafter for others, have been suggested to lead to the activation of pathologic neural circuits during adolescence or young adulthood (sometimes owing to severe stress), which leads to the emergence of positive or negative symptoms or both.

The neurodevelopmental abnormalities may result from embryologic maldevelopment, often caused by prenatal infections (Brown 2012; Khandaker et al. 2013). A "2-hit" model proposed by Keshavan posits that maldevelopment during two critical time points (early brain development and adolescence) combines to produce the symptoms associated with schizophrenia (Keshavan 1999; Keshavan and Hogarty 1999). According to this model, early developmental insults may lead to dysfunction of specific neural networks that would account for premorbid signs and symptoms observed in individuals who later develop schizophrenia. During adolescence, excessive elimination of synapses (pruning) and loss of plasticity may account for the emergence of symptoms (Fatemi and Folsom 2009).

Genetic Risks

Schizophrenia clearly runs in families. The risk of developing schizophrenia in the general population is somewhat less than 1 %, while the prevalence for parents of children who are known schizophrenics is 12 %. The morbidity risk for schizophrenia for full siblings of schizophrenic patients is 13–14 %. The risk for children with one schizophrenic parent is 8–18 %. If both parents are schizophrenic, the morbidity risk for their children may be as high as 50 %. In the case of twins, heterozygous twins have the same risk as other siblings, while homozygous (identical) twins have a concordance rate for schizophrenia of approximately 50 % (However, there is much variability in the concordance rate depending on the study, from practically 0–86 %.).

Pathophysiology and Genetics of Schizophrenia

In spite of the demise of the term dementia praecox, cognitive disturbance has recently become a cornerstone of understanding schizophrenia. Schizophrenia is conceptualized as a neurodevelopmental disorder resulting in a reduction in cortical volume and dysfunctions in glutamatergic, GABA (γ-aminobutyric acid)ergic, and dopaminergic transmission. There seems to be a hyperfunction of the mesolimbic and a hypofunction of the mesocortical dopaminergic transmission. Mesocortical dopaminergic transmission is stimulated by glutamatergic transmission and reduced by GABAergic transmission, and it plays an important role in working memory often disturbed in schizophrenia (Barch and Ceaser 2012; Kegeles et al. 2012). There is evidence of dysfunction in schizophrenia of the GABAergic cortical chandelier cells that synchronize the firing of the glutamatergic pyramidal cells, which are necessary for proper functioning of the working memory. A fundamental disturbance in schizophrenia seems to be an inefficiency of the prefrontal cortex, particularly the dorsolateral area, in processing information, and increased "noise" in the local microcircuit function (Anticevic et al. 2012; Kyriakopoulos et al. 2012).

At least 15–18 single nucleotide polymorphisms (SNP) have been identified as candidate

genes for the susceptibility to schizophrenia including catechol O-methyltransferase (COMT) (chromosome 22q), dysbindin-1 (chromosome 6p), neuregulin-1 (chromosome 8p), metabotropic glutamate receptor 3 (GRM-3) (chromosome 7q), glutamate decarboxylase 1 (chromosome 2q), and disrupted-in-schizophrenia 1 (DISC1) (chromosome lq). It is important to note that these genes are not here to "cause schizophrenia," but are rather genes important in various neural, immunologic, and other normal functions the disruption of which may code for a risk of developing brain dysfunction, which may result in psychotic symptoms (and/or bipolar symptoms as in DISC1 gene).

The COMT gene affects prefrontal cortical function by changing dopamine signaling in the prefrontal cortex and brainstem. GRM-3 shows similar results on prefrontal function and has an effect on expression of various glutamate synaptic markers. DISC1 affects hippocampal anatomy and function. Dysbindin-1 seems to be a general cognitive capacity gene that is underexpressed in the cortex of schizophrenic patients (Nickl-Jockschat et al. 2012; Snyder and Gao 2013).

Schizophrenia is not a simple genetic disease; rather, it is a syndrome contributed to by susceptibility genes that have functions other than conveying susceptibility to schizophrenia, and by early experiences, developmental factors, and stress (King et al. 2005).

Evolutionary Considerations

Schizophrenia has conferred a reproductive disadvantage on the afflicted. Why, then, is schizophrenia extant at more or less a constant rate across human populations? An obvious explanation is that the alleles that, in certain combinations, may predispose one to schizophrenia may be involved in other functions that are adaptive. Some of these may be involved in creativity and eccentricity. In addition, the susceptibility genes may represent variations of ubiquitous genes subserving basic functions of the human brain. Crow proposed that schizophrenia may represent an extreme of normal genetic variation in the communication (Crow 1997a, b, 2012) between the two hemispheres that is critical in language, a uniquely human acquisition. He postulates that Schneiderian first-rank symptoms such as thought insertion and withdrawal may represent a dysfunction of the coordinated hemispheric communication—a right hemispheric intrusion into left hemispheric linear thinking. Schizophrenia may represent an extreme of variations in the interconnectivity of various structures of the brain, particularly those involved in social cognition and the working memory.

Regression and Projection

A prominent feature of many schizophrenic patients is the phenomenon of regression, a psychological defense mechanism characterized by a retreat to an earlier, child or infant-like way of experiencing the world accompanied by childlike or infantile behavior. In severe cases, patients may assume a fetal position with thumb sucking. Another defense mechanism often seen in schizophrenia, particularly in the paranoid type, is projection, by which the patient attributes to others the thoughts, feelings, or traits that are unacceptable to oneself; for example, when an aggressive impulse is projected, the patient may see others as having malicious thoughts against him or her and plotting harm.

As discussed earlier, schizophrenic patients often manifest cognitive deficits, especially in filtering out extraneous stimuli, in recognizing social cues, in the ability to change sets, and in concreteness. Primary process thinking, characterized by illogicality, nonlinearity, and pictorial thinking rather than linguistic, may be also prominent.

Socioenvironmental Factors

Seasons and Infection

There is evidence that being born in the winter is associated with a higher risk of schizophrenia and mood disorders (Torrey et al. 1997). However, schizophrenia with deficit symptoms may be associated with being born in the summer (Messias et al. 2004), and may be associated with intrauterine cytomegalovirus infections (Khandaker et al. 2013; Torrey et al. 2006).

Role of Stress

Stressful early experiences particularly associated with low socioeconomic class and a ghetto urban environment may precipitate schizophrenia

in vulnerable individuals as there is a higher prevalence of schizophrenia in these groups (Brown 2011). The handicap of schizophrenic illness also often causes the affected persons to slide down the socioeconomic ladder (drift hypothesis). Abnormally stressful family interactions may contribute to the development of schizophrenia (e.g., a "double bind"—a "no win" situation for a child). Exacerbation of schizophrenia, especially to the point that it is severe enough to warrant hospitalization, seems to be associated with stress, and particularly associated with expressed negative emotions by family members (Cechnicki et al. 2013; Lenior et al. 2005).

Diagnosis of Schizophrenia in CL Setting

DSM-5 specifies that during a 1 month period, at least one delusion, hallucination, or disorganized speech was present, and has an additional symptom that may include grossly disorganized or catatonic behavior and/or a negative symptom. It further specifies that continuous signs of the disturbance persist at least for 6 months.

In the consultation-liaison setting, the diagnosis of schizophrenia in the presence of psychotic symptoms usually involves the following steps:

1. Rule out delirium, the most common cause of psychosis in the general hospital.
2. Determine by the history and collateral information whether the patient has a history or family history of psychiatric evaluation/treatment; if positive, the probability increases that the patient has a primary psychiatric condition such as schizophrenia or mood disorder.
3. Determine whether the patient's medical condition or a drug used to treat the condition is reported to be associated with psychosis. In this case, **Psychotic Disorder Due to Another Medical Condition** may be diagnosed.
4. Determine whether the patient used recreational drugs that might explain psychotic symptoms. In this case, **Substance/Medication-Induced Psychotic Disorder** may be diagnosed.

As it is rare for a medical patient to have the first schizophrenic break in the general hospital, every effort should be made to determine whether the patient has a prior history of psychotic episode. Even if a patient is known to be schizophrenic, delirium and substances can exacerbate underlying psychosis.

19.3.3 Other Primary Psychoses

If a mood disturbance (depression, euphoria, hypomania/mania) is prominent, then psychosis associated with a mood disorder may be suspected. If the history indicates that the psychotic symptoms are present only during periods of mood disturbance, then depression or mania with psychotic features may be diagnosed (see Chap. 15). When the history reveals that psychotic symptoms are present even when the mood disturbance is in remission, then a **schizoaffective disorder** may be diagnosed. If the psychotic symptoms are transient in a patient who has borderline personality disorder (see Chap. 25), then they may be part of the micropsychotic episodes associated with that syndrome. If such symptoms coexist with symptoms of posttraumatic stress disorder (PTSD), they may be part of the dissociative phenomena common in PTSD. If the psychotic symptom is confined to a delusion, then the diagnosis of delusional disorder may be appropriate.

As a final common pathway phenomenon, the psychotic symptoms, regardless of comorbid syndromes (e.g., depression, borderline personality, PTSD), may have common sets of susceptibility genes and pathophysiology. Most positive psychotic symptoms, regardless of the diagnosis, respond to antipsychotic medications. Except in schizophrenia and psychosis associated with mental retardation and dementia, negative symptoms are rare. Of note is that the prolonged use of first-generation antipsychotics (e.g., haloperidol) may cause negative symptoms such as flattening of affect.

19.3.3.1 Catatonia

Catatonia is a syndrome characterized by marked psychomotor disturbance in the form of decreased motor activity and decreased engagement during

interview. This may alternate with periods of extreme agitation. During decreased motor activity, there may be catalepsy (waxy flexibility), mutism, negativism, or stupor. There may be peculiar motor activity such as stereotypy.

DSM-5 does not treat catatonic syndrome as a separate class but classifies catatonia as being one of (1) catatonia associated with another mental disorder, e.g., psychotic, bipolar, depressive disorder, (2) catatonia due to another medical condition, and (3) unspecified catatonia.

19.3.3.2 Schizotypal (Personality) Disorder

This is usually classified as a personality disorder (See Chap. 25), characterized by odd, eccentric thinking and behavior. This is also listed as Schizophrenia Spectrum Disorder because some consider this personality trait to be genetically related to schizophrenia.

19.3.3.3 Delusional Disorder

This disorder is characterized by one or more persistent delusions (duration 1 month or more), but not quite meeting the criteria for schizophrenia. Except for the consequences of delusions, the functioning of the patients is not usually seriously impaired.

Delusional disorders may be subtyped into: erotomanic type, grandiose type, jealous type, persecutory type, mixed type, or unspecified type.

19.3.3.4 Brief Psychotic Disorder

Psychotic episode of less than 1 month duration, with eventual full return to pre-morbid level of functioning. Usually considered to be stress-related. May be postpartum onset or with catatonia. About 9 % of first onset psychosis in the United States may be diagnosed as brief psychotic disorder (APA 2013).

19.3.3.5 Schizophreniform Disorder

This diagnosis is given to schizophrenia-like psychotic episode that eventually recovers within 6 months. "Provisional" diagnosis may be made if recovery has not yet occurred. Approximately two thirds of patients who receive the initial provisional diagnosis of schizophreniform disorder progress to the final diagnosis of schizophrenia (APA 2013).

19.4 Management and Treatment of Psychosis

19.4.1 Immediate Treatment in the General Hospital

Immediate treatment of psychosis in the general hospital involves (1) treatment of agitation (see Immediate Management of Agitation in Chap. 4), (2) treatment of psychotic symptoms, and (3) plans for follow-up.

For the treatment of psychotic symptoms, a first- or second-generation antipsychotic should be considered (Table 19.1). The main clinical differences between first-generation (or typical, so-called because they are all dopamine receptor blockers) antipsychotics and second-generation (or atypical and they have multiple actions on multiple receptors) antipsychotics are as follows: (1) first-generation antipsychotics have more extrapyramidal side effects, whereas second-generation antipsychotics are less likely to cause them; (2) first-generation antipsychotics are effective for positive symptoms only, whereas second-generation antipsychotics are effective for positive symptoms and also may be effective to varying degrees for negative symptoms, and (3) second-generation antipsychotics are associated with the metabolic syndrome (see below). Use of second-generation antipsychotics has been associated with an increase in mortality and the risk of stroke in elderly demented patients.

All antipsychotics may lower **seizure** threshold, may be associated with neuroleptic malignant syndrome (NMS; see below), may increase prolactin levels, and may cause tardive dyskinesia. Cardiotoxic effects such as **QTc prolongation** are common with antipsychotic agents, particularly thioridazine and ziprasidone. For patients with QTc over 450 ms, all psychotropic drugs should be used with caution, and for QTc over 500 ms, antipsychotic drugs should ordinarily not be used—benzodiazepines may be used to sedate the patient if necessary.

Table 19.1 Commonly used antipsychotics

Medication	Dose	Major side effects
First generation (*typical*)		
Haloperidol	0.5–15 mg/day po	EPS ++, TD, NMS QT prolongation, reduced seizure threshold
	1–100 mg/day IV	QT prolongation, torsades de points, reduced seizure threshold, NMS
	0.5–10 mg/day IM	EPS +++, QT prolongation, NMS, reduced seizure threshold
Haloperidol decanoate depot injection	50–100 mg IM q 4 weeks	As above
Perphenazine	2–32 mg/day po	Sedation +, EPS +, TD, reduced seizure threshold, NMS
	2–24 mg/day IM	Sedation +, EPS ++, NMS, reduced seizure threshold
Chlorpromazine	25–900 mg/day po	Orthostatic hypotension, sedation +++, anticholinergic, EPS +, TD, NMS, reduced seizure threshold
	25–500 mg/day IM	As above
Second generation (*atypical*)		
Olanzapine	2.5–30 mg/day po	Sedation, etc
	2.5–30 mg/day IM	As above
Risperidone	1–8 mg/day po	Sedation +, EPS +, QT prolongation, weight gain +, NMS
Quetiapine	25–900 mg/day po	Sedation +++, orthostatic hypotension, weight gain ++, NMS
Ziprasidone	40–160 mg/day po	Sedation +, orthostatic hypotension, QTc prolongation, EPS +, NMS
	10–40 mg/day IM	As above, usually for short term only
Aripiprazole	10–30 mg/day po	Orthostatic hypotension, reduced seizure threshold, constipation, akathisia

EPS extrapyramidal symptoms, *GI* gastrointestinal, *NMS* neuroleptic malignant syndrome, *TD* tardive dyskinesia

19.4.2 Maintenance Pharmacotherapy of Psychosis

Most psychosis associated with delirium, both due to medical disease or substance related, will clear up when the delirium clears. If the psychotic syndrome persists even when other signs of delirium abate, or when the diagnosis of a primary psychosis such as schizophrenia has been established, maintenance pharmacotherapy is usually necessary to manage the psychotic symptoms. Successful maintenance therapy may allow the patient to maintain a functional status in the society.

19.4.2.1 Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study

This large NIMH-sponsored multicenter study sought to examine the safety and effectiveness of second generation antipsychotics (olanzapine, quetiapine, risperidone, and ziprasidone) and a first generation antipsychotic, perphenazine, in treating schizophrenic patients (Lieberman et al. 2005; Meyer et al. 2005). The primary outcome measure, time to discontinuation, served as an index of effectiveness and was remarkably short; only 26 % of subjects completed the 18-month trial on the medicine to which they were initially randomized. Subjects receiving olanzapine experienced a slightly longer time to discontinuation. Olanzapine showed greater effectiveness than the other agents despite its association with significant metabolic disturbance, especially weight gain. Perphenazine unexpectedly showed comparable levels of effectiveness and produced no more extrapyramidal side effects than the other agents. Despite modest prolactin elevation, risperidone was the best-tolerated medication. In Phase 2, clozapine demonstrated better effectiveness compared to other second generation antipsychotics (SGA) for subjects who discontinued their Phase 1 medication because of efficacy. Olanzapine and risperidone showed greater effectiveness in the

tolerability pathway. Improvements in cognition were modest among all the agents in Phase 1, and perphenazine was no less effective in improving cognitive performance than the SGAs. Cost-effectiveness analysis revealed a significant advantage for perphenazine, due to the impact of the high-priced, brand-name SGAs on overall health care costs (Manschreck and Boshes 2007). Aripiprazole and ziprasidone are less implicated in weight gain and metabolic syndrome and are less sedating than other SGAs.

There is evidence that genetically informed personalized medication regimen may become efficacious in the use of antipsychotic medications (Liu et al. 2012).

19.4.3 Notable Serious Side Effects of Antipsychotic Drugs

19.4.3.1 Extrapyramidal Symptoms, Tardive Dyskinesia

Parkinsonism-like symptoms, for example, muscle rigidity, tremor, bradykinesia, dystonias, and akathisia, are associated with the dopamine antagonism of antipsychotic drugs. With first-generation antipsychotics, particularly haloperidol and fluphenazine, the incidence of extrapyramidal symptoms (EPS) may approach 90 %, particularly in young males. Acute dystonias, such as torticollis, may be treated with diphenhydramine 50–100 mg IV or benztropine 1–2 mg IM. Extrapyramidal symptoms are usually controlled with anticholinergic drugs such as benztropine or antihistaminics such as diphenhydramine. Akathisia may respond to beta-blockers, such as propranolol 20–40 mg t.i.d. or q.i.d.

Tardive dyskinesia, a side effect of prolonged use, particularly of first-generation antipsychotics, is characterized by choreoathetoid movements of the tongue, lips, and extremities. There is no effective treatment for this condition.

19.4.3.2 Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a potentially fatal syndrome associated with the use of dopamine-antagonist antipsychotics. Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, delirium, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, cardiac dysrhythmia). Sialorrhea and incontinence may occur. There is often elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), leukocytosis, and acute renal failure. Extrapyramidal signs such as tremor, rigidity, and cogwheeling are common. Differential diagnoses include infection, anticholinergic toxicity, the serotonin syndrome (see Chap. 7), heat stroke, and central nervous system (CNS) disease (e.g., encephalitis).

If NMS is suspected, all antipsychotic drugs should be discontinued, and the patient should be intensively monitored and supportive treatment given. Pharmacotherapy may include dantrolene (a muscle relaxant, an inhibitor of calcium release from sarcoplasmic reticulum), 1–3 mg/kg IV initially, and then 10 mg/kg/day IV or po in divided doses. Dopamine agonists, such as bromocriptine, 2.5–10 mg t.i.d. po, gradually titrated, or levodopa/carbidopa (Sinemet) 25/250 t.i.d. or q.i.d., may be used. During the acute phase, for behavioral control, benzodiazepines should be used rather than antipsychotics. If antipsychotic treatment becomes necessary after the resolution of NMS, for at least two weeks, it should begin in low doses very cautiously with careful monitoring.

19.4.3.3 Metabolic Syndrome Associated with Second-Generation Antipsychotics

Metabolic syndrome or syndrome X, consisting of insulin resistance, impaired glucose regulation and type II diabetes mellitus, obesity, hypertension, hypertriglyceridemia, increased low-density lipoprotein (LDL), and low high-density lipoprotein (HDL) cholesterol levels, may be associated with second-generation antipsychotics. Appetite stimulation through the blockade of histamine H_1 and noradrenergic A_1 receptors seems to be the underlying mechanism (Zarate et al. 2004). Clozapine and olanzapine seem to be most associated with this syndrome (Hartling et al. 2012), risperidone and quetiapine may be intermediate in risk, and ziprasidone and aripiprazole seem to have minimal risk for this syndrome.

Patients receiving second-generation antipsychotics should be monitored for weight, body mass index, fasting glucose, and the lipid profile for possible development of the metabolic syndrome. If such development is suspected, switching to drugs less likely to cause the syndrome should be considered, and dietary and exercise programs should be initiated as well as possible medical intervention, including the use of weight loss medications such as sibutramine, orlistat, and rimonabant (Filippatos et al. 2008; Fujioka 2006).

19.4.3.4 Drug Interactions

Common Considerations

The sedative effect may be accentuated with concurrent use of other sedating agents including alcohol. Orthostatic hypotension may be potentiated with the use of other hypotensive agents. Most antipsychotics, due to the dopamine antagonist action, may antagonize the effects of levodopa and other dopamine agonists. Most antipsychotics are metabolized by the cytochrome P-450 enzyme systems in the liver; enzyme inducers such as carbamazepine decrease the antipsychotic blood levels, and enzyme inhibitors such as ketoconazole increase the blood levels. In general, antipsychotics do not necessitate changes in dosing of other medications.

Olanzapine

Drugs that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance; thus a dosage increase of olanzapine may be necessary. Inhibitors of CYP1A2 may inhibit olanzapine clearance. Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine and may result in a mean increase in olanzapine.

Olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Risperidone

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone. Carbamazepine and other enzyme inducers may decrease the effective level of risperidone by 50 %. Coadministration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment. Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5- to 2.8-fold and threefold to ninefold, respectively.

Quetiapine

Enzyme inducers such as phenytoin, carbamazepine, barbiturates, rifampin, and glucocorticoids may increase the oral clearance of quetiapine up to fivefold, necessitating an increased dose. Caution should be exercised if phenytoin is withdrawn and replaced with a noninducer (e.g., valproate). Coadministration of quetiapine and divalproex increases the mean maximum plasma concentration of quetiapine by 17 % without affecting the extent of absorption or mean oral clearance. Thioridazine increases the oral clearance of quetiapine by 65 %. Cytochrome P-450 3A inhibitors (e.g., ketoconazole, itraconazole, fluconazole, and erythromycin) may reduce oral clearance of quetiapine and may result in a 335 % increase in maximum plasma concentration of quetiapine. Quetiapine reduces the oral clearance of lorazepam.

Aripiprazole

Drugs that induce CYP3A4 (e.g., carbamazepine) may increase aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels. If aripiprazole is to be coadministered with quinidine, a potent CYP2D6 inhibitor, the aripiprazole dose should be reduced to half of its normal dose. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, should be accompanied by similar dose reductions. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not

undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Ziprasidone

Ziprasidone should not be used with any drug that prolongs the QTc interval. Carbamazepine, an inducer of CYP3A4, may increase the clearance of ziprasidone and lower blood levels. Ketoconazole, a potent inhibitor of CYP3A4, may increase blood levels of ziprasidone by about 35–40 %.

Haloperidol

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, and elevated serum enzymes, BUN, and fasting blood sugar level) followed by irreversible brain damage has occurred in a few patients treated with lithium plus haloperidol. A causal relationship between these events and the concomitant administration of lithium and haloperidol has not been established. Patients receiving such combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear (Boora et al. 2008; Normann et al. 1998). Rifampin reduces plasma haloperidol levels by about 70 %.

19.4.4 Psychosocial Management

Experiencing psychotic symptoms in a general hospital is frightening for the patient, especially if these symptoms had not been experienced before. The consultant should inform the health care professionals that most acute psychotic experiences in the medical setting are caused by delirium or side effects of medications and that they should reassure the patients that the symptoms, frightening as they are, are transient, and that both the underlying cause and the symptoms can be treated. For patients who are paranoid, explaining each procedure and medication before they are administered can be helpful.

As psychotic patients are often hypervigilant, the environment should be as quiet as possible, and any discussion about the patient should take place well out of earshot of the patient to reduce ideas of reference and misinterpretation.

For patients with existing primary psychosis, recognition by the health care personnel that such patients may have special needs for privacy and that their behavior may be unusual, may be helpful.

An important aspect of the psychosocial management of chronic psychotic patients is ensuring that the patient continues ongoing outpatient psychiatric treatment after discharge.

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Substance Related and Addictive Disorders

20

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Contents

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20.1 Introduction

Substance abuse is a major problem in consultation liaison psychiatry, disproportionate to the degree of substance abuse in the community. Twenty to thirty percent of consultations in a general hospital have been reported to involve a substance abuse diagnosis, and this has been consistent over time (Bourgeois et al. 2005; Alaja et al. 1998).

A number of medical complications, direct and indirect, occur due to the use of substances of abuse, and result in medical admissions. Motor vehicle accidents, falls, and other kinds of trauma are so frequently associated with substance use that trauma services routinely do urine toxicology to screen new admissions for drugs and alcohol (Silver & Sporty 1990).

The consultation-liaison psychiatrist is typically called upon to diagnose and treat patients for the substance abuse problems that are present. Motivating the patient for treatment and/or making some kind of long-term treatment plan is often the main reason for the consult. In addition, there may be an acute problem associated with intoxication or withdrawal that needs to be assessed and managed. These issues are discussed with a focus on the practical issues facing the consultation-liaison psychiatrist (Haber et al. 2009).

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20.2 Alcohol

The consultation liaison psychiatrist will frequently be called to assist in the care of patients with alcohol use disorder.

20.2.1 Diagnosis

DSM-5 lists 11 criteria, 2 of which are required to diagnose alcohol use disorder. These criteria include tolerance, withdrawal, loss of control of use, craving, and various adverse effects on activities and functioning. The patient can be considered in early remission if no criteria are met for at least 3 months, and in sustained remission if no criteria are met for at least 12 months. A separate diagnosis, alcohol intoxication, is diagnosable if alcohol causes clinically significant behavioral or psychological problems and one of the following: slurred speech, incoordination, unsteady gait, nystagmus, impairment in attention or memory, and stupor or coma. Most of these signs aren't readily elicited when the patient is examined in the emergency room or in a hospital bed. For the consultation-liaison psychiatrist, the importance of diagnosing alcohol intoxication is to avoid too early treatment of alcohol withdrawal, possibly exacerbating the intoxicated state.

Alcohol withdrawal is a separate disorder caused by the reduction in or cessation of heavy, prolonged alcohol use. Two or more of certain signs or symptoms are required to make the diagnosis. These include autonomic hyperactivity such as diaphoresis or rapid pulse, hand tremor, insomnia, nausea or vomiting, transient sensory illusions or hallucinations, agitation, anxiety, and generalized seizures.

The diagnosis of alcohol withdrawal delirium is specified in a separate section of DSM 5. It requires a disturbance in attention and cognition, such as disorientation and fluctuating states of awareness, all of which are due to alcohol withdrawal.

The most common reason for psychiatric consultation with the alcoholic patient has to do with the prevention or treatment of alcohol withdrawal. Alcohol withdrawal delirium, or delirium tremens, can be life threatening, and it is important to treat this condition vigorously if this diagnosis is suspected. Referring physicians may be confident that alcohol withdrawal delirium is present, or they may be unsure or unaware of it and think that a functional psychosis is present instead. In addition to a history of alcohol dependence and a mental status consistent with delirium, physical signs are usually present and help clarify the diagnosis. These include tremor, increased deep tendon reflexes, and often ankle clonus, all signs easily checked at the bedside during the consultation. Vital signs will usually indicate autonomic instability, but these are nonspecific and cannot be relied upon alone. The likelihood of alcohol withdrawal producing symptoms is related to a number of factors, including the duration of drinking, the amount of alcohol consumed on average per day, and the age and weight of the patient. It is common for the patient to underestimate the amount of alcohol imbibed. On rare occasions the patient may overestimate the amount, particularly if the patient knows this may lead to more vigorous drug treatment. Collateral information can be extremely helpful in determining the extent of alcohol dependence.

20.2.2 Treatment of Alcohol Withdrawal

Case vignette: *A 220-lb*, *55-year-old man with a history of alcohol abuse developed delirium 2 days after being hospitalized for a medical problem. The psychiatric consultant*, *suspecting alcohol withdrawal*, *recommended diazepam*, *20 mg orally every 2 h unless asleep. Within 3 days he had fully recovered and the dose was rapidly tapered. When the patient was confronted with the fact that his delirium had been due to alcohol withdrawal*, *he insisted that he never drank more than three or four beers per day. His wife*, *however*, *pointed out that he drank a case of beer or more every night*.

There are a number of methods for managing alcohol withdrawal. The benzodiazepines are the treatment of choice due to effectiveness and the

lack of toxicity. The general principle is to give benzodiazepines in sufficient doses to ameliorate the delirium. This usually means that the patient will go to sleep, after which the delirium often breaks (Kotorii et al. 1982).

Structured protocols have been recommended for determining the dose of the benzodiazepines. A common one is called CIWA (Clinical Institute Withdrawal Assessment). In this protocol the dose of benzodiazepines is determined by rating various signs and symptoms consistent with alcohol withdrawal. Studies have shown that in a population of alcohol abusers in which no one goes into alcohol withdrawal delirium, less benzodiazepines are likely to be used than another method involving giving a fixed dose. No studies have been reported of CIWA's effectiveness for patients already in actual alcohol withdrawal delirium. Thus, it is possible that this protocol may not be reliably effective enough for the population of alcoholics that are actually going to go into withdrawal. Practically, this protocol may be of little value on a medical floor where the nurses are not familiar or experienced in its use (Bostwick and Lapid 2004). They are unlikely to keep track of the relatively complicated ratings necessary to determine the benzodiazepine dose. If this protocol is ordered on a medical floor, the patient will commonly get very little in the way of benzodiazepines, irrespective of the clinical condition (Stanley et al. 2005).

A similar, but even more complicated protocol has been tested in surgical patients. This protocol was triggered using lorazepam with the development of any alcohol withdrawal symptom, but almost half of these patients went on to develop delirium anyway. It is not known if the protocol reduced the number of patients who would have developed delirium or not, but the author's observation that short-acting benzodiazepines can trigger alcohol withdrawal symptoms is consistent with this study. In any event, such a protocol would require extensive training of nurses, however, and practicalities would make it difficult to use (Neyman et al. 2005).

A much simpler technique that can be easily managed on the medical ward is to give a long-acting benzodiazepine on a fixed schedule, and monitor frequently to see if the dose needs to be adjusted. If the patient is found to be in withdrawal delirium, **20 mg of diazepam every 2 h can be given and the dose held if the patient is asleep**. If there is no improvement after two or three doses, the dose needs to be raised accordingly. By holding the dose if the patient sleeps, excessive and prolonged sedation will be avoided. This is an easy protocol for the nurses to follow, and they will not experience difficulties with it.

There is some controversy about which benzodiazepines are superior, with the argument based on whether the short acting lorazepam is superior because it is not solely metabolized by the liver (as it is also secreted in urine), or whether long-acting benzodiazepines are superior because they do not wear off rapidly and will not enhance the precipitation of withdrawal symptoms every few hours. The literature consists mostly of opinion. I could find no reports of problems associated with long-acting benzodiazepines in patients with liver disease. If one does not continue to dose when the patient is sleeping, the patient is not likely to be overdosed due to inability to metabolize the drug. On the other hand, there are reports where the delirium is exacerbated by the use of intermittent short-term benzodiazepines, not uncommon in this author's experience. When the benzodiazepine wears off it seems to stimulate the withdrawal, just as giving alcohol, and then letting it rapidly wear off, might be expected to do. If the short acting benzodiazepines are given frequently, however, such as by continuous intravenous drip, then this should not be a problem.

Once the delirium breaks, and the patient is able to sleep soundly, the benzodiazepine can be tapered very rapidly. If the patient is mentally clear, tapering the benzodiazepine over 2–3 days should cause no problems.

To prevent or treat Wernicke's encephalopathy, thiamine 500 mg IV should be given three times a day for 3–5 days (Parker et al. 2008; Patient.co.uk 2014). Such patients should continue thiamine 100 mg per day.

Some alcohol dependent patients who have had numerous episodes of delirium tremens and have been alcoholics for a long time may not

completely clear from their episode of withdrawal delirium. They may have a residual dementia (Korsakoff's psychosis). If alcohol is not reintroduced they may slowly improve over a period of months. When the mental status changes seem to have stabilized, benzodiazepines are probably no longer useful and they can increase the probability of cognitive disturbance.

20.3 Opioids

Consultations involving issues associated with prescription pain medications are discussed in Chap. 22. In this section, the focus is on patients using illicit opioids.

Not infrequently, heroin addicts are hospitalized for medical conditions, and psychiatric consultation is requested. Referring physicians are often quite uncomfortable with these patients, not understanding their lifestyle, and communication is difficult. The psychiatric consultant should attempt to begin treatment for their narcotic dependence to the extent possible while they are in the hospital. Indeed, such patients are a captive audience while receiving medical treatment; sobriety is maintained with its benefits on cognition. A relationship can be developed and they will not run away. A psychotherapeutic intervention, be it support, confrontation, or motivational enhancement (Baer et al. 1999) has a better chance to take hold.

The opioid addict should not be forced to endure withdrawal as a punishment for drug abuse. There is no evidence that this leads to a better outcome. Detoxification should occur as comfortably as possible in the hospital while the patient is being treated for a medical condition. Ideally, the consultant knows how long the patient will be in the hospital, and this determines the speed of detoxification, especially when outpatient follow-up compliance cannot be assured, as is usually the case.

Case example: *A 33-year-old man was admitted for cellulitis of the leg. He was heroin dependent, and when seen the day after admission, he complained that he was "jonesing" (a slang term for being in withdrawal). He was postured in a curled up position, and had piloerection and dilated pupils. He had not slept the previous night. Administration of 20 mg methadone made him comfortable after an hour. He stabilized on 15 mg twice per day, was eating well, sleeping satisfactorily, and pupils were about 3 mm in diameter. He complained that he still felt as if he were in withdrawal and thought 45–50 mg of methadone per day would do the trick. Instead, he was told that discharge was anticipated in a week, and he would be detoxified and encouraged to go to a drug treatment program. He insisted that he be maintained on methadone, and that the dose should be raised, because he would follow up with a methadone program where they were expecting him and would maintain him on 95 mg per day. He was told that if the program were indeed going to maintain him, this could be done in the hospital, but it would have to be coordinated with the methadone program. He reluctantly gave permission to contact them since this was the only possibility he could get his desired dosing schedule, and this was done, but the story turned out differently. The patient was indeed known to the methadone treatment program, but he had never followed through to enter treatment or even be detoxified. The program would need to carefully evaluate him before considering accepting him as a client—they would not automatically accept him for maintenance on 95 mg, or any dose.*

The patient was counseled on what to do to get in the program. He was told that for the remaining time in the hospital he would be given a liquid solution of methadone to regulate the dose better, and it was advisable that he not be told the dose. He balked at this. He was then told that if he insisted on knowing the dose, it would automatically be lowered each time because his complaints might reflect anxiety, but if he did not know the dose, his complaints would be evaluated carefully with every attempt being made to keep him comfortable. He agreed to not be told his dose. He was given a 30 cc liquid solution of juice and varying doses of methadone. He was started at 9 mg three times per day, with a reduction of 2 mg per dose the next day, and 1 mg per

dose each day after that. At discharge, he was given a solution of 1 mg per 30 ml, and told to take 1 tablespoon (15 ml) every 12 h until none was left. He was given 90 ml. Even if he took it all at once, it would not hurt him, being too small a dose to resume a physical dependence. In any event, he would have had a week of psychotherapy to motivate him to enter a treatment program, and he would have a greater opportunity for such, being free of an opioid habit.

Heroin addicts may or may not try to hide their addiction when they are seen in the general medical hospital often for trauma. It is not uncommon that they will try to smuggle in a supply of heroin with them to use while they're being treated.

Case example: A 32-year-old man was admitted to the hospital with a broken mandible. Three days after admission he demanded to see a psychiatrist. He stated that he had brought a supply of heroin with that, but had not anticipated that his hospitalization would be longer than 2 days, so he had run out. He believed he was experiencing opioid withdrawal and desperately wanted help. Although 20 mg of methadone can often be expected to alleviate heroin withdrawal, this patient claimed that his supply was very good stuff, and indeed, after 30 mg of methadone he was still very uncomfortable and had dilated pupils. The next day he was given 40 mg and his pupils went down to 3 mm, at which time he felt comfortable. The dose was then reduced steadily each day while he was in the hospital. He revealed his multiple social problems to the psychiatric consultant during follow-up visits. After a few days, he acknowledged that heroin was at the center of his problems, and he agreed to placement in a residential treatment program.

In some hospitals, the use of methadone for detoxification is discouraged. This is unfortunate since there is no restriction on the use of methadone for detoxification from opioid dependence in the hospital when the patient is admitted for treatment a medical condition. Clonidine is sometimes recommended as an alternative. The use of this drug can be appealing, since it is not a narcotic, and it does suppress some withdrawal symptoms. It is only partially effective in this regard, however, and large doses are often needed, which can interfere with the concurrent medical treatment. Furthermore, the patient is likely to remain much more uncomfortable in contrast to methadone, and clonidine itself will have to be tapered (Ling et al. 2005).

Reports of the utility of buprenorphine in the hospital setting are increasing. Evidence is accumulating that buprenorphine has advantages over methadone in the treatment of some opioid addicts (Gowing et al. 2009). For heroin addiction, sublingual dosing of 4–24 mg over 24 h will likely eliminate withdrawal symptoms. The dose can then be rapidly tapered over a few days, or even stopped after 1 day, and the patient is likely to remain physically comfortable, with minimal to no withdrawal symptoms. Follow-up drug treatment after discharge from the hospital is critical, however, or else the relapse rate is extremely high.

Buprenorphine is a major therapeutic advance in the treatment of opioid use disorders. It is a partial agonist at the mu opioid receptor. Clinically, this means there is a ceiling effect and raising the dose beyond a certain point has essentially no effect. Thus, respiratory depression rarely occurs even in overdose situations, unless the individual has no tolerance to opioids or mixes buprenorphine with other drugs or alcohol. In the treatment of opioid withdrawal, one or two doses is usually all that is needed to eliminate withdrawal symptoms and restore the patient to reasonable comfort. Caution is warranted, however, to make sure the patient is actually in opioid withdrawal. Dilated pupils, clammy skin, piloerection, insomnia, poor appetite, and body aches are clinical signs of withdrawal that predict a good immediate response to buprenorphine.

If the patient has high doses of opioids in his/her system, then buprenorphine can precipitate withdrawal symptoms. This is because buprenorphine affiliates to the mu opioid receptor more strongly than most other opioids, and will replace them on the receptor. Being only a partial agonist, however, it may not stimulate the receptor enough to prevent the withdrawal symptoms caused by loss of the other opioid. This is particularly a

problem if the patient had been taking methadone at doses of more than 20–30 mg daily for extended periods of time. In that case, methadone must be tapered to a dose less than 30 mg, the amount depending on how long they had been taking methadone daily. To continue treatment with buprenorphine in outpatient follow-up, the prescriber must have an additional waiver on his/her narcotics license to prescribe buprenorphine for opioid use disorders.

20.4 Stimulants: Amphetamines and Cocaine

The stimulant drugs amphetamine, methamphetamine, and cocaine have much in common, with the primary clinical difference being duration of action with cocaine wearing off much more rapidly. Amphetamine pills were a common source of substance abuse problems in the 1960s and 1970s. A smokable form of methamphetamine became widely abused in the 1980s in Hawaii (Jackson 1989), and it has since spread throughout the country. Stimulant abuse with methamphetamine is now common although cocaine remains most popular in the Eastern part of the USA and is also widely prevalent in the rest of the country. Stimulants are the cause of many hospital admissions, and consultation-liaison psychiatrists frequently are consulted (Baberg et al. 1996). Cardiac complications are often present in otherwise young, healthy-appearing individuals (Hawley et al. 2013)

Some of these patients are in amphetamine or cocaine withdrawal, sleeping most of the time and quite hungry. They may appear severely depressed when awake. If the depression does not clear in 2 or 3 days, it may need specific treatment. These patients are usually not management problems, but will have varying degrees of denial about their problem. When they are confined to the hospital because of their medical problem, there is an opportunity to confront their denial and strongly recommend treatment and a change in their lifestyle. Ideally, there is a significant other that is supportive in the hospital and encourages the person.

Sometimes the patient is belligerent, even psychotic, with a positive drug screen for amphetamines and/or cocaine, and the question becomes, does the patient have an intrinsic psychosis, such as schizophrenia, or is it a stimulant-induced psychosis (especially with amphetamine because of the long duration of action)? If an amphetamine or cocaine psychosis is present, standard antipsychotic medication, often in low doses, quickly reverses the psychosis, and then the issue is arranging follow-up treatment. Sometimes the family will want to attribute a first psychotic break from a functional disorder as being solely due to drugs, because of the potentially better prognosis.

Many communities will not have specific stimulant oriented drug treatment programs available. Referral, then, must be to a more generic substance abuse program. A residential program should be considered. Patients are unlikely to seek such a program unless they are motivated sufficiently by their deteriorating social and occupational functioning, or if they need a good record to combat legal troubles. It the patient remains depressed and is suicidal, inpatient psychiatric admission may be required. For the higher-functioning patient, referral for outpatient psychotherapy may be more appropriate, and for the patient unmotivated for a residential program, it may be more realistic.

20.5 Benzodiazepines and Sedative-Hypnotics

Benzodiazepine dependence and abuse are common problems complicating medical cases seen by the consultation-liaison psychiatrist. When used beyond the short-term, the risks are likely to exceed the benefits (Johnson and Streltzer 2013). Commonly, they are not the only drug of abuse. In a series of somatoform pain disorder cases, a majority of prescription opioid-dependent patients were also benzodiazepine dependent (Streltzer et al. 2000). Benzodiazepines are widely sought after by street addicts and used in combination with stimulants and opioids (Ibañez et al. 2013) Short acting benzodiazepines, such

as alprazolam, are usually preferred because of their rapid-acting effects, but diazepam and clonazepam, which have long durations of action, are also problematic since the dependency that develops with long-term use is difficult to overcome.

Intoxication with these drugs causes sedation and sometimes disinhibition. Signs of intoxication include ataxia, nystagmus, loquaciousness, and dysarthria. Consultations are usual after overdoses, but somnolence and the intoxicating effects of these drugs need to wear off before a reliable history can be obtained and a satisfactory evaluation can be done.

Withdrawal symptoms are similar to alcohol, but they occur less commonly and are milder. In cases of long-term dependence on high doses, withdrawal seizures and delirium can occur. Usually, however, withdrawal is manifested by insomnia and irritability, and intense craving can occur. Withdrawal may be seen as frequently or more so in patients not suspected of being substance abusers, but who have been prescribed benzodiazepines on a chronic basis. The elderly are particularly susceptible even with relatively low dose prescriptions (Moss and Lanctot 1998). When a patient becomes agitated several days after being in the hospital with no apparent behavioral problems, benzodiazepine withdrawal should be considered. Withdrawal from long-acting benzodiazepines can occur 5–10 days after cessation of the drug.

Treatment of benzodiazepine withdrawal is similar to that of most drugs of abuse, specifically, substitution of a cross-tolerant long-acting drug, and tapering the dose over time. It is most effective and safest to use another benzodiazepine for this purpose. Anticonvulsants have been advocated also, but it is not clear how effective they would be in cases of severe withdrawal. The most difficult situation to manage occurs when the patient has been dependent on high-dose long-acting benzodiazepines for a long time, for example, diazepam 80 mg daily or clonazepam 8 mg daily for several years. For safety and to avoid discomfort, a *very gradual tapering schedule* should be used, over perhaps 4–6 months, with larger dose decreases prescribed in the beginning, and smaller dose decreases at the end. Since an inpatient is likely to be discharged in days, or occasionally weeks, careful outpatient follow-up and coordination must be planned.

A common clinical problem during an acute admission is that the referring physician does not want the patient to cause any difficulties, and is willing to prescribe whatever is needed to keep the patient quiet until discharge, leaving the problem unattended to. The consultation-liaison psychiatrist is advised to persist attempting to keep the patient's long-term needs foremost, because the inpatient setting provides a prime opportunity to intervene in the pathological process.

Although it should not make any difference physiologically, the author has found it often psychologically helpful to switch to a different long-acting benzodiazepine during the detoxification process. For example, if a patient were dependent on diazepam, switching to an equivalent dose of chlordiazepoxide (less 20–25 % to begin detoxification) provides the psychological advantage that the patient is immediately free from the drug that he or she had been unable to reduce. Contextual associations have not developed with the new drug, and, thus, compliance with further reductions is more likely.

Case vignette: *A 32-year-old*, *single woman was hospitalized for an infection requiring intravenous antibiotics. She was quite demanding*, *prompting a psychiatric consultation request. The consultant discovered that she had been a psychiatric patient most of her adult life and had made several suicide gestures. She carried diagnoses of borderline personality disorder*, *bipolar disorder*, *and polysubstance abuse. She acknowledged using clonazepam*, *her preferred medication*, *for years in varying amounts. She averaged about 8 mg per day over the past year.*

Assessing that this dependency was instrumental in causing her erratic behaviors and functional deterioration, *she was told that clonazepam would not be prescribed in the hospital*, *but she would receive alternative medication that would prevent any withdrawal symptoms. She was anxious about this*, *but limits were set*, *and she was prescribed chlordiazepoxide*, *50 mg*, *four times per day. The consultant visited her frequently for*

support and encouragement. She became quite pleased with herself that she was free of the clonazepam, and became a compliant patient during the rest of the hospitalization. She followed up with the consultant psychiatrist after discharge. Her chlordiazepoxide dose was systematically lowered every 2–4 weeks, and in 6 months, she was free of benzodiazepines. For the next 3 years, she attended monthly group therapy sessions, remaining clean of all substances of abuse. She was employed, and borderline behaviors had ceased.

In this case, the use of chlordiazepoxide had the advantage of being a higher milligram dose than her clonazepam, reinforcing in her mind that she was being adequately medicated. In addition, instantly stopping the drug she had been dependent on for so long, and yet remaining comfortable, was a huge psychological boost. This made the detoxification process go much more smoothly, even though detoxification using clonazepam would have been physiologically the same.

Abuse of non-benzodiazepine sedative-hypnotics is rare, fortunately, compared to 40 years ago. Two abusable sedative drugs that are still problems, however, are butalbital, a barbiturate, and carisoprodol. Butalbital is present in older combination products, such as Fiorinal, Fioricet, and Esgic, that are sometimes prescribed for headaches. Barbiturates can be lethal in overdose, and they are highly addicting. Withdrawal can be dangerous, causing seizures, delirium, and death. Carisoprodol, known as Soma, is sometimes prescribed as a muscle relaxant. It is metabolized to meprobamate, an old barbiturate-like sedative popular in the 1950s. It has become a sought after street drug of abuse (Reeves et al. 1999). It is most often taken by chronic pain patients who are dependent on opioids.

Another drug that is not often recognized as a sedative-hypnotic but can produce similar dependency and withdrawal symptoms is baclofen (Leo and Baer 2005; Rolland et al. 2014). This drug is indicated for spasticity associated with multiple sclerosis, but it is being used more often for nonspecific chronic pain. It is probably used chronically mostly by pain patients prone to dependency.

If an inpatient has a known history of taking at least 3–4 doses of a sedative-hypnotic daily for more than a couple months, the potential for serious withdrawal symptoms (similar to alcohol withdrawal) must be anticipated. Substitution of barbiturates and/or sedative hypnotics with phenobarbital, and then tapering the dose, works well for detoxification. Whether detoxification is required depends on the dose times the duration that it was taken. Detoxification is likely to be needed if the patient were taking three or more doses daily for a substantial period of time. Fifteen milligram of phenobarbital, three times per day, should comfortably cover four to five doses of carisoprodol, baclofen, or butalbital in any combination per day. Tapering should be slow because withdrawal is dangerous. Two to three weeks is safe for the lowest doses, and dependence on higher doses should take longer. Attempting to detoxify by simply gradually reducing the dose of the offending drug is typically quite uncomfortable (because of the short duration of action) and the patient will resist.

An advantage of phenobarbital is that it can cover dependencies on multiple substances, including barbiturates, benzodiazepines, alcohol, and sedative-hypnotics. A co-occurring opioid dependence requires the addition of an opioid for detoxification, however.

Case vignette: *A 52 year-old woman was admitted to the medical floor after passing out at home, bruising her head. Urine drug screen on admission was positive for barbiturates, benzodiazepines, and opioids. She complained of headaches and chronic back pain. She was vague about her prescribed medications and her outpatient treating physicians. She denied daily medication use, or ever taking more than four pain pills per day, but her husband reported that he had seen her take "ten at a time." On admission exam, she did not have dilated pupils or piloerection that might be present in opioid withdrawal. She had a mild tremor of the outstretched hands, and a positive glabella reflex, which is often present in barbiturate withdrawal. She appeared anxious, asking for medications, and eager to be discharged from the hospital. She was placed on 15 mg of*

phenobarbital twice per day, which made her comfortable. Medical workup was negative. She was tapered off the phenobarbital over a few days and referred to the pain clinic psychiatrist for follow-up.

20.6 "Club drugs," "Bath Salts," and Others

Other substances of abuse, including the so-called club drugs, are occasionally an issue in medical patients, leading to hospitalization. Club drugs are so-called because they tend to be used in dance clubs and at "rave" parties. The psychiatric consultant may be called to see patients admitted on medical services for altered mental status. Patients without a history of prior psychosis who appear bizarre and psychotic may be experiencing of reaction to one of several kinds of drugs commonly referred to under the rubric of "club drugs."

Some of these have been around for well over a decade. These include ecstasy, gamma hydroxybutyrate (GHB), and ketamine (Freese et al. 2002). Ecstasy (MDMA—3,4-methylenedioxymethamphetamine) has been around for half a century and is illegal. It is an amphetamine like drug purported to increase empathy, physical energy, and self-confidence. It can cause derealization, impaired decision-making, jaw clenching, headaches, gait disturbance, increased blood pressure and pulse, and sweating. It is thought to increase serotonin release and inhibit its reuptake. Deaths have occurred, often in association with hyperthermia (Freese et al. 2002).

GHB is available by prescription for certain conditions (narcolepsy). It is easily made, however, and is sold illegally under various names. Its effects are somewhat similar to alcohol, but episodes of unconsciousness are more frequent and unpredictable. They tend to occur in young males who are simultaneously using alcohol and other drugs. Dependent users who abruptly stop experience withdrawal similar to alcohol. Treatment with benzodiazepines has been recommended (Miró et al. 2002).

Ketamine is a phencyclidine (PCP) derivative originally developed as a human anesthetic agent. Recently it has been proposed as a rapid treatment for intractable depression (Browne and Lucki 2013). It is an NMDA antagonist. It can produce cognitive disturbances and symptoms resembling schizophrenia. It is relatively safe in overdose.

Newer club drugs include synthetic cathinones, piperazine derivatives, kratom, methoxetamine, synthetic cannabinoids, and salvinorin A. (Davis 2012).

Synthetic cathinones, such as mephedrone, are commonly referred to as "bath salts," and are sold under various names such as Ivory Wave and White Dove. These were first identified as drugs of abuse in the USA in 2008. They stimulate the release of dopamine, norepinephrine, and serotonin, as well as inhibit their reuptake. They are used for feelings of euphoria and increased energy but can have severe adverse stimulant effects including tachycardia, hypertension, hyperthermia, arrhythmias, severe agitation, psychosis, and self-mutilation.

Repeated use may cause persistent visual hallucinations and paranoia. The presentation be include extreme agitation (Winstock 2012; Imam et al. 2013; Gunderson et al. 2013). ECT has been reported to effectively treat persistent psychosis unresponsive to antipsychotics (Penders et al. 2013).

Piperazine derivatives (bezylpiperazine—BZP) also are marketed under a variety of names, such as Cosmic Jet and Exotic Super Strong. They also produce stimulant effects and can cause palpitations, anxiety, and nausea and vomiting (Arbo et al. 2012).

Synthetic cannabinoids, often termed "Spice" or "Fake Weed," are sprayed on any variety of plant matter and smoked. They can be much more dangerous than marijuana causing severe anxiety, hyperemesis, psychosis mimicking schizophrenia, acute kidney injury, and a withdrawal syndrome (Penders 2012; Van der Veer and Friday 2011; Nacca et al. 2013).

Kratom (mitragynine) is a potent mu opioid receptor agonist and produces dose-related

opioid effects (Hassan et al. 2013). Methoxetamine (Kmax, MXE, legal ketamine) is an NMDA receptor antagonist and can cause anxiety and paranoia. It is a derivative of ketamine promoted as legal and bladder-friendly. However, it appears to have more adverse effects than ketamine ranging from mood disturbances to acute cerebellar toxicity (Corazza et al. 2013).

Salvinorin A comes from *Salvia divinorum*, a mint herb, and goes by such names as "Magic Mint" and "Salvia Zone." It is taken for its hallucinogenic effects. It is a kappa opioid receptor agonist and can lead to persistent psychosis (Roth et al. 2002).

Often the specific drug taken is not identified, and even if it is, treatment is nonspecific and symptomatic, usually including antipsychotics or benzodiazepines (Bialer 2002).

20.7 Nicotine

The consultation liaison psychiatrist is rarely requested to see a patient because of nicotine dependence. Nevertheless, the consultant has the opportunity to make an impact on smoking in patients that are being seen primarily for other problems.

Smoking is much less prevalent than it was in years past. It is still considered, however, the leading preventable cause of morbidity and mortality in the USA and much of the world. Among substance abuse patients, it is a common comorbidity. Smoking cessation is not associated with adverse effects on mental health. To the contrary, a recent study demonstrated mental health benefits. Indeed, depression was improved as much as with antidepressant medication (Taylor et al. 2014).

There are a number of different aids for smoking cessation, most of which involve nicotine replacement. These include gum, patches, lozenges, nasal spray, and electronic cigarettes. All of these increase quit rates 50–75 % (Stead et al. 2012).

Antidepressant drugs have also increased quit rates, at about the same frequency as nicotine replacement therapies. The most studied antidepressants for smoking cessation have been bupropion and nortriptyline, with no differences shown among any antidepressant studied (Mahvan et al. 2011).

Varenicline is a medication that is a partial agonist at a subtype of nicotinic acetylcholine receptors (Faessel et al. 2010). It is at least as effective as other aids, and may be more effective. Early reports that it may cause depression and suicidality have not been born out (Cinciripini and Karam-Hage 2014).

Electronic cigarettes have become very popular alternatives to tobacco cigarettes, and users claim that they help them to quit smoking. E-cigarettes are battery powered devices that vaporize nicotine solutions for inhalation. The nicotine dose can be controlled, and tobacco tars are not present. Toxins have been found in the vapor, but to a much lesser degree than tobacco smoke (Goniewicz et al. 2013). Studies show that quit rates using e-cigarettes seem to be as good as or better than other smoking cessation aids (Bullen et al. 2013).

Patients seen in the general hospital are often ill and may not feel like smoking, or be much less interested in smoking during that period of time. Motivation to quit smoking may be enhanced and it is worthwhile for the consultation psychiatrist to encourage this. Simple advice from a physician may double the quit rate (Stead et al. 2013). For the hospitalized patient that is not allowed to smoke, but has uncomfortable cravings, a nicotine patch is often useful, since it is easily applied and requires a minimum of nursing time.

When working with a substance abuser, it is a good idea to also talk about smoking cessation. Such a patient may initially reject this direction by saying that they want to concentrate on their cocaine abuse or their prescription opioid dependence before thinking about stopping smoking. In response, one can suggest that in the long run, stopping smoking may be the most important thing they can do for their health. I have also found it useful to suggest that addiction could be considered one big thing and that smoking is just a part of it, which may be best tackled at the same time as the other drugs. It is important to use motivational enhancement techniques, not demanding that they quit or giving the message

that they are weak if they do not quit. Rather, it works best to help them develop their own motivation for quitting and they can be told that it is something to keep in mind when they are ready to give it a try. I have been pleasantly surprised at the number of patients who do stop smoking in conjunction with treatment for their substance abuse. Furthermore, even bringing up the subject, as long as it is done in a noncritical manner, lends credibility to the consultant as being interested in the patient's health, as opposed to making moral judgments about substance abuse. Even if they do not attempt to quit, cooperation regarding substance abuse treatment may increase.

20.8 Conclusion

Substance abuse related problems are frequent in patients seen by the consultation-liaison psychiatrist. Intoxication and withdrawal symptoms can complicate or obscure the presentation of medical symptoms, and the consultation-liaison psychiatrist is able to be of great help if familiar with these conditions. Comorbid psychiatric conditions, such as anxiety and depression are also common in the substance abuse population, but the consultation-liaison psychiatrist is well advised to make sure that the substance abuse issues are understood before treating those conditions, especially with medication. This is because such symptoms may be alleviated when the substance abuse issues are under control, and a rapid use of psychotropic medication may reinforce the substance abuser's tendency to see drugs as the answer to any type of discomfort or dysphoria, rather than the cause.

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Somatic Symptom and Related Disorders

21

Hoyle Leigh

Contents

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21.1 Vignettes

Vignette 1. An 11-year-old girl was admitted to the pediatrics service for inability to walk due to paralysis of her left lower extremity. One morning, upon awakening, she found that she was unable to move her left thigh and leg and had to stay in bed. On admission, she had flaccid paralysis of her thigh and legs as well as stocking-like hypoesthesia. All labs and imaging studies were within normal limits except for slight anemia. Hoover sign (Chap. 34) was positive. The patient told the psychiatric consultant that she and her family had recently moved from another city, and she had enrolled in a new school where she had no friends. She missed her old friends, particularly a boy with whom she was close, which she kept a secret from her parents. As she talked about how much she missed her old school, she felt that she was beginning to feel some more sensation in her left leg and thigh. The consultant recommended physical therapy. In 2 days' time, the patient recovered enough movement and sensation in her left extremity that she was able to be discharged. In the meanwhile, she and her parents agreed that she could phone her old friends frequently. A psychiatric follow-up appointment was made.

Vignette 2. A 35-year-old woman who works as a nurse's aide in a convalescent home was admitted to the medical service with high fever of unknown origin. Labs revealed neutrophilic leukocytosis with shift to left. Vital signs revealed

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sinus tachycardia with high fever (104 F). Blood culture revealed *E. coli* septicemia. During the night, the nurse happened to notice that she was injecting something into her IV line. The syringe the patient used to inject into her IV line turned out to contain fecal material.

Vignette 3. A 43-year-old woman, who is on disability from long-standing epilepsy, was admitted to the hospital for increasing seizures. During a previous hospitalization, a 24-h EEG showed generalized seizure activity while she was having a grand mal seizure. Lately, however, she was also experiencing seizures during which she was "thrashing about" and at least partly conscious. Another 24-h EEG revealed only movement artifacts and no seizure activity. A psychiatric consultation was requested for "pseudoseizures." During interview, the patient told the consultant that she had increased stress at home because her daughter had lost her job and moved in with her with her three young children. The daughter was addicted to drugs and the patient found herself having to care for the young children as well as her husband, who was disabled with advanced complications of diabetes mellitus.

21.1.1 Introduction

Somatic symptom disorder is a new diagnostic category in DSM-5 and is characterized by the prominence of somatic symptoms associated with significant distress and impairment (APA 2013). In contrast to DSM-IV which emphasized the absence of medical explanation for the symptoms, DSM-5 emphasizes the *positive symptoms and signs of distressing somatic symptoms plus abnormal thoughts*, *feelings*, *and behaviors in response to these symptoms*.

The category of somatic symptom and related disorders includes somatic symptom disorder, illness anxiety disorder, conversion disorder (functional neurological symptom disorder), psychological factors affecting other medical conditions, factitious disorder, and other specified and unspecified somatic symptom and related disorder. In DSM-5, five of the DSM-IV diagnoses, i.e., somatization disorder (Briquet's Syndrome), undifferentiated somatoform disorder, hypochondriasis, pain disorder associated with psychological factors, and pain disorder associated with both psychological factors and a general medical condition, are reduced to just two—somatic symptom disorder and illness anxiety disorder (Dimsdale et al. 2013). Approximately 75 % of patients who would have been diagnosed as hypochondriasis according to DSM-IV would now, according to DSM-5, be diagnosed with somatic symptom disorder (because they have one or more somatic symptom), while about 25 % who do not have any somatic symptom would be diagnosed with illness anxiety disorder.

Of special note is that what used to be called *pain disorder* (*chronic pain syndrome*, *psychogenic pain*, *pain disorder associated with psychological factors*, *etc*.) is now just a part of somatic symptom disorder. As chronic pain is an important entity in CL psychiatry, it is discussed in further detail in Chap. 22.

21.2 Historical Considerations

The classical diagnosis of hysteria involved physical symptoms, which were postulated to be caused by wandering uterus (*hystera* in Greek) by Hippocrates (b. 460 BCE) (Meyer 1997). It was considered to be confined to females. According to this theory, various symptoms of hysteria were caused by the interaction of the uterus with other organs. For example, if the uterus comes towards the liver, the female suddenly becomes speechless and clenches her teeth. The treatment was pushing beneath the liver with the hand and tightening a bandage below the ribs, and by opening the mouth and administering a most fragrant wine, followed by the application of malodorous fumigations into the nostrils (Olsen, 1994). More "definitive" treatments included attempts to tie down the uterus through pregnancy or keeping it moist through frequent intercourse so that it would not try to seek out the moisture of other organs (Meyer 1997).

During the dark ages and early Renaissance, irrationality and misogyny prevailed. Malleus Maleficarum (The Witches' Hammer, 1487), written by two Dominican inquisitors, Spenger and Kramer, set forth the procedure for diagnosis (torture) and treatment (execution) of witches, many of whom were suffering from mental disorders including hysteria. For example, a sign of being a witch was to have an anesthetic spot on the skin.

Hysteria became the subject of intense investigation in the nineteenth century, when it seems the prevalence was quite high. Jean Martin Charcot (1825–1893), Professor of Neuropathology and Physician in Charge at Salpetriere Hospital in Paris, obtained worldwide renown for his use of hypnosis in diagnosing and treating hysteria. He believed that susceptibility to hypnosis was pathognomonic of hysteria, a condition that he believed was caused by a degeneration of the brain. His pupils included Sigmund Freud, Joseph Babinski, Pierre Janet, Georges Gilles de la Tourette, and Alfred Binet.

Sigmund Freud (1856–1939) learned hypnosis under Charcot, returned to Vienna to practice its use in treating hysteria, and wrote, with his colleague and mentor, Josef Breuer, *Studies on Hysteria* (1895), which postulated that the patient's psychological traumas and conflicts caused the symptoms of hysteria. Freud eventually gave up the use of hypnosis in favor of free association, and founded psychoanalysis.

The term, *conversion*, is based on psychoanalytic theory. If an external stimulus or situation threatens to awaken a repressed psychological conflict, the ego converts the psychological conflict into a somatic symptom that represents a symbolic resolution of the conflict. For example, someone a person meets may unconsciously remind him of his father, toward whom he has murderous impulses. The impulse must be repressed because it can cause overwhelming anxiety if it became conscious. The patient's right arm becomes paralyzed, the arm with which the patient might have attacked the father figure. The resolution is that he cannot strike the person (father symbol) as the arm is paralyzed, appeasing the superego, but at the same time the paralysis draws attention to the instrument of aggression, thus partly serving the id's murderous impulse. The *primary gain* in the conversion syndrome is the prevention of the overwhelming anxiety that would arise if the psychological conflict were to become conscious. The *secondary gain*, a commonly used term, is any potential benefit arising from being sick (in this case, paralyzed), such as attention, not having to go to work, etc. Conversion disorder is the only diagnosis in the DSM III/IV and DSM-5 that, at least in name, presumes a psychodynamic etiology.

Conversion symptoms are now considered to be body language expressions of a psychological distress that may be determined by many factors including psychodynamic, cultural, socioeconomic, and genetic-constitutional factors (Maisami and Freeman 1987).

DSM II used the term, *psychophysiologic disorders*, to denote emotional factors affecting physical symptoms, especially those resulting from autonomic activation due to stress. The term was used in contradistinction to *conversion disorder* which denoted symptoms attributable to motoric, somatosensory, and special senses. *Psychophysiologic disorders* were what remained of the "psychosomatic" illnesses (See Chap. 1).

DSM-5 recognizes that, while the "classical psychosomatic" illnesses such as ulcerative colitis and peptic ulcer are no longer believed to be any more "psychosomatic" than immunologic/infectious, there is wide acceptance of the notion that psychological factors such as stress and coping styles contribute to the state of immunocompetence and even cellular aging (Entringer et al. 2013; Epel et al. 2004; Shalev et al. 2013). DSM-5 now includes these syndromes within Psychological Factors Affecting Other Medical Conditions discussed below.

Strictly speaking, conversion symptoms should be considered to be a subset of *psychological factors affecting medical condition*, and we use the latter broad diagnostic term for both syndromes although this is not exactly correct use of the terminology according to DSM-5 as it splits off neurologic symptoms into *conversion* (*functional neurological symptom*) *disorder*. Thus, we would diagnose both Vignette 1 and

Vignette 3 as psychological factors affecting medical condition, although they would both qualify for conversion disorder in DSM-5.

21.3 Somatic Symptom Disorder

DSM-5 defines somatic symptom disorder as one or more somatic symptoms that are distressing or result in significant disruption in daily life and excessive thoughts, feelings, or behaviors related to the symptoms or related health concerns with at least one of the following: (a) excessive and persistent thoughts about the seriousness of the symptoms, (b) persistently high level of anxiety about health or symptoms, or (c) excessive time and energy spent on these symptoms or health concerns. It also specifies that the state of being symptomatic should be persistent (typically more than 6 months) even if any one somatic symptom may not be continuously present. The specifiers may be: with prominent pain, persistent, and severity specifiers or mild, moderate, and severe.

According to DSM-5, patients with these disorders typically have multiple symptoms including pain, and the symptoms may be specific or general (e.g., fatigue). The symptoms may or may not be associated with another medical condition, e.g., a patient may be disabled with somatic symptom disorder following an uncomplicated myocardial infarction.

The prevalence of somatic symptom disorder is estimated to be 5–7 % in the general population, and more in females than in males (APA 2013).

Many factors underlie the predisposition to somatic symptom disorder including genetic factors interacting with experiential factors such as childhood abuse, the development of temperamental neuroticism (Laceulle et al. 2013; Vinberg et al. 2013), and the trait of somatic amplification (Barsky et al. 1988; Freyler et al. 2013; Geisser et al. 2008; Yavuz et al. 2013). Other contributing factors include recent stress, low socioeconomic and educational status (thus lower coping skills), and cultural influences (e.g., emotional distress expressed as somatic discomfort/pain).

There is high comorbidity with both medical diseases and depression and anxiety.

Treatment of somatic symptom disorder should be multifaceted and include a recognition of the distress experienced by the patient, an explanation of the mind's tendency for somatic amplification in some individuals, reassurance that there will be careful medical observation and follow-up of the symptoms, stress management and relaxation training including mindfulness training (Reif et al. 2013; Zangi et al. 2012), activity/exercise therapy, and cognitive behavioral therapy (Hoerster et al. 2012; Nakao et al. 2001; Voigt et al. 2013). Antidepressants, hypnotics, and anxiolytics may be judiciously utilized when target symptoms are present. Duloxetine may be particularly useful in patients with prominent pain symptoms (and it is advertized as a pain medication), and mirtazapine may be useful in patients who have both insomnia and depressive symptoms.

Secondary gain can be prominently influencing symptoms in certain settings, such as chronic pain treatment settings and disability compensation. In these settings, medications should be used very cautiously due to the likelihood that target symptoms may be exaggerated, and drugs can psychologically reinforce them. See Chap. 22 for further discussion of treatment of chronic pain.

21.4 Illness Anxiety Disorder

As discussed earlier, about 3/4 of patients diagnosed previously with hypochondriasis who have physical symptoms of some kind now belong to the somatic symptom disorder category, and the remaining 1/4 of patients *without* any physical symptoms but who have excessive worries about being sick now attain the diagnosis of *illness anxiety disorder*.

A more detailed discussion of *hypochondriasis*, which is no longer a DSM diagnosis, is found in Chap. 23.

DSM-5 defines illness anxiety disorder as preoccupation with having or acquiring a serious illness *and* somatic symptoms are *not* present, or if present, are only mild in intensity. If another medical condition or a high risk of developing a

medical condition (e.g., strong family history) is present, the preoccupation is clearly excessive or disproportionate. There is a high level of anxiety about health and the person is easily alarmed about health status, and engages in excessive health related behaviors (e.g., repeated checks for signs of illness) *or* engages in maladaptive avoidance (e.g., doctor's appointments, hospitals). DSM-5 further requires that an illness preoccupation has been present for at least 6 months. Two specifiers are provided: care-seeking type and care-avoidant type.

Illness anxiety disorder is quite frequently seen in medical and primary care settings. The prevalence ranges from 1.3 to 10 % in community surveys, and in ambulatory medical populations, 3–8 % (DSM-5). There is no gender difference.

This disorder may be precipitated by major life stress or threat to health. About 1/3–1/2 of patients with this disorder have a transient form (DSM-5).

Basic principles of treatment for somatic symptom disorder discussed above apply to illness anxiety disorder, including careful monitoring and follow-up, cognitive behavioral therapy, mindfulness training, psychoeducation, as well as SSRIs (Greeven et al. 2009; Hedman et al. 2010; Lovas and Barsky 2010; Williams et al. 2011).

21.5 Conversion Disorder (Functional Neurological Symptom Disorder)

21.5.1 Definition

DSM-5 defines conversion disorder as one or more symptoms of altered voluntary or sensory function *and* an incompatibility between the symptom and recognized neurological or medical conditions. The symptom or deficit must also cause clinically significant distress, impairment in social, occupational, or other areas of function, or warrants medical evaluation. Specifiers include by symptom type (with weakness or paralysis, with abnormal movement, with swallowing symptoms, with speech symptom, with attacks or seizures, with anesthesia or sensory loss, with special sensory symptom—e.g., visual, olfactory, auditory, with mixed symptoms), acute episode or persistent, and with psychological stressor or without psychological stressor.

21.5.2 Clinical Presentations

Common presentations include paralysis or paresis of a limb, glove-like anesthesia, seizures, blindness, and mutism. In conversion disorder, there is often a history of multiple somatic symptoms. The onset is often associated with psychological stress or trauma, and dissociative symptoms such as derealization, depersonalization, and dissociative amnesia.

Transient conversion symptoms are common, but the exact prevalence is unknown. According to DSM-5, the onset of nonepileptic seizures peaks in the third decade, and motor symptom onset peaks in the fourth decade. The prognosis is considered to be better in younger children than in adolescents and adults. Conversion disorder is 2–3 times more common in females than in males.

21.5.3 Contributing Factors

History of childhood abuse or neglect may be predisposing factors as well as maladaptive personality traits. Stressful events often precipitate the symptom (Nicholson et al. 2011). There may be some neurologic basis for conversion symptoms, particularly relating to the CNS processing of stress. Recent studies show that conversion symptoms are associated with functional brain changes (Burgmer et al. 2006; Vuilleumier 2005). Functional neuroimaging studies indicate that there are selective decreases in the activity of frontal and subcortical circuits involved in motor control during conversion paralysis, decreases in somatosensory cortices during conversion anesthesia, and decreases in visual cortex activation during conversion blindness. There is also increased activation in limbic regions, such as cingulate and orbitofrontal cortex in conversion

syndrome (Aybek et al. 2008; Perez et al. 2012; Scott and Anson 2009).

Comorbidities include anxiety disorders, particularly panic disorder, depressive disorders, as well as other somatic symptom disorders. Comorbidities with other medical conditions are also common, especially seizure disorder.

21.5.4 Diagnosis

The diagnosis is often a diagnosis of exclusion of physical diseases that might explain the symptom. The conversion symptom itself is not associated with peripheral tissue pathology except for possible disuse atrophy.

If the symptom of anesthesia is incompatible with the dermatome, or paralysis of an extremity is positive for the Hoover sign (See Chap. 34), then a presumptive diagnosis of conversion may be made. The presence of stress, past history of unexplained somatic symptoms, and identifiable psychological conflict that may underlie the symptom are important considerations in making the diagnosis of conversion disorder. It should be emphasized, however, that all of the above may also be present, and, in fact, may precipitate or exacerbate a medical disease. Conversion is largely a diagnosis of exclusion, and a retrospective one, as the symptoms often clear spontaneously. Conversion "hysteria" has been frequently misdiagnosed, i.e., symptoms of a medical or a neurological disease, particularly multiple sclerosis, have been attributed to conversion. The rate of such misdiagnosis, however, has been declining (29 % in 1950s, 17 % in 1960s, and 4 % since 1970s) (Stone et al. 2003). However, as late as 2002, up to 50 % of patients diagnosed with conversion motor paralysis, an organic medical condition was found (Heruti et al. 2002).

21.5.4.1 Hypnosis and Sedative Interview as a Diagnostic Tool

Hypnosis is used today primarily as an adjunct in diagnosing the conversion component of a medical symptom. As hypnosis is a dissociative state in which memories and ideas that are not normally conscious can become accessible, the psychological meanings of physical symptoms may become clear. To the extent that psychological factors that may have caused the conversion symptoms might be attenuated in hypnotic state (disinhibition), paralysis of muscles in conversion syndrome may become functional during the hypnotic state (including reversal of mutism), as well as dysfunction of organs of special senses, such as conversion blindness or deafness (Halligan et al. 2000). It is important to note, however, that any dysfunction, including organic ones, may be ameliorated to an extent under hypnosis due to the strong motivation hypnosis elicits. (See Chap. 34 for further discussion). Likewise, sedative drugs such as lorazepam and sodium amytal can be administered intravenously to induce a semiconscious state with reduced cortical inhibitory activity. As in hypnosis, psychological factors associated with a physical symptom may be elucidated in that state, as well as reversal of the dysfunction. When symptom removal has been demonstrated during either hypnosis or drug-induced semiconscious state, it is important to give the suggestion to the patient that she/he will be able to maintain the function after the session to the extent the patient is able. This permits the patient to maintain, reduce, or be relieved of the symptom to the extent permitted by the psychological conflict that caused it.

21.5.5 Treatment

As conversion symptoms often resolve spontaneously, an important goal of treatment is to prevent secondary complications such as disuse atrophy or excessive secondary gain that may work against recovery.

Physical therapy is often the treatment of choice for paralysis or paresis. In addition to preventing disuse atrophy, it provides both a motivation and a face-saving reason for recovery (Ness 2007; Oh et al. 2005). Likewise, speech therapy is indicated for mutism (Bota et al. 2010).

Psychotherapy is indicated both to deal with the underlying psychological conflicts and states (e.g., depression, anxiety) that may have resulted in the body language expression (symptom) as

well as to reduce the noxious effects of stress. Various forms of psychotherapy may be utilized, including exploratory psychotherapy, narcoanalysis, cognitive-behavioral therapy, and family and supportive therapies. In a case of globus hystericus, successful behavioral treatment has been reported (Donohue et al. 1997).

Pharmacotherapy is indicated for associated or underlying conditions such as depression (Hurwitz 2004).

21.6 Psychological Factors Affecting Other Medical Conditions

21.6.1 Definition and Diagnosis

In the sense that the physical symptoms are prominently affected by psychological factors, all somatic symptom disorders may be considered to be a subset of psychological factors affecting a physical condition. According to DSM-5, however, this diagnosis has the essential feature of the presence of one or more clinically significant psychological or behavioral factors that adversely affect a medical condition by increasing the risk for suffering, death, or disability. These factors may have influenced the course of the medical condition by a close association between the psychological factor and the onset, development, exacerbation of the medical condition, or delayed recovery from the medical condition. The factors may also interfere with the treatment of the medical condition, or they may constitute additional health risks, or the factors may influence the underlying pathophysiology, precipitation or exacerbation of the symptoms, or necessitate medical attention. The specifiers may be mild, moderate, severe, and extreme (e.g., life-threatening on ignoring of heart attack symptoms).

DSM-5 states that psychological and behavioral factors include psychological distress, patterns of interpersonal interaction, coping styles, and maladaptive behaviors such as denial of symptoms or poor adherence to medical regimen. Common clinical examples include anxiety exacerbating asthma, a diabetic patient manipulating insulin to lose weight, a woman ignoring a lump in the breast, etc. Takotsubo cardiomyopathy and hypertension arising from chronic occupational stress are given as examples. Thus, affected medical conditions in this category can be those with clear pathophysiology (e.g., diabetes, cancer), functional syndromes (e.g., irritable bowel syndrome, fibromyalgia), or idiopathic medical symptoms (e.g., pain, fatigue, dizziness), but excludes functional neurologic symptoms which are categorized under conversion Disorder.

DSM-5 states that the diagnosis of psychological factors affecting other medical conditions should be reserved for situations in which the *effect* of the psychological factor on the medical condition is evident, and abnormal psychological or behavioral symptoms that develop as a result of a medical condition should be diagnosed as an adjustment disorder.

In any case, *psychological factors affecting medical condition* presupposes an identifiable medical condition. Psychological factors may then be identified that may have contributed or may be contributing to the precipitation, exacerbation, course, and treatment/rehabilitation of the patient. The psychological factors may be psychiatric syndromes or symptoms, personality traits, stress, etc. This is a useful diagnosis as many medical diseases and symptoms are exacerbated or exaggerated by stress, anxiety, and depression, and, in fact, "psychogenic" symptoms may coexist with an organic disease. We recommend the use of the term, psychological factors affecting medical condition to include all somatoform (somatic symptom) conditions with the exception of illness anxiety disorder and factitious disorder, particularly in CL settings, as it tends to reduce the organic vs. psychogenic dichotomy in complex medical complaints. At the same time, making the diagnosis often helps to include the psychological factors in the overall treatment plan.

Prevalence of this condition is unknown, but DSM-5 states that this is a more common diagnosis than somatic symptom disorders in U.S.

private insurance billing data. This is not surprising as many CL psychiatrists will use this diagnosis to encompass conversion disorder and somatic symptom disorder diagnoses as well as stress-induced medical conditions and other conditions affected by psychological factors.

21.6.2 Treatment

Treatment should be geared for both the medical condition and the psychological factors that affect it.

Stress management, relaxation training, mindfulness training, supportive psychotherapy and family therapy are some of the modalities that should be considered in stress-related conditions (Fish et al. 2013; Lipschitz et al. 2013; Solomon et al. 1984). Psychoeducation and treatment of depression is important in problems with adherence and rehabilitation (Belzeaux et al. 2013; Garcia-Perez et al. 2013; McGillicuddy et al. 2013; Monroe et al. 2013).

If anxiety and/or depression is present, appropriate medications should be considered. Some patients may be physiologically hypersensitive to anxiety in the particular organ system, such as diarrhea and tachycardia, and may respond well to relatively high doses of benzodiazepines. Sufficient doses of benzodiazepines should be prescribed for such patients as there is no evidence that they become habituated to it as long as it is used short term (Lasagna 1977). The CL psychiatrist should make it clear that benzodiazepines should only be used short term as chronic use may cause habituation and addiction, especially short acting benzodiazepines such as alprazolam. For some patients with prominent cardiovascular symptoms associated with stress, or for performance anxiety, beta-blockers, particularly propranolol may be helpful in relatively small doses (e.g., propranolol 10 mg tid prn either PO or sublingually). Stress-induced and functional syndromes (e.g., irritable bowel syndrome, pseudoseizure) are best conceptualized as a neurobiologic syndrome requiring an integrated approach (Sharpe and Carson 2001; Stone et al. 2012).

21.7 Factitious Disorder

21.7.1 Definition and Clinical Presentations

According to DSM-5, the essential feature of factitious disorder is the falsification of medical or psychological signs in oneself or others that are associated with the identified deception. Factitious disorder imposed on self is defined as: (a) falsification of physical or psychological signs or symptoms, or induction of injury or disease, associated with identified deception, (b) the individual presents self to others as ill, impaired, or injured, (c) the deceptive behavior is evident even in the absence of recognizable external rewards, and (d) it is not better explained by another mental disorder such as psychosis. The specifiers include single episode or recurrent episode.

Factitious disorder imposed on another (previously factitious disorder by proxy) is factitious disorder in which the patient presents another individual (victim) to others as ill, impaired, or injured. The patient, not the victim, receives the diagnosis.

The diagnosis of factitious disorder requires demonstration that the individual is taking surreptitious actions to misrepresent, simulate, or cause the signs or symptoms in the absence of obvious external rewards. In contrast, there is obvious external reward in *malingering*.

Many patients with factitious disorder engage in very painful and potentially lethal self-induction of medical conditions (Vignette 2). They often undergo painful medical procedures and treatments without any apparent gain other than being sick. Many patients seem to be in a trance-like state when they self-induce serious illness. They may develop complications from surgical procedure, scars ("geographic abdomen"), and are at risk of developing drug dependency. For many patients, being a patient with serial hospitalizations may practically become a life-long career. *Sick role addiction* may explain such behavior

Factitious disorder is often seen in individuals with childhood trauma and deprivation and who have few interpersonal relationships. Among patients in general hospitals, about 1 % are considered to have factitious disorder (DSM-5). There are more female (72 % in one study) than male patients, and about half of the female patients were health care workers (Krahn et al. 2003). The patients may have some knowledge of the health care setting either through occupation or in close contact with medical illness (e.g., caring for a chronically ill person). Many are comorbid for other psychiatric conditions including depression, anxiety, substance use, and the borderline personality disorder.

Factitious disorder was known as Munchausen's syndrome in the past. Baron von Munchausen was an eighteenth century German aristocrat who told fantastic and boastful adventure stories. In Munchausen's syndrome, or factitious disorder, patients falsely present or self-induce symptoms and/or signs of a disease and seek medical help, often in the emergency room. They may move from hospital to hospital to receive care.

Factitious disorder imposed on another (*Munchausen's syndrome by proxy*) refers to a condition in which a parent or caretaker deliberately exaggerates or fabricates or induces a physical or psychological-behavioral problems in a child or others. Through this symptom, the parent or caregiver receives attention as well as the victim.

21.7.2 Diagnosis

The diagnosis of factitious disorder is usually made by exclusion of other causes of the symptoms and signs, and/or observation of self-induction/contamination of a medical condition (e.g., infection, ingestion of poison, diuretics or other drugs, etc.) or specimen (e.g., stealing blood from a phlebotomist's cart and pouring it into a bedpan that the patient used).

Laboratory tests may also help in diagnosing factitious disorder (Kenedi et al. 2011; Kinns et al. 2013). For example, in factitious hypoglycemia with insulin abuse, the C-peptide level, which is secreted with endogenous insulin, will not be increased whereas it is increased in insulinoma (Neal and Han 2008).

Once the diagnosis of a factitious disorder is made and the patient has been informed of it, the patient usually leaves the hospital, often against medical advice, only to present again in another hospital.

21.7.3 Management

Management is geared toward prevention of unnecessary and potentially harmful procedures and surgery once the diagnosis has been made. Self-induced illness, however, may be serious and require immediate medical treatment (Vignette 2). Explaining to the patient that the patient may not be fully aware of the psychological factors that contribute to the factitious illness may help develop a collaborative relationship with the physician.

Confrontation with the patient has not been shown to be effective (Krahn et al. 2003; Steel 2009).

Psychotherapy geared to enhancing the patient's coping and interpersonal skills may be helpful, as well as treatment of often coexisting psychiatric conditions, especially anxiety, depression, and borderline personality.

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Chronic Pain (Somatic Symptom Disorder with Predominant Pain)

22

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Contents

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The consultation-liaison psychiatrist is consulted fairly often for problems related to pain. This may vary substantially, however, depending on the presence of pain specialists from other disciplines, typically anesthesiology, and the consultation-liaison psychiatrist's interest in and comfort with pain problems. If the consultation-liaison psychiatrist accept these consults, however, and is considered knowledgeable, requests for help will be frequent.

22.1 Case Examples

The following are examples of typical pain-related consult requests:

A 42-year-old woman is 6 days postoperative from back surgery. She insists she is in excruciating pain, but the surgeon thinks that she should be having minimal pain by now. This case may involve more than simple undertreatment of acute pain. Since there has been preoperative back pain, possibly for some time, she may have been using opioid pain medicationss and become tolerant. If so, more than the usual acute pain medications may be required. Even more importantly, it may become difficult to reduce the opioid dose even if surgery is successful. Consideration might be given to switching to a long-acting opioid, such as methadone, or extended-release morphine, and systematically tapering the dose, often as an outpatient.

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A 68-year-old woman with cancer pain is fearful of taking pain medications, but she appears to be very anxious and uncomfortable. This case may well involve more than just encouraging her to take her pain medications. The meaning of the cancer in the context of her life should be explored. She may need to grieve the loss of her health. Psychological support should also help her to consider the options for pain control.

A 50-year-old homeless man with MRSA (Methicillin-resistant Staphyloccus aureus) cellulitis, constantly demands pain medications, but sleeps most of the day. The assessment should consider the likelihood that subjective desire for pain medications will not be consistent with objective indicators of pain, such as the nature of the medical condition, sleep, appetite, and activity levels. There may be an addiction problem associated with this man's diminished ability to care for himself.

A 70-year-old man, whose pain is treated with fentanyl and lorazepam, becomes delirious. Delirium can be a complication of pain medication, especially if the dose is too high, or there is a preexisting cognitive disturbance. The geriatric population is particularly vulnerable. Lorazepam is especially likely to cause cognitive disturbances (O'Neill et al. 2004).

A 48-year-old woman claims that she suffers from fibromyalgia. She has nonphysiological findings on exams. Patients may carry a diagnosis in which the signs and symptoms are suspect with regard to reliability and validity. Common diagnoses in which this is the case include fibromyalgia, myofasciitis, reflex sympathetic dystrophy, and temperomandibular joint syndrome. Consults are often appropriately requested to assess for psychological issues.

Some pain consults are addiction related; a 36-year-old woman heroin addict has an acute medical condition causing pain. The referring physician wonders whether the pain should be treated. It is not helpful to "punish" an addict by not treating pain. Because she is likely tolerant to opioids, she will need higher than usual doses of opioid pain medications. As the acute pain abates, however, opioid doses must be carefully reduced so that she is not discharged with a bigger habit than she had on admission. Of course, the hospitalization presents an opportunity to motivate her toward treatment.

A 45-year-old man in a methadone maintenance program is hospitalized with acute pain. Physicians are often uncertain how to manage such patients, and psychiatric consultation is requested. There are generally two options. The easiest is to maintain the patient on his daily dose of methadone, and add short-acting opioids, such as morphine, as needed for control of the acute pain. Doses will need to be higher than usual because of tolerance. The other option is to raise the methadone dose sufficiently to produce analgesia. This requires that the consultant be familiar and comfortable with methadone dosing. It is important that permission be obtained from the patient to contact the methadone program so the patient's maintenance dose can be verified. If the patient has lied, and is not tolerant to the dose of methadone claimed, serious respiratory depression to the point of death can occur.

A 40-year-old man has used daily opioids for back and leg pain for 8 years, and doses have reached very high levels. Patients taking megadoses of opioids often have medical admissions to rule out various medical conditions when they may be having complications from their opioid use. The complications can include abdominal pain from severe constipation, or even bowel obstruction, withdrawal symptoms from using up their pain pills too quickly, and altered mental status. The problem must be recognized to devise a treatment plan, which necessarily requires coordination with the prescribing physicians.

22.2 Comorbidities

Mental disorders are common in chronic pain populations (Streltzer 2011) With regard to acute pain, mental disorders, including substance use disorders, and disorders involving impulsivity may render the individual prone to accidents and other trauma.

The consulation-liaison psychiatrist who is asked to do a consult on a pain patient can

assess four categories of potential psychiatric comorbidity: (1) psychiatric disorders that happen to be present in addition to a pain state without any etiological connection between the two; (2) psychiatric disorders that are, at least in part, presumed to be caused by the pain state; (3) psychiatric disorders that contribute to the experience of pain; and (4) psychiatric disorders that are part and parcel of the pain state, usually a somatic symptom disorder. Each of these four categories will be discussed in turn.

Psychiatric disorders that happen to be present in addition to a pain state may or may not be significant influence on the pain state. The psychiatric condition may influence communication style, which can affect the reporting of pain, making it more difficult to assess. This is particularly apparent in disorders affecting thought and communication, such as schizophrenia or delirium.. The mental disorder can also alter the perception of pain and influence the affective response to pain. A flat affect and loose or illogical associations of thought make evaluation of the subjective pain experience quite difficult, particularly if a schizophrenic disorder is not recognized.

Case example: Schizophrenia: An acutely paranoid woman beginning hemodialysis for end-stage renal disease complained of pain and discomfort when needles were inserted to begin dialysis. She concluded that the dialysis machine was the devil, and the nursing staff were the devil's assistants. After treatment with antipsychotic medication, this delusion disappeared she accepted thrice weekly dialysis treatments.

Comorbid psychiatric conditions may complicate the doctor-patient relationship and affect compliance with and response to treatment. The patient with comorbid substance abuse may continually seek narcotic analgesics, feigning or exaggerating pain, making the actual pain state very difficult to assess. From a clinical perspective, many consider substance abuse or "addiction" to be the major comorbid condition of concern.

Psychiatric disorders that are, at least in part, presumed to be caused by the pain state can include depressive, anxiety, and adjustment disorders. These emotional reactions are determined by the context of the pain state, its meaning, and the patient's constitutional tendency to worry, be fearful, be discouraged, be resilient, and so forth. When chronic pain is poorly responsive to treatment, or associated with substantial disability, a mood or anxiety disorder is often present. Even though the origin or the persistence of a chronic pain state may not have a clear pathophysiology, some clinicians automatically accept the pain complaints at face value and view most psychiatric issues as responses to the pain state rather than being involved in its generation. The induction of a psychiatric condition in response to the pain state has been termed the "diathesis-stress model" (Dersh et al. 2001). This model posits that there is a preexisting vulnerability that precipitates a psychiatric disorder under the stress of a painful condition.

Psychiatric disorders that contribute to the experience of pain are most often thought to be anxiety or depression. An anxious person, say, one who has experienced severe life stresses, might react with increased pain from a painful physical condition. A patient in the midst of a depression also might dwell on his or her pain excessively. In terms of personality factors, there is a great deal of interest in the so-called "catastrophizing" cognitive style, which makes the pain state more disabling and less responsive to treatment (Wolff et al. 2008).

Psychiatric disorders in which the pain state is part of the disorder include the somatic symptom disorders, using DSM-5 terminology. In these conditions the patient is morbidly preoccupied with pain. In the not uncommon situation where pain cannot be adequately explained on medical grounds, and nonphysiological and inconsistent findings are present on physical examination, the patient usually qualified for a DSM IV diagnosis of a somatoform pain disorder, but may not qualify for a DSM-5 diagnosis if hypochondriacal concerns are not present. One study comparing DSM IV and DSM-5 criteria, however, found a high degree of overlap (Boscarino et al. 2011).

Case example: Somatic symptom disorder with persistent pain: A 42-year-old married woman immigrated to the United States, and was only able to obtain employment as a laundry

worker. One day she bumped her head unloading a large washing machine. She initially complained of headaches, and over a period of a few weeks she became preoccupied with complaints of neck pain, back pain, shoulder pain, and dizziness. She was unable to work. Medical evaluations and imaging tests were unrevealing of significant pathology to explain the various pains. Physical therapy caused increased pain complaints.

This woman had multiple sites of pain following a trivial injury. Her condition was intractable to all treatment attempts. She was focused on verifying her disability rather than looking for ways to get better. Her family took over all her responsibilities at home, and she sought medical disability from work.

A national comorbidity study, sampling over 9,000 subjects in 2001–2002, found that 19 % reported a 1-year prevalence of chronic spinal (i.e., neck and back) pain. Of these, 35 % had a comorbid mental disorder, mostly depression and anxiety disorders. In addition, almost 69 % had another chronic pain condition, suggesting a high percentage of somatoform pain disorder (Von Korff et al. 2005). The authors concluded that comorbidity contributes greatly to societal burdens of chronic spinal pain. Given the likelihood that many of the chronic pain subjects had multisomatoform pain, it is probable that a significant number of these had somatoform disorders not diagnosable by the study methodology.

Most population studies have similar findings and limitations, demonstrating a high prevalence of anxiety and depressive disorders in pain patients, but not evaluating for somatoform disorders, and not evaluating whether prescribed drugs are part of a substance use disorder. Personality disorders are not often assessed, but when they are the prevalence is usually high.

While most population studies have been crosssectional, a prospective study, surveying over 6,600 respondents in 1998 and again in 2001 looked not at the association of mental disorders with pain, but at the association of mental disorders with the initiation of opioid treatment for pain. It found that the presence of a mental disorder (major depression, dysthymia, generalized anxiety disorder, or panic disorder) greatly increased the likelihood of initiation into regular use of prescribed opioids for chronic pain. This was also true to a lesser extent for the presence of substance abuse in 1998, but not alcohol abuse. This period of time in the United States is associated with the encouragement and rapid rise of opioid prescribing for chronic pain. The authors of the study suggested that practitioners might have been attempting to treat relatively poorly differentiated state of mental and physical pain (Sullivan et al. 2006).

Chronic pain studies often do not control for opioid therapy, which can be a confounder. Opioids may produce their own mental effects, and these can be subtle or intermittent. In addition, patients may worry about their ability to function, which may be compromised by chronic opioids. There is substantial evidence that opioids given chronically contribute to disability, although some authors assert (with little evidence) that unmanaged pain (meaning without opioids) would be more disabling.

In a study of veterans receiving opioids for chronic back pain compared to those only receiving NSAIDS but with identical pain ratings, depression, personality disorders, and history of substance abuse were more common in the veterans receiving opioids. Comparing the opioid-treated group to the nonopioid-treated group. Depression was found in 65 % versus 20 %, substance use disorder was present in 43 % versus 13 %, and a personality disorder was found in 14 % versus 1 %, all significant at $p < .001$. There was no difference in the two groups in anxiety disorders or psychosis. In this sample, the average daily morphine equivalent dose was only 46 mg, a low dose in today's clinical population (Breckenridge and Clark 2003). It is possible that the comorbidity in opioid-using chronic pain patients would be even greater in a population using larger doses.

In conclusion, a great deal of psychiatric comorbidity is present in chronic pain states, and particularly so in those being prescribed opioids. Whether opioid prescription causes psychiatric disorders or is a response to them cannot be definitely determined by these mostly crosssectional studies.

22.3 Consultation with the Opioid-Dependent Chronic Pain Patient

In the past, consultations often involved undertreatment of acute pain (Marks and Sachar 1973; Streltzer and Wade 1981). For at least 20 years, however, most pain-related consultation requests involved chronic pain patients, particularly those using opioids (Streltzer 1994). This is because acute pain is more effectively treated, often allowing the patient to determine the dose of pain medication through patient-controlled analgesia, resulting in less need for psychiatric consults involving acute pain. This more liberal prescribing policy has carried over to the treatment of chronic pain in some circles, but because of substantial differences in the body's physiological response to chronic opioid intake versus short-term intake, chronic pain patients are now much more prone to medical and psychological complications.

The treatment of chronic pain has changed significantly in the United States in recent years. It is far more complex than it used to be, because the consultation-liaison psychiatrist is now more likely to see pain patients being maintained on opioids. This was relatively rare in 1980 and has now become commonplace (von Korff and Deyo 2004). In the 1980s, literature began to appear that suggested that some chronic benign pain patients were benefitted by treatment with long-term opioids (Portenoy and Foley 1986). Anecdotal cases were minimally described, and improvement in functioning was generally not claimed. Patients who previously had been described as "pain-prone" (Engel 1959) or hypochondriacal, with the treatment being primarily psychological, were now being prescribed opioids with increasing frequency and, in the 1990's, through the present, ever higher doses (Martin et al. 2008).

In recent years, a trend opposing this liberal prescribing of opioids has been gaining momentum. The explosion of mortality and morbidity associated with opioid prescribing has steadily risen (Paulozzi and Ryan 2006). In reaction to this, both the scientific literature and the lay press are increasingly describing the lack of safety and effectivenss of chronic opioid therapy (Katz 2010; Juurlink et al. 2013). Organizations concerned with the treatment of chronic pain are issuing treatment guidelines incresingly restrictive of chronic opioid therapy. The American Pain Society and the American Academy of Pain Management issued guidelines in a joint statement in 1997 that actively promoted chronic opioid therapy for chronic pain (The American Academy of Pain Medicine 1997). In a joint publication in 2009, however, they retreat a great deal from their enthusiasm for such a treatment approach (Chou et al. 2009) They concluded that evidence of efficacy was weak, as was evidence for almost all the previously suggested procedures to insure safety based on "expert opinion."

Editorials are now frequently seen in prominent journals calling attention to problems associated with excessive prescription of opioid pain medications (Sullivan et al 2010; Von Korff 2010; Von Korff et al. 2011). The solution to this over prescription has thus far eluded the medical community, however. One school of thought has promoted the use of risk management strategies to solve the problem. Recommendations involve screening for past substance abuse behaviors and only prescribing opioids for chronic pain when alternative treatment methods have been tried first. This school of thought recommends close monitoring of the patient once the decision to prescribe opioids on a long-term basis has been made. Treatment contracts are often recommended. These appear to sometimes make the prescribing physician more comfortable, but evidence is lacking for their effectiveness as an adjunct to managing pain. The use of treatment contracts and frequent urine drug screens makes this type of management similar to what is used in drug treatment programs. Most prescribing practitioners do not have the training, resources, or experience to provide such management however. While such management is legal under the guise of pain management, this may often be more accurately described as office-based treatment of opioid dependence. Office-based treatment of opioid dependence with controlled

substances is legally allowed only to practitioners who have obtained a special license to use buprenorphine for such treatment.

With regard to risk management, it appears that the major risk factor in the development of opioid dependence (or an opioid use disorder) is *exposure*. Many patients that are seen in consultation have no significant past history of substance abuse but have become dependent on opioids following a medical and surgical condition that was treated overzealously and overlong with opioids. This dependence is usually associated with adverse consequences including anxiety about taking the drug frequently enough to avoid withdrawal discomfort, irritabiliy, sleep disturbance, and impairment in social and occupational activities.

In conjunction with this dramatic increase of opioid prescription, emergency room data indicates that problems with prescription narcotic drugs have mushroomed in recent years (The DAWN Report 2004) . Evidence is emerging that death rates associated with unintentional overdoses of prescription pain medications are rapidly increasing also (MMWR 2005).

A typical case involves a middle-aged man or woman with chronic musculoskeletal pain who had been prescribed opioid drugs, such as codeine, hydrocodone, or oxycodone, and whose dose escalated over time from a few tablets per day to higher and higher doses, eventually reaching a relatively stable plateau. Such a patient is likely to receive a prescription for a fixed daily dose of an opioid, usually with the availability of additional "breakthrough" opioids, as needed for pain not controlled by the fixed dose. The patient will report that this additional medication is taken only as needed, but if the consultation-liaison psychiatrist persists in determining how often it is actually taken, he or she will discover that it is roughly the same amount each day, and the amount prescribed monthly remains the same from month to month.

The pain complaints tend to be continuous all day long, and they often have spread beyond their original location and increased in subjective intensity. The patient reports that narcotic pain medications are the only effective method of temporary relief, as other modalities such as physical therapy do not affect the overall course of the chronic pain.

The patient's history will include hospitalizations for additional testing, complications of the medication regimen, or a concurrent condition, and during these admissions a psychiatric consult may be requested. In some settings, the patient will be referred for consultation as an outpatient. The referring physician suspects psychological issues maintaining the pain, or worries about addiction, or is simply at a loss as to how to help the patient and hopes the consultation-liaison psychiatrist will come up with something useful.

To provide effective consultation, the consultation-liaison psychiatrist needs to know what condition might be causing pain, and to what degree objective findings are present, not just the patient's subjective report. Also, the consultation-liaison psychiatrist should know the limitations of common controversial pain diagnoses that are likely to have psychological factors involved. Such diagnoses include fibromyalgia, reflex sympathetic dystrophy (also known as complex regional pain syndrome), temperomandibular joint syndrome, and others. In addition, there are diagnoses that are not controversial, but can be questionable as far as the degree of pain being caused, or even the relationship to the pain. Examples include carpal tunnel syndrome, degenerative disc disease, and chronic migraine headaches.

22.4 Evidence for the Loss of Analgesic Efficacy with Chronic Opioid Intake

The consultant should also know the evidence of the lack of analgesic efficacy of chronic opioid intake on pain. The evidence, cited below, is compelling at the cellular, physiolgical, experimental, epidemiological, and clinical levels.

Nerve cells involved in pain pathways adapt to chronic opioid intake through a number of chemical mechanisms (White 2004). These processes seem to overlap in a redundant fashion. For example, administration of chronic opioids suppresses the function of intracellular cyclic AMP. This leads to an adaptive response, an

upregulation of adenylyl cyclase and the system responsible for synthesizing cyclic AMP. This upregulation of the cyclic AMP system leads to increase in cyclic AMP response element binding protein, an intracellular peptide that stimulates RNA to make dynorphin in those cells capable of responding, including the pain transmitting cells of the dorsal horn of the spinal cord (Nestler 2001). Dynorphin is associated with an abnormal pain sensitivity or hyperalgesia (Vanderah et al. 2000). It is present under conditions of painful stimulation, is associated with pain behaviors when is injected into animals, and it is increased by the chronic administration of opioids in a manner similar to that induced by painful stimulation.

Another chemical mechanism has to do with the upregulation of NK1 receptors and substance P (King, et al. 2005). These are involved in transmission of pain impulses and are also induced by chronic opioid administration. An increasing number of intracellular compounds are found to be associated with pain induced by chronic opioids, including cholecystokinin (Xie et al. 2005), and orphanin/FQ (Stinus et al. 1995). Thus, cellular responses to stimulation by long-term exogenous opioids are multiple and overlapping, and they counteract, and ultimately reverse the acute analgesic effects. Inflammatory cytokines have recently been discovered to be elicited in the central nervous system under the influence of chronic opioids, also causing hyperalgesia, and diminishing long-term immune responsiveness (Hutchinson et al. 2011).

Animal studies consistently show a vigorous acute analgesic response to morphine in the opioid-naive animal. In contrast, pretreatment with morphine results in a much less robust response to morphine treatment of a painful stimulus. Furthermore, after a period of time, morphine administration causes increased pain sensitivity, the opposite of acutely administered morphine (Ibuki et al. 1997).

The evidence is convincing that the same phenomena occur in humans. Several studies have confirmed that methadone maintenance patients are more sensitive to experimental pain than controls who do not take daily opioids (Jamison et al. 2000; Doverty et al. 2001) Furthermore, Rosenblum, et al. (2003), found that methadone maintenance patients reported much more chronic severe pain than a control group of nonopioid-using drug abusers in treatment programs. In addition, the longer one had been on methadone maintenance the more chronic pain was reported.

The belief that chronic opioids maintain their analgesic effectiveness is belied by the fact that methadone maintenance patients on very high doses of the powerful analgesic are not protected from pain at all. Despite being maintained on doses of this powerful analgesic that would be lethal in other patients, if they need surgery, or have an acute painful condition, they do not need less pain medication, they need more than opioid-naive individuals to effectively combat acute pain (Compton, et al. 2000). Studies of nonsubstance abusing chronic pain patients reveal the same enhanced pain sensitivity to chronic opioid therapy (Hay et al. 2009).

There is also evidence that patients with somatic symptom disorders are more likely to become dependent on daily opioids. Patients with serious injuries rarely take daily opioids in the long term. Patients with a somatoform pain disorder are more likely to have pain that spreads to new sites from the original injury, to have more diagnostic tests, to have nonphysiological findings on exam, and to have received more treatments, such as physical therapy, than those with more serious injuries (Streltzer, et al. 2000) Thus, when a consultation is called for a chronic pain patient, careful consideration must be given to the possibility of a somatic symptom disorder being present.

As summed up by Ballantyne and Mao (2003), the use of chronic high-dose opioids for the management of pain is neither safe nor effective. It is likely to contribute to morbidity and mortality in a vicious cycle of pain leading to prescription of higher doses of opioid analgesics, which will induce greater pain sensitivity. Doses that appear to be stable over months, or even a few years, are likely to escalate when viewed from a longer-term perspective, unless something happens to disrupt this process (Streltzer and Johansen 2006).

Disruptions tend to occur because of medical complications, or loss of the prescribing doctor.

Treatment of opioid dependence for chronic pain can be effective. We followed 100 consecutive patients referred to a pain consultation clinic from a primary care clinic. In the majority of cases, daily opioid dependence was present. Almost all of these cases were detoxified from opioids. Nonopioids were substituted for pain management and, given in the context of psychological support, resulted in a beneficial outcomes. This mirrors studies from the 1970s when multidisciplinary pain clinics were first being formed (Newman et al. 1978).

When chronic pain is associated with objective findings explaining the pain, it can most often be treated with nonopioid analgesics and various coping strategies can be effective. In some cases chronic pain patients who are not dependent on opioids are somatizers, and may have a somatoform disorder, or hypochondriacal traits, and can be treated according to the principles for treating somatoform disorders. Opioids are not a good treatment for psychological issues, although the patient's energy may be displaced to focus on opioid intake, and the other psychological issues are masked.

22.5 Principles of the Consultation Intervention

The referring physician usually feels a responsibility for the overall well-being of the patient. In the inpatient setting, however, there can be pressure to make the difficult, chronic pain patient content by whatever means possible, leaving long-term goals and limit setting for outpatient care after discharge. This approach can make such outpatient management all the more unlikely to occur. The consultation-liaison psychiatrist will naturally focus on the immediate problem when requested, but is well-advised not to forget the long-term needs of the chronic pain patient.

Case example: A 70-year-old woman with a history of multiple hospitalizations for chronic pain and COPD was well-known by nursing staff for constantly demanding more pain medications, whatever her comfort level appeared to be. The hospital has a pain management team that had been consulted and recommended a higher dose of long-acting opioids plus "breakthrough" short-acting opioids. This had been done in prior admissions, with patient satisfaction. After discharge, however, the patient would soon be readmitted with similar complaints. Psychiatric consultation was called because the patient intermittently would not make sense in her verbalizations. It became clear that opioid intake was influencing the mental status, and that the patient was consuming opioids in a manner unrelated to objective findings. The primary physician agreed to let the psychiatric consultant manage the pain medications. As the patient was detoxified, she became lucid, and her complaints were well-managed by nonopioid analgesics and daily visits. At discharge, the nurses report that she had never looked so good.

Case example: A 36-year-old man was hospitalized because of an excruciating headache unrelieved by extended-release oxycodone, 240 mg, three to four times per day. The headache partially improved on intravenous morphine, given via a patient-controlled analgesia pump, with the total dose averaging an astonishing 95 mg/h. At that dose he could sleep and converse without apparent cognitive impairment. The referring physician had consulted various specialists in the past and tried many different treatments. He was at a loss at this point, and just wanted help. The patient gave a history of suffering migraine headaches since age 22. His sister and mother had similar headaches. Originally, his headaches had been only occasional, and well-controlled with medication. The headaches got progressively worse in severity, however, and by the time he was 29, he was using opioid analgesics daily. His opioid doses gradually rose, with temporary benefit whenever he raised the dose, but then the headaches would become worse again. He had been hospitalized with increasing frequency because of intractable pain, or complications from high-dose opioids. He was now on his highest dose yet, and his internist was at a loss where to go from here.

The consultation-liaison psychiatrist recognized that the patient's headaches were probably

due to a combination of rebound headaches associated with opioids and the enhanced pain sensitivity produced by them. He discussed this assessment with the patient, who was simultaneously intrigued by the potential of not living with constant pain yet fearful of changing his habits, having several times experienced severe withdrawal discomfort and pain. He stated he would think about reducing his pain medications, but since he was beginning to feel a little better he wanted to go back to his oxycodone, but at a higher dose.

The consultant pointed out that the patient had been through this many times before, and the recommendation was going to have to be what the consultant thought was best. Moreover, he was sure that the referring physician would agree with the recommendation, since he had discussed it with him already. The consultant assured the patient that he would visit him every day and monitor his comfort closely.

The patient-controlled morphine was changed to a fixed dose of intravenous morphine, initially at 70 mg per hour. Each day this was reduced by 10 mg, until it reached 40 mg per hour, when it was then reduced by 5 mg per day. The patient was assured that should he feel severe pain coming on, he could ask for something. He wanted to know what, and was told it would be haloperidol, a major tranquilizer with analgesic effects that would not interfere with his other medications or the changes in narcotic dose. It would be given intramucularly for more rapid effect. If it did not help, it would be changed.

The patient asked for the injection several times the next day, and once or twice each day for the remainder of his hospitalization. The dose was 0.5 mg, low enough to minimize the possibility of side effects. More importantly, he was visited daily. The psychiatric consultant carefully listened to his concerns. Minor adjustments were made to his treatment as a result, and the narcotic dose consistently came down. He was praised for how well he was doing, and after a few days, he would greet the consultant with a smile.

When his dose was down to 25 mg/ h, there was pressure to discharge him, since he looked so comfortable. He was then switched to oral methadone 15 mg three times a day for the first day, being reduced to 10 mg three times a day in 3 more days when he was discharged. He was then placed on an outpatient tapering schedule over 2 weeks, and was seen twice as an outpatient. He was put on an anticonvulsant by a neurology consultant for headache prophylaxis. Otherwise he was taking only acetaminophen and a rare haloperidol tablet. He gratefully stated that his life had been restored to him. Three months later he phoned the consultant, reported he was doing well, and talked about his sister who had migraine headaches also and was dependent on prescription narcotics.

This case example is consistent with the rapidly accumulating evidence that daily opioids, at least in high doses, enhances pain sensitivity in general, and clinically, dependency issues are a major problem. . It was necessary for the patient's primary physician to allow the detoxification. Perhaps most importantly, the patient had to see that the consultant had his best interests in mind, and would stick with him through the psychologically stressful change in habits.

The detoxification went surprisingly smoothly considering the huge dose of opioid to which the patient was tolerant. Reducing a continuous intravenous dose is not difficult in the hospital because the dose is constant without the fluctuations that occur with oral dosing or if the patient controls the dose.

22.5.1 Treatment

A treatment model (Streltzer 2001) for which there is evidence of effectiveness (Anooshian et al. 1999) proved successful in these patients (see Table 22.1).

Once the assessment has been made that opioid dependence is adversely influencing the patient's condition, the consultation-liaison psychiatrist will do well to undertake or guide treatment utilizing as many of the following steps as feasible.

Explanation of the role of opioids in maintaining chronic pain and enhancing pain sensitivity.

The patient should be told of the changes to the pain regimen and given a rationale for doing this. An appropriate message might be, "It is only

Table 22.1 Treatment of the opioid-dependent chronic pain patient

1. Explain how opioids contribute to chronic pain
2. Detoxification
3. Nonopioid pain management
4. Psychological support
5. Coordination of care
6. Simultaneous counseling about health behaviors (smoking, diet, exercise, attitude)

natural that you are seeking to relieve your pain. You have been unsuccessful, however, despite very high doses of pain medications. In fact, these medications (opioids) have contributed to your chronic painful condition. Your body needs to recover from the changes induced by the constant intake of opioids, and it is likely that you will become stronger and feel better as a result."

Despite the anxiety engendered by modifying habitual ways of medicating pain, this approach, when given confidently, often inspires hope. For many patients, this makes sense because they have suspected that the medication is a problem and they have become dependent upon it.

Other patients are convinced that they need opioids and cannot live without them. This is similar to the cigarette smoker who believes smoking is something he or she cannot stop, despite all the warnings about the health consequences. These patients will argue that opioids are not the problem but the solution. Such a patient may resist change, but still do well if the physician is supportive but strict in eliminating opioids. The physician does best by not focusing on addiction as an issue, but rather insisting that the best long-term solution for the pain is not the use of (high-dose) opioids that will enhance pain sensitivity.

22.5.1.1 Detoxification

Once the level of opioid dependence is estimated, the dose can be fixed and steadily reduced. Opioid substitution with methadone works particularly well. Methadone is a useful opioid with which to switch for detoxification, not just because of its excellent and reliable absorption, but because a relatively small dose can cover large doses of other opioids, when the patient has been taking the other opioids chronically. There appears to be less crosstolerance to methadone, perhaps because of its NMDA blocking activity (Gorman et al. 1997). This is true only temporarily, however, and tolerance and opioid-induced hyperalgesia will develop readily with methadone with steady use. Tables in textbooks tend to be based on single-dose studies, but clinical situations often involve patients who have had chronic dosing, and this influences the equivalent dose of another opioid, particularly if the duration of action is different.

Methadone is remarkably powerful in a patient naive to this drug, so care must be taken not to start with too high a dose.

Methadone metabolism changes with use and duration of action lengthens each day (Gourlay et al. 1986; Mercadante et al. 1996). A technique that works well for inpatients recovering from acute pain on top of a chronic opioid dependence (other than methadone) is to give methadone every 4 h for three doses, then every 6 h for three doses, then every 8 h, which allows the patient to sleep through the night. For outpatients, three times daily dosing is satisfactory. Mild constriction of the pupils (Verebely et al. 1975) indicates an appropriate methadone effect.

Compared to methadone, short-acting opioids are less comfortable for the patient during detoxification because of fluctuating blood levels, and they do not allow a comfortable sleep through the night. Extended-release morphine does not have a build-up effect and may be immediately given every 12 h, but it is much less reliably absorbed and dosing is more difficult to predict (Gourlay et al. 1986). Detoxification with extended-release morphine can work with the motivated patient, but it is less comfortable than proper dosing with methadone. Extended-release oxycodone has less flexibility in dosing schedules, and if the patient uses up the prescription too rapidly, withdrawal symptoms are intense, stimulating substantial pain behaviors. If the patient is on high doses to start with, detoxification with this drug is exquisitely difficult.

Detoxification using sublingual buprenorphine, a partial mu opioid receptor agonist, is the easiest, safest, and most comfortable, but the

patient must have a base average of only 30 mg or so of methadone or its equivalent. Because buprenorphine binds so tightly to the receptor, it displaces other opioids. Since the other opioids will be full agonists, their displacement at high doses will stimulate withdrawal. A useful technique is to detoxify with methadone down to 30 mg or less, and then switch to sublingual buprenorphine after 24–48 h of abstinence from methadone. Once this is accomplished, the patient could be discharged from the hospital, or leave against medical advice, which may occur with chronic pain patients, and even if no further buprenorphine is taken, minimal to no withdrawal symptoms will occur.

Case example: A 48-year-old man had been treated vigorously with opioid pain medications following surgery 5 years before. He was never weaned off the opioids, and instead his dose gradually rose until he was taking 120 mg of extended-release oxycodone plus 40 mg of immediate-release oxycodone daily. He had been unable to reduce his dose depite seeking to do so on several occassions. He was prescribed methadone as a bridge to buprenorphine. He was instructed to discontinue all oxycodone and substitute methadone 5 mg qid for 1 day, followed by 5 mg tid for 2 days. Then sublingual buprenorphine/naloxone was initiated. The first few days he took 4/1 mg four times daily. Pain did not improve, but did not worsen and he was more comfortable with this regimen. Within 2 weeks he had reduced his total intake to 8/2 mg daily and felt more functional. He was told to treat pain symptoms with acetaminophen, and this proved satisfactory.

22.5.1.1.1 Manage Pain with Nonopioid Medications Simultaneously with Detoxification

Most of the time, the psychiatric consultant will be dealing with patients whose chronic pain is related to a stable condition. The objective medical findings will be those found for most patients who are not dependent on opioid pain medications. The primary need of the patient for opioid medications, then, is psychological, related to conditioning factors and the opioid dependence itself. The patient should be told that the opioids used for detoxification are not actually treating his pain but are eliminating the enhanced pain sensitivity caused by the opioids. Pain treatment will be with other medications. Most often, acetaminophen is satisfactory. The next choice would be nonsteroidal antiinflammatory medications.

The long-term opioid-dependent patient will often reject these choices saying that they do not work. The patient can be told that, of course, they do not work while he or she is dependent on high-dose opioids, but as the pain sensitivity improves, they may once again work as they should.

In addition the patient will do best if told that an as-needed pain medication will be available on request. Psychologically, this is most effective if the medication is given intramuscularly. The medication should be one that will not cause adverse side effects. This can be an antihistamine, such as hydroxyzine, 25 mg IM, or a neuroleptic, such as haloperidol, 0.5 mg IM. These medications can be introduced as adjunctive pain medications that potentiate the opioid effect (Breivik and Rennemo 1982; Schreiber et al. 1997). The patient should be told not to ask for this medication unless absolutely necessary and to try to take it as little as possible. Psychologically, the patient who is most dependent will then be more likely to think that this is a powerful medication, and it will satisfy them for at least 2 or 3 days, during which time detoxification is occurring and the patient is getting better. Tricyclic antidepressant and anticonvulsant drugs can be used also. These will not solve the pain problem, however, and are best used in small doses to avoid adverse effects.

22.5.1.1.2 Provide Psychological Support

Perhaps the most important element of detoxification is the psychological support that can be provided to the patient. The patient must be supported through that critical stage where long-established drug taking habits are changing (Streltzer 1980). The chronic patient will be quite anxious and often dubious of this new approach. The frequent visits, listening to the patients' concerns, and providing confident explanations often repeatedly, goes a long way. When the patient realizes that the consultant is very interested in their well-being

and not simply leaving orders that will make him suffer and then disappearing, the patient begins to develop some trust in the consultant. Because these patients are often demanding, it is tempting not to see them very often, or not until specifically called. It works much better however, and in the long run more efficiently, to make frequent visits even when things are quiet.

22.5.1.1.3 Coordinate Care with Other Providers and with Key Family Members

Coordinating care with the staff and the referring physician is critical so that they understand the treatment and do not inadvertently sabotage it. A house officer covering at night, unfamiliar with the case, may order opioids when the patient complains of pain, rather than utilizing the prn medications available. For outpatients, the physician who had been prescribing the opioids must be contacted to prevent a return to the former medications that were causing the problem.

Spouses or other family members can be extremely helpful unless they are opioid dependent themselves, or abusing and diverting the drugs. Family frequently recognize opioid-related problems when the patient does not. They can help the patient comply with his alternative medications, and they can encourage increased functionality. The encouragement and appreciation of family members can help solidify and sustain the patient's improvement.

22.5.1.1.4 Reinforce Health Behaviors in General

Many if not most of these patients smoke. It is a good idea to talk to him or her about smoking and encouraging consideration of quitting. The patient can be given advice about stopping smoking if any interest is expressed. Some patients will indicate that with all other problems and a medication dependency, smoking is the last thing to worry about. It is still useful to recommend stopping smoking simultaneously with the detoxification process, as it is part of health behaviors in general, and you are concerned with the patient's over all health status. Even if the patient does not show interest in stopping smoking, the underlying message to the patient is that he or she is not just being considered addicted to medications, but that his or her health is the primary consideration. This helps with rapport and trust over the whole process.

Similarly to discussing about smoking, other health behaviors should be brought up. There should be some questions and encouragement with regard to diet and exercise. Finally it is helpful to talk about attitude, encouraging a positive attitude about the patient's willingness to go through this process and to develop a healthier lifestyle. In fact, he or she can be told that the most difficult part of all of this is the psychological part, breaking old habits. Many patients want to see themselves as psychologically strong, and this approach may spur them on to have a more positive attitude toward getting better.

22.6 Conclusion

The psychiatric consultant may receive frequent requests for help with chronic pain patients, especially if they are opioid dependent. Successful consultation requires knowledge about pain syndromes, particularly somatic symptom disorders, pain medications, and treatment approaches. Treatment involving detoxification and nonopioid pain medications with psychological support can be quite effective.

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Hypochondriasis and Somatization Disorder: New Perspectives

23

Don R. Lipsitt

Contents

23.1 Introduction

The blurred boundaries between illnesses presenting with somatic symptoms confronts both psychiatrists and primary care physicians with one of the most challenging issues in patient care (Lipsitt 2000). On a typical day in a general physician's office, perhaps 50 % or more of the patients with physical complaints will have no definitive explanation for their ailment (Simon et al. 1996; Kroenke and Mangelsdorff 1989; Kroenke 2003; Baumeister and Harter 2007; Smith and Dwamena 2007). The patients present with distress from fatigue, chest pain, cough, back pain, shortness of breath, and a host of other painful or worrisome bodily concerns. For most, the physician's expression of interest, taking a thorough history, doing a physical examination, and offering reassurance, a modest intervention, or a pharmacologic prescription suffices to assuage the patient's pain, anxiety, and physical distress. But for some, these simple measures fall short of their expected result, marking the beginning of what may become a chronic search for relief, including frequent anxiety-filled visits to more than one physician, and in extreme cases even multiple hospitalizations and possibly surgery.

The longer and more persistently this pattern appears, the more likely it will generate referrals to specialists for expert consultation, potential iatrogenic illness, greater frustration in both the primary physician and the patient, and ultimately

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dysfunctional patient–physician relationships with inappropriate labeling of the patient as a "problem" or "difficult" patient, and perhaps even worse (Lipsitt 1970; McCahill 1999). This pattern of medical care seeking has been well documented for hundreds of years, accompanied by earnest attempts to understand and describe the phenomenon. Robert Burton's (1621) *Anatomy of Melancholy* described the melancholic and hypochondriacal person. Crediting Hippocrates, Galen, and others, Burton described hypochondriasis (or "windy melancholy") as an illness that "most commonly [begins with] fear, grief, and some sudden commotion, or perturbation of the mind in such bodies especially as are ill-disposed" (p. 249). The symptoms, he said, are "so ambiguous," that "the most exquisite physicians cannot determine of the part affected" (p. 269). The challenge has changed little since Burton's day.

This difficulty of diagnosis has been reflected through the ages, as one term has been supplanted by another (Wessely et al. 1999) in attempts to quell the discomfort of uncertainty that surrounds patients with multiple recurring physical symptoms; these terms include spinal irritation, hysteria, dissociation, neurasthenia, functional disorder, psychophysiological disorder, psychosocial complication, psychosomatic illness, somatization, and unexplained medical disorder (Shorter 1992). Most recently, the term "medically unexplained symptoms" (MUS) has supplanted most others as perhaps the most benign of these "explanatory" terms (Creed et al. 2010).

The term *somatization* had, for some time, become controversial (Martin 1999; Wessely et al. 1999; Mayou et al. 2005) in its broad application to patients whose physical symptoms motivate them to seek medical care and to take medications in hopes of finding relief from what distresses them (Lipowski 1988; Kravitz 2001; Walters et al. 2008; Taylor et al. 2012). An entire spectrum of somatizing (or somatoform) disorders had been enshrined in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association 1994), now superceded by a new, modified classification that has attempted to address the issue of somatizing disorders (DSM-5, American Psychiatric Association 2013). For historical purposes, I will present a brief review of the concept of somatization and will address two of the more commonly confused somatoform disorders: hypochondriasis and somatization disorder, followed by their contemporary reclassification (Voigt et al. 2010).

23.2 The Concept of Somatization

Coined first, not, as conventionally thought, by the German psychoanalyst Wilhelm Stekel, but by his translator in 1925 (Marin and Carron 2002), who was searching for an approximation to the German *organsprache* (organ-speech), the word *somatization* at first was close to Freud's concept of conversion. When Stekel (1943) later used the word in an English-language book on dreams, he defined it as the bodily representation of a deep-seated neurosis, the expression of mental conflict through organ language (Kellner 1991). Freud (1986) (1905) had called it "somatic compliance" in his early studies of hysteria, referring to the symbolic representation in particular organs of an otherwise insoluble emotional conflict.

Somatization achieved some popularity as a way to comprehend the variety of ways in which mind and body seemed to interact. The word was considered helpful to establish a bridge between such diverse conditions as hypochondriasis or conversion and, for example, irritable bowel syndrome or chronic fatigue syndrome. The term and concept were gradually almost universally disapproved if not abolished, giving rise to the movement to reconsider somatoform disorders in DSM-5 (Martin 1999; Dimsdale et al. 2007; Kroenke 2006).

Theories about somatization are scarce, although there is general agreement that it represents a process rather than a diagnosis, more appropriately acknowledged as merely a descriptive term, much as fever might be for a host of diseases (Kirmayer and Young 1998). At least one group of authors has attributed this process to abnormalities of attachment in early life (Waller et al. 2002; Pedrosa et al. 2008). A more

psychoanalytic explanation is provided by the Viennese psychoanalyst Max Schur (1955), who was also Freud's primary care doctor. Schur's theory provides a developmental model; the infant's undifferentiated somatic responsiveness to all stimuli gives way, with developing language and ego mastery, to a more desomatized state with normal emotional adaptation. In this theory, trauma or developmental failure causes normal adaptation to revert to a previous somatic state in which physical representation becomes the major response mode.

Given our common developmental heritage, we are all (including physicians)—in one sense or another and one time or another—somatizers. But it is only those individuals concerned about or distressed enough by their physical reactions to seek medical attention or take medications who are labeled "somatizers." Such individuals tend to attribute their somatic symptoms to signs of physical illness, even in the absence of pathologic medical findings, just as do physicians otherwise unable to make a definitive "organic" diagnosis. Consulting a primary care physician often marks the beginning of what, for many, becomes a lifelong quest for relief.

23.3 Classification

Classification is an earmark of science and especially medicine, wherein the recognition of similarities and differences permits manageable groupings for research, communication, and treatment with the greatest parsimony. Major contributions to medicine by the earliest physicians like Hippocrates and Galen addressed this problem in efforts to understand and treat the many symptoms they encountered in their patients. In time, progress is achieved through constantly evolving and, it is hoped, better classifications.

In mental illness, classification and "official" recognition of a uniform nomenclature of mental disease is a rather recent and elusive enterprise. Beginning with the collection of hospital statistics in 1917, classification gradually paid more attention to diagnosis and treatment, with the first DSM classification established after World War II.

23.3.1 From DSM-I to DSM-5

From the very earliest days of efforts to classify mental disorders, how to characterize somatization clearly presented a very sticky problem (Lipsitt 1996). In spite of attempts to clarify different somatizing disorders described as distinct entities, the spectrum of somatoform disorders is large, diffuse, and often defying of definitive diagnosis (Wessely et al. 1999). While sometimes distinguishable one from another, they all share the symptomatic representation of somatization.

Physicians, frustrated by the challenge of accurately diagnosing patients with medically uncertain syndromes, may pejoratively simply characterize such patients as "somatizers" in cases that in previous decades have called forth such utterances of frustration as "crock," "gomer," turkey," or worse (Lipsitt 1970). Sometimes obsolete or undifferentiated diagnoses such as neurasthenia or chronic fatigue syndrome are resorted to. More recent references have been to "medically unexplained symptoms" (Creed et al. 2010). The Japanese literature refers to "unidentified clinical syndrome" or "vegetative syndrome" (Takii et al. 1994). All have been controversial or unacceptable.

Because most patients with unremitting physical symptoms of uncertain origin are more likely to consult a general physician than a psychiatrist, patients with somatoform disorders are seen infrequently in general psychiatric practice and more frequently by psychiatrists who work closely with nonpsychiatrist colleagues in medical or consultation-liaison settings. It often falls to the consultation-liaison psychiatrist to treat or manage these patients in the medical setting or to adopt a pedagogical relationship with primary care physicians to help them treat these patients.

In choosing the subclassification of psychophysiologic autonomic and visceral disorders, the authors of the first edition of the DSM (DSM-I) wrote, "This term is used in preference to 'psychosomatic disorders,' since the latter term refers to a point of view on the discipline of medicine as a whole rather than to certain specified conditions. It is preferred to the term 'somatization reactions,' which term implies that these disorders are simply another form of psychoneurotic

reaction" (American Psychiatric Association 1950, p. 29). Thus, the place of somatization in the lexicon and theory of psychiatric disorder has had a long and controversial journey (Pilowsky 1969).

A large number of practicing psychiatrists and others, in attempts to lend some structure and common language to the vast field of "unexplainable" medical syndromes, finally located the unifying concept of somatization in a separate formal classification. Beginning in 1980, the third edition of the standardized nomenclature (DSM-III, American Psychiatric Association 1980) introduced the category of somatoform disorders and somatization, replacing the previous catalog of so-called psychophysiological disorders. The fourth edition (DSM-IV, American Psychiatric Association 1994) replaced the diagnosis of atypical somatoform disorder with undifferentiated somatoform disorder in an attempt to make diagnosis correspond more closely to actual clinical experience. It also reduced the number of symptoms for diagnosis of somatization disorder from 35 to 4 thematic areas of pain, gastrointestinal, sexual, and pseudoneurological. The authors of DSM-IV acknowledged that "Undifferentiated Somatoform Disorder was considered a candidate for possible deletion from DSM-IV [but] was retained only because of its familiarity and possible utility in primary care settings" (Frances et al. 1995, p. 280). DSM-5 has finally succumbed to the challenge of distinguishing various somatoform disorders by "lumping" them into one category of Complex Somatic Symptom Disorder.

A case history helps to elucidate the commonalities of somatizing patients, as well as the diagnostic and therapeutic challenges of sometimes confusing clinical presentations and their classification.

23.4 Case History (Part 1)

Melissa, an attractive, intelligent black college student, was referred to a psychiatrist at the age of 27 by her primary care physician (PCP) requesting help with "this complex and problematic young woman." He had been seeing her for about a year for complaints of left-sided abdominal as well as pelvic pain and urinary frequency. Having failed to obtain relief with over-the-counter medications, she urgently sought medical help and recommendations. Her physician, a highly skilled and competent young doctor, assiduously pursued an explanation for her symptoms, including referrals to a gastroenterologist, two urologists, and three gynecologists; they added equivocal diagnoses of gastroenteritis, esophageal reflux, irritable bowel syndrome, cervical inflammation, and diverticulosis to her medical history.

Because of a fear of cancer, she also underwent several cystoscopies with vaginal and urethral biopsies, with negative results. Her repeated thorough physical examinations and all laboratory and procedural studies were within normal limits. On verbal referral to the psychiatrist, Melissa's doctor revealed that he was "concerned about the frequency of her visits to a hospital emergency room and to various physicians," and also "about the increasing aggressiveness of the workups she was receiving despite essentially negative data."

The consulting psychiatrist found Melissa to be a willing, if doubting, patient, eager for "anything that will help the pain" and "get my life back on track." He learned that she had experienced a "painful belly" since around age 5, that her mother and father both had "drinking problems" and took her to doctors at a young age. Father was an advertising executive who had lost his job; mother worked as a secretary and battled a skin disorder for many years.

Melissa revealed little capacity, in spite of her obvious intelligence, for any psychological assessment of her distress or her relationships to family and others. She had been close to a grandfather who died of colon cancer, and she remembers thinking "catastrophic thoughts" when she first began to have crampy periods around age 12. Her grandmother had died of diabetes only a few years previously.

In spite of her long-standing struggle with vague pains, Melissa managed to do her college work reasonably well until she began a sexual relationship with a boyfriend. At that time, all of her pains escalated, with additional throbbing

sensations in her urethra, painful intercourse, and painful urinary frequency. As repeated referrals turned up no satisfactory explanation for her symptoms, she became more and more anxious and demanding in seeking medical care. She read the medical literature and raised questions about illnesses she thought she might have. Attempts at reassurance by her doctors had fallen on deaf ears. To her doctor, she was also beginning to seem depressed. She had begun to complain of additional symptoms including back and hip pain and constipation.

The psychiatrist recommended to Melissa's physician that he see her on a regular basis, but severely curtail further surgical and medical workups. Although she did not seem a candidate for psychotherapy, listening to her story and tolerating her complaints without an urge to "do something" might be of some help. Prescribing an antidepressant (beginning with small doses) could possibly ameliorate both pain and depression, but should not be administered with any optimistic promise of fast (or any) results. He suggested that a stable, continuous patient–physician relationship could potentially offer the greatest therapeutic benefit and that definite appointments should be made unrelated to occurrence or intensity of symptoms.

23.5 Diagnosis

23.5.1 Hypochondriasis

To qualify for a diagnosis of hypochondriasis in DSM-IV criteria, Melissa would have to fulfill the following: (1) a persisting preoccupation with having a serious disease based on misinterpretation of symptoms, despite normal findings on medical evaluation and reassurance; (2) the preoccupation is not of delusional intensity and is not confined to a circumscribed concern about appearance, as in body dysmorphic disorder; (3) the preoccupation causes significant distress or impairment of function; (4) the duration is at least 6 months; and (5) the preoccupation is not secondary to generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, major depressive episode, separation anxiety, or another somatoform disorder.

Melissa's intense anxiety and depressive accompaniment to her somatic concerns, with her increasing frustration, began to affect her relationships, at least with her recent boyfriend, but it is not clear which comes first—concern about pelvic distress worsening her sexual performance, or interpersonal tensions resulting in physical expression. She has not yet shown evidence of psychotic ideation, unreasonable preoccupation with bodily appearance, or significant impairment in her schoolwork. Cancer phobia does seem to have played a part in prompting physicians to repeatedly try to reassure her, with biopsies and other instrumentations, that she is not afflicted with this disease, although she does not feel reassured. And while her major symptoms do appear to be of recent onset, there is clear evidence of long-standing somatic preoccupation, at times even with "catastrophic" fears.

While we might be inclined to accept a diagnosis of hypochondriasis for Melissa, examining other dimensions of this disorder and comparing it later to another somatoform condition—somatization disorder—may provide more clarity.

23.5.1.1 Clinical Features and Patient Behavior

A physical complaint is the most common entrée to a medical care scenario. It is the "bread-and-butter," so to speak, of medical practice, and nothing is considered unusual when a patient first complains of a cough, a backache, fatigue, or dizziness. It is only when such symptoms resist remission with routine or simple measures and interventions that a physician's antennae become attuned for "more than meets the eye." Each physician's threshold for such alertness varies, and some may be tolerant of months or even years of chronic complaint without physical findings before acquiescing to a different view than a strictly biomedical one. Since somatizing patients themselves are not often inclined to use emotional language to describe their distress, their physicians may be dissuaded from exploring this dimension of the patient's experience. Increasing chronicity often leads to escalating frustration,

even restrained anger. Physicians become increasingly aggressive in pursuit of elusive physical etiologies and patients become more and more disappointed in the reports of specialists to whom they are referred for extensive and expensive evaluations. The pinnacle of such dynamics is often a series of dysfunctional patient–physician relationships, "doctor-shopping," and resort to marginal remedies of often doubtful worth (Lipsitt 2001a). If psychiatric referral is regarded an "end-of-the-line" gesture, it is often made with distorted or inappropriate preparation by the physician and inadequate understanding and resentment by the patient. While this pattern of behavior by itself does not distinguish hypochondriasis from other somatoform disorders, it does begin to characterize the field in which patient and physician will engage one another.

23.5.1.2 Epidemiology and Prevalence

Many individuals manifest a hypochondriacal orientation toward life, a kind of health anxiety, while very few actually qualify for a bona fide diagnosis of hypochondriasis. Originally thought to be a disease only of men, it is now recognized as an equal opportunity illness, affecting men and women in similar numbers. Because good epidemiologic studies rely on valid measures of the disease, an illness with such a long, colorful, and changing history does not lend itself easily to such investigation. Recent studies, using such standardized scales as the Whitely Index, the Somatic Symptom Inventory (of the Minnesota Multiphasic Personality Inventory, MMPI), and the Illness Worry Scale, have suggested that hypochondriasis is a valid distinguishable disorder (Speckens 2001).

Prevalence rates, highly dependent on populations examined, have ranged from 1 to 25 %. A worldwide population study, involving 15 sites, established a prevalence rate of 2.2 % for hypochondriasis in general populations (Gureje et al. 1997). Making fine distinctions among illness phobia, illness fear, bodily preoccupation, and disease conviction is not easy and will alter prevalence rates considerably. It is this very difficulty of assessment that has led to reconsideration of classification in DSM-5 (Mayou et al. 2005; Dimsdale et al. 2007; Kroenke et al. 2007; Dimsdale and Creed 2009).

23.5.1.3 Diagnosis

An extremely broad and lengthy spectrum of somatizing primary and secondary disorders makes diagnosis more challenging. Some clinicians prefer simply to describe "hypochondriacal tendencies," or "evidence of somatization" rather than use the specific designation of hypochondriasis, unless the condition almost reaches the threshold of somatic delusion. Of course, consultation and treatment that depend on a specific diagnosis to be eligible for reimbursement by insurance companies will be designated with that formal somatizing disorder that appears most salient in the patient's history and presentation. Controversy prevails among clinicians as to when hypochondriacal behavior represents low-level "illness worry," reasonable attentiveness to physical needs, a personality disorder, or a variant of obsessive-compulsive disorder (Tyrer et al. 1990).

23.5.1.4 Methods of Assessment

The clinician's assessment of patients for hypochondriasis includes a careful review of prior history, considering all physical investigations and the course of the illness. A good current interview attends to how the patient relates to his or her body, the language used to describe symptoms, and the interactive nature of the encounter as engaged, avoidant, trusting, or doubtful. The past history of the patient–physician relationships sometimes predicts future relationships but should not be exclusively relied on. The patient's capacity for collaborative exploration may define the level of opportunity (or absence) for developing a trusting alliance. A readiness to accept reassurance may anticipate the patient's postexamination response to findings, supportive comments, and suggestions.

Observing patients' reactions of fear, anxiety, or neutrality in discussion of symptoms or diseases, as well as distorted thinking and erroneous knowledge about them, can establish patients' hypochondriacal attitudes toward their symptoms.

While somatizing patients referred for psychiatric assessment may become angry at their primary physician for implying that their physical

symptoms are not real, not important, a sign of "craziness," or evidence of desperation in their physician, they may nonetheless be willing to comply with paper and pencil assessments, such as the Structured Diagnostic Interview for Hypochondriasis (SDIH) (Barsky et al. 1992); the Illness Behavior Questionnaire (IBQ) (Pilowsky et al. 1984); the Somatosensory Amplification Scale (SSAS) (Barsky et al. 1990); and the Whitely Index (WI) (Pilowsky 1967). Illness Attitude Scales (IAS) are available for more extensive assessment (Kellner et al. 1983–1984). Inclusion of an assessment of typical coping responses to ordinary (as well as extraordinary) life stresses sheds light on the patient's illness behavior (Pilowsky 1969).

Of all the above-cited assessments, the Whitely Index is perhaps the most useful and easiest to administer with individual patients. It is available at http://www.uib.no/med/avd/med_a/gastro/wilhelms/whiteley.html. How the elicited data are utilized in either medical or psychiatric practice depends on each physician's individual practice style.

23.5.1.5 Research

There has been increasing interest in researching the etiology, prevalence, and treatment of hypochondriasis (Fink et al. 2004). The search for pharmacologic agents that can bring relief to sufferers of hypochondriasis has been especially robust, with continuing need for random controlled trials that can promote the clinician's confidence in everyday practice (Fallon 2001; Kroenke et al. 2006; Fallon et al. 2008; Schweitzer et al. 2011). To the extent that hypochondriasis is accompanied by depression, anxiety, or obsessive-compulsive disorder, there is good research evidence that drugs found effective in those conditions will bring some symptomatic relief to hypochondriacal patients without necessarily changing the basic disorder. Other studies have shown that thoughtful application of reassurance can be useful with patients not ordinarily considered amenable to this intervention (Starcevic 2001).

A growing interest in the relative efficacy of cognitive-behavioral treatment, both in groups and individually, has fostered research that validates this approach (Warwick et al. 1996; Simon 2002; Lidbeck 2003; Barsky and Ahern 2004; Allen et al. 2006; Escobar et al. 2007; Greeven et al. 2007). Reports of the application of interpersonal psychotherapy based on attachment theory premises offers an unsubstantiated promise of effective intervention (Stuart and Noyes 2006; Pedrosa et al. 2008).

In post-Hippocratic days, hypochondriasis was acceptably attributed to disorders of various organs, such as the spleen, liver, stomach, and lungs, until evolving science was able to rule out such etiologies, rendering symptoms "unexplainable." Now, science is also beginning to fill in the blanks of the "mysterious leap from mind to body" with potentially explanatory findings in neurocircuitry and molecular metabolites (Stein and Muller 2008; Brondino et al. 2008; Garcia-Campayoa et al. 2009; van den Heuvel et al. 2011). Imaging and neuroendocrinologic research, while exciting and promising, has not yet achieved transferability to the practicing psychiatrist or internist eager to treat somatizing patients.

23.5.1.6 Hypochondriasis and Primary Care

It is the primary care physician who is and will continue to be the mainstay of care for the millions of somatizing patients in the health care system (Smith et al. 2006, 2009), although their interest in treating somatizing patients is generally lacking (Salmon et al. 2007). Because physicians are trained primarily to detect physical rather than emotional illness (the biomedical approach), inordinate amounts of time can be squandered searching for physical explanations for "mysterious" presenting complaints (Salmon et al. 2004). The risks include delayed recognition, diagnosis and treatment, high and excessive utilization of medical resources, unreasonable and unnecessary costs, and prolonged suffering before the essential diagnosis and intervention are instituted. Such pitfalls can be avoided with the collaborative assistance of psychiatrists or other mental health professionals (Lipsitt 1996; Katon et al. 1999; Schaefert et al. 2013).

The presentation by the patient of a physical complaint does not automatically put the physician in mind of a somatoform disorder (Salmon et al. 2004). Nonetheless, with increasing chronicity and a lack of explanatory physical findings, the continuing presence of unexplained physical symptoms should place this category of disorders close to the top of a differential diagnosis list. The entire category of somatoform disorders offers a number of often overlapping options besides hypochondriasis: conversion disorder, pain disorder, somatization disorder, and undifferentiated somatoform disorder. Once symptoms are ruled out as due to a general medical condition, substance use/abuse, body dysmorphic disorder, other mental disorders, and malingering or factitious disorder, the primary care physician is faced with a perplexing choice. And for the PCP, unfamiliar with the nuances of the many subsyndromal somatized presentations, the somatizing patient presents a formidable and ultimately frustrating challenge. However, there is promise that reclassification of somatoform disorders will ease the PCP's task (Rosendal et al. 2005; Sumathipala 2007).

A frequent solution to the diagnostic dilemma is a "seat of the pants" maintenance approach that may either plateau to a tolerable truce or arrive at some critical nodal point where marked change is called for (Lipsitt 2009; olde Hartman et al. 2009b). However, if the predominant clinical picture is one of somatic expression of a fear of having a disease, the PCP might reasonably settle on the diagnosis of hypochondriasis and acceptably maintain the patient, employing recommended management principles (Lipsitt 1987; Bass and Benjamin 1993; Margo and Margo 2000; Servan-Schreiber et al. 2000a, b; Simon 2002; Avia and Ruiz 2005; Henningsen et al. 2007; Hatcher and Arroll 2008).

23.5.1.7 The Patient–Physician Relationship in Hypochondriasis

In those instances where a trusting working relationship is not established between the somatizing patient and his or her PCP, the resulting perturbations run the risk of creating a dysfunctional, discordant, or ruptured relationship (Lipsitt 2001b; Hahn 2001). Mutual dissatisfaction, distrust, and frustration leading to anger can result in excessive referrals by the physician and futile "doctor-shopping" by the patient. The physician's capacity for empathy may be diminished in such a context, and the propensity for labeling the patient may be invoked (Margo and Margo 2000). Branding a patient a "problem patient" may unfortunately establish an unwarranted profile that adheres to the patient throughout his or her medical "career." This clinical hazard prevails whenever symptoms are "unexplainable" (Lipsitt 2001b), and being told of a "somatization disorder" may be experienced not only as unhelpful but also offensive to the patient.

23.5.1.8 Specific Aspects of Treatment

Management and treatment of hypochondriacal patients utilize principles applicable to all somatizing patients: respectful acceptance of the patient's complaints and symptoms; listening with patience to the (usually physical) narrative; thoughtful restraint about psychological interpretation, referral, or prescription; and emphasis on care rather than cure. The judicious use of medication (as yet insufficiently proven with good randomized controlled trials) for accompanying anxiety, depression, or obsessive-compulsive tendencies may produce some improvement but not sufficient to terminate treatment. Whether individual or in groups, supportive or cognitive-behavioral, all treatment rests on a platform of a trusting patient–physician relationship, and continuity of care with regular appointments at increasingly wider intervals according to the patient's tolerance and agreement.

If there is a distinguishing feature of treating patients with hypochondriasis, it probably resides in the challenging nature of complaints and persistent presentation of elusive and changing symptoms. This fluctuating pattern may severely test the clinician's tolerance more than disorders that show greater consistency in symptomatic expression. Acknowledging Melissa's diagnosis as a somatoform disorder, the next most likely possibility is somatization disorder, formerly known (pre-DSM) as Briquet's syndrome (Guze 1983).

23.5.2 Somatization Disorder

To qualify for a diagnosis of somatization disorder (SD) by DSM-IV criteria, Melissa would have to fulfill the following criteria: (1) a history of many physical complaints over a period of years, with onset before age 30, with significant impairment for which treatment is sought; (2) at any time during the course of the illness, there must have been (a) four pain symptoms in at least four different sites or functions such as during menstruation or urination; (b) at least two gastrointestinal symptoms; (c) at least one sexual symptom other than pain, e.g., irregular periods or erectile dysfunction; (d) at least one pseudoneurologic symptom not limited to pain, e.g., weakness, blindness, seizures, amnesia; (e) for each of these symptoms, appropriate investigation either fails to reveal a medical disease or substance use that fully explains it, or, if a medical disease is found, the symptoms or functional impairment far exceed what might be expected from the disease; and (f) the symptoms are not intentionally produced or feigned, as in factitious disorder or malingering.

Before examining each of these criteria in Melissa's case, a general clinical profile is offered.

23.5.2.1 Clinical Features and Patient Behavior

Patients with SD are likely to attribute their distress to the symptoms themselves rather than, as in the case of hypochondriasis, to their meaning, and to more assertively seek symptom relief. Patients with SD are more likely to be women, often with histrionic coloring in their personality (compared to the more obsessional quality of hypochondriacal patients). They may also present themselves more dramatically in their help-seeking fervor, and rather than reject offers of help, show greater receptivity to whatever might be offered (or not). They may also reveal a stronger family history of personality disorder, alcoholism, or sociopathy. Physicians may be impressed with the multiplicity of prior symptoms, diagnoses, and surgeries beginning at an early age. When patients with suspected SD are asked how long they have been sick, a common response is "all my life." The general picture is one of greater stability than that in hypochondriasis.

23.5.2.2 Epidemiology and Prevalence

Although the incidence of subsyndromal somatization as seen in primary care is quite high, SD in the general community is thought quite rare, according to the Epidemiologic Catchment Area (ECA) Study (Swartz et al. 1990), estimated at 0.13 %. A recent study of 119 primary care patients revealed a documented prevalence of only 1 % SD (Lynch et al. 1999). Patients referred for psychiatric evaluation from primary care resources have been estimated from 6 % (Katon et al. 1984) to 34 % (Smith 1995). It is precisely this marked variability that has prompted a desire for reclassification (Sharpe and Carson 2001).

23.5.2.3 Diagnosis

Having derived from an earlier diagnosis of Briquet's syndrome (or hysteria), SD is more likely than hypochondriasis to show a kinship with conversion disorder. Pierre Briquet, a French neurologist, was the first to free the definition of hysteria from its primitive notions of abnormalities of female reproductive organs, namely the "wandering uterus." In 1859, he described a dramatic syndrome with 59 different accompanying symptoms in women, many of which were of a sexual or painful nature. Briquet regarded this illness very seriously and attributed it to a brain defect in "that portion of the encephalon where affective functions are located" (Shorter 1992, p. 212). Perley and Guze (1962) established the validity and stability of the syndrome, which was subsequently renamed somatization syndrome (Bass 1990) in the DSM-III.

Because of the cumbersome diagnostic criteria, Briquet's 59 symptoms were reduced to 37, of which 13 were considered sufficient to establish the presence of SD. Even this degree of abbreviation was found unwieldy, heralding an abridged set of criteria showing consistency with DSM-III-R criteria (Smith 1995). The DSM-IV specifies a requirement of eight symptoms from the criteria as specified above. Escobar

and associates (1989) devised the Somatic Symptom Index (SSI), requiring only four symptoms for males and six for females to reach diagnostic significance and concordance with DSM criteria. Syndromes that do not fulfill SD criteria but show other characteristics of the disorder were ultimately classified as undifferentiated somatoform disorder, a diagnosis now subsumed under Complex Somatic Symptom Disorder in DSM-5 (Sykes 2012).

23.5.2.4 Methods of Assessment

In addition to the usual history, physical examination, and assessment of illness behavior, screening instruments are available (but probably seldom used) for use in primary practice (Othmer and DeSouza 1985; Swartz et al. 1986). A unique method of assessment and treatment has been developed by Wickramasekera (1989) using tests of hypnotizability and neuroticism to identify the tendency to somatize, then selectively used in a variant of biofeedback treatment; the complexity of this approach, while creative in its implementation, renders it unlikely as a method that can be integrated into primary care practice (Lipsitt 1998).

23.5.2.5 Research

To date, as with hypochondriasis, there is no definitive treatment for SD, although interest in the promise of cognitive-behavioral therapy (CBT) continues to grow (Kroenke and Swindle 2000; Allen et al. 2002; Simon 2002; Escobar et al. 2007; Kent and McMillan 2009). Reports indicate some variable success with noncontrolled educational approaches that help patients reattribute their physical symptoms to psychosocial stressors (Goldberg et al. 1989; Salmon et al. 2007). The ability of PCPs to effectively follow suggested management guidelines was impressively demonstrated in a randomized controlled study using only a consultation letter to assist physicians in the management of patients with SD (Smith et al. 1986). Patients were managed more effectively, with decreased utilization and a 49–53 % savings in cost of health care, although physical and emotional characteristics remained essentially unchanged. A replicated study was able to demonstrate emotional and physical changes (Rost et al. 1994). Nevertheless (Cochrane Summary 2010) of such interventions suggests that benefits are too weak to be attributed to more than the therapist-patient relationship. Eight-session group therapy in a randomized controlled trial with 70 SD patients demonstrated lasting physical and emotional improvement 1-year poststudy (Kashner et al. 1995; Greeven et al. 2007). Regarding targeted pharmacotherapy, anecdotal and case series reports suggest potential benefit from paroxetine (Okugawa et al. 2002; Fallon et al. 2008), nefazodone (Menza et al. 2001), and other selective serotonin reuptake inhibitors (SSRIs) (Viswanathan and Paradis 1991; Fallon 2001; Stahl 2003), but controlled studies are largely lacking and current thinking is that benefits from psychopharmacologic agents are attributable to amelioration of affective components of illness (Cochrane Summary 2007, 2009a, b, 2012).

23.5.2.6 Somatization Disorder and Primary Care

Again, as with hypochondriasis, the primary care physician must often resort to "seat of the pants" approaches (Lipsitt 2009). The consultation-liaison and primary care literature offer empirical guidelines for the primary practitioner, but most general physicians are either too burdened by competing practice demands or lack the foundation skills and knowledge to support application of recommended interventions. Interest in treating the somatizing patients leans toward the biologic, drug-prescribing side of the interventional spectrum; results often compound the disappointment and frustration of managing SD patients in office practice. Untutored efforts at psychiatric referral may result in aborted attempts to procure specialist advice or care. Some early experience with team or collaborative approaches would appear to show some promise (Lipsitt 1996; Smith 1995; Katon et al. 1999; Schaefert et al. 2013).

23.5.2.7 The Patient–Physician Relationship in SD

Repeated failures at well-intentioned therapeutic efforts may generate either increasingly aggressive attempts at treatment or resignation and

withdrawal from the patient (olde Hartman et al. 2009a). Either vector is likely to escalate tension in the relationship, to the point of rupture. This end point adds to the patient's history of a succession of failed relationships with physicians; in the meantime, the patient's search goes on for someone who can listen without feeling overwhelmed, who is not impelled to act, and who can hold a middle ground that gives stability, confidence, and quiet reassurance to the patient.

23.5.2.8 Specific Aspects of Treatment and Management

Recommended approaches to treatment are cited in the above sections. But guidelines unfortunately are more general than specific (Kroenke 2007; Smith and Dwamena 2012). If there are differences in working with hypochondriacal patients as contrasted with SD patients, they may relate to a difference in entrenchment of patterns of illness behavior and relative time spent in the "sick role." The SD patients have usually had more of a "career" in unremitting illness, disappointment, frustration, and anger, while those with hypochondriasis are more often in the beginning stages of their illness and may even be able to apply a modicum of insight to their plight. In either situation, gratification for the dedicated physician comes slowly, but it is rewarding when some small change occurs. Group approaches, using cognitive behavioral techniques, have found favor partly because of a more economic method and a lower intensity of interaction with therapists (McLeod et al. 1997; Lidbeck 2003; Barsky and Ahern 2004).

23.6 Case History (Part 2)

At this point, can we really distinguish Melissa's diagnosis as either hypochondriasis or somatization disorder (olde Hartman et al. 2009a; Smith et al. 2005)? If we must make a choice for purposes of documentation or therapeutic selection, it is evident that uncertainty reigns. As far as presentation goes, Melissa does manifest multiple symptoms, strong concern that she could have cancer, difficulty being reassured about her negative workups, a history of failed patient–physician relationships, multiple specialist referrals, operative explorations, and an early onset of physical concerns. There is a history of alcoholism in the family as well as an environment of physical illness and death. Possibility of personality disorder also exists.

The most salient features of hypochondriasis are perhaps the preoccupation with the idea of serious or fatal illness and the inability to be reassured. SD is more characterized by an early persisting history of multiple somatic symptoms. Melissa did complain of lifelong "digestive problems," as well as constipation and other physical problems from the age of 5, and she is not yet 30. She had pain on menstruation, hip and back pain, urethral pain, and a long history of "belly pain." Her nonpainful sexual or reproductive symptoms included urinary frequency and difficult intercourse. There is no evidence that her symptoms represent conversion and would thus cast doubt on a full diagnosis of SD.

We are left with the clinical picture of a woman who most certainly has a somatoform disorder, but clearly defining it as hypochondriasis, somatization disorder, undifferentiated somatoform disorder, or even pain disorder presents a perplexing clinical challenge. At this time in her clinical course, it may be less important to make a definitive diagnosis (other than somatoform disorder) than to apply the general principles of working with somatizing patients of all diagnostic types. Designation as Complex Somatic Symptom Disorder in DSM-5 offers pragmatic appeal.

Therefore, how might we be of assistance to Melissa and her concerned, diligent physician?

23.7 The Consultation-Liaison Psychiatrist's Role in Somatization

Because of consultation-liaison (CL) psychiatrists' immersion in medical settings and familiarity with comorbidities, they are well equipped to be of help to both the somatizing patient and the physicians who seek solutions to understanding and caring for them. Although their prevalence in

the general community is rather rare, they constitute a burdensome challenge to physicians as both inpatients and outpatients. Whether providing direct therapy or only consultative recommendations and support for the PCP, the CL psychiatrist employs and transmits to the referring physicians those principles of interviewing and management alluded to earlier. The CL psychiatrist is familiar with a biopsychosocial approach, psychodynamic concepts, stress theory, general medicine, and psychopharmacology, permitting a pragmatic, flexible approach.

The CL psychiatrist's ability to conduct a medical-psychiatric interview enables patients to give essential data in an empathic, respectful setting without feeling threatened or rejected, an experience that may seem rather rare for them. Knowing when to withhold or confront patients with psychological interpretations enables the CL psychiatrist to address the patient's worries and fears without puzzling or frightening the patient with emotional (rather than physical) language. The CL psychiatrist has learned to curb therapeutic zeal with these patients, and transmitting this attitude to the PCP has a powerful effect in reducing the PCP's guilt and frustration about poor results. Perhaps most useful of all, the CL psychiatrist can instruct the referring physician in how to create a supportive holding environment for the patient by reducing workups, referrals, and desperate interventions, and instead offering the patient regular (even if infrequent, but definite) appointments.

In the general hospital setting, when somatizing patients are admitted for medical care, the CL psychiatrist can help patients adapt to the sick role, and to endure or minimize pain, fear, and denial. He or she can serve as a "bridge" between the patient and the caregiving staff, who may need help in understanding the patient's illness behavior and minimizing negative countertransference reactions. Even brief engagement with the somatizing patient and hospital staff can have a profound psychotherapeutic effect (Lipsitt 2002).

Writing a jargon-free explanatory consultation note with clear recommendations for post-hospital management helps the primary care physician maintain the discharged patient. An alliance established in the hospital may carry into the outpatient setting. In the outpatient setting, the CL psychiatrist can make himself or herself available for supportive collaborative assistance on an as-needed basis; this can sometimes be a prelude to easy future referral for more specific combined pharmacotherapy/psychotherapy. Depending on the patient's interest and receptivity, various treatment measures can be suggested, whether cognitive-behavioral therapy, individual, group, psychosocial, pharmacological, or others (Allen et al. 2002; Lipsitt and Starcevic 2006).

23.8 Conclusion

Melissa represents a population of patients relatively common in general medical practice. While somatization is nonspecific, it covers a wide spectrum of disorders. There is little definitive treatment and most effective interventions have derived from an abundance of clinical literature describing experience with these patients (Allen et al. 2002). The bedrock of any treatment is likely to be a trusting patient–physician relationship. A case can be made for Melissa's diagnosis bridging both hypochondriasis and somatization disorder, but diagnosis per se may be less important than recognizing the presence of the somatization process, its impact on the patient's behavior, and its influence on the nature of the patient–physician relationship (Creed 2006). Designating the clinical picture as Complex Somatic Symptom Disorder (with qualifying options) by DSM-5 criteria minimizes the need to make the difficult distinctions between somatoform disorders. The CL psychiatrist can work effectively with primary care clinicians to help many such patients adapt to a lifestyle that will optimize if not totally change their ability to experience satisfaction, pleasure, and gratifying relationships. Likewise, for the physician, there is also the likelihood of immeasurably improving his and her usual workday. Saving the excessive costs of inappropriate health care utilization is a welcome by-product (Lipsitt 1992).

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Obsessive-Compulsive and Related Disorders

24

Hoyle Leigh

Contents

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24.1 Vignettes

1. A 66-year-old man was admitted to the hospital when he was found by a neighbor unconscious in the hallway of his apartment. When the paramedics came into the apartment, they found that the whole apartment was literally filled with old newspapers that were stacked to the ceiling in each room. Even the refrigerator was filled with newspapers, and there was no food in it.
2. A 30-year-old woman was referred to the psychiatrist by a cosmetic surgeon as she wanted cosmetic surgery on her nose for the fourth time. Each time, she was convinced that there was something wrong in the way her nose appeared, first it was too big, then it deviated to the right, then to the left, in spite of all objective evidence that there was no deviation. Body dysmorphic disorder was diagnosed.
3. The mother of an 18-year-old man sought consultation for her son, who has been stuck in his room for several days, repeatedly making and remaking his bed. He had not been able to get out of the room because as soon as he came out, he had to go back into the room to remake his bed.

24.2 Introduction

Obsessive-Compulsive and related disorders have in common persistent or recurrent uncontrollable ideas and/or behaviors that are

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dysfunctional. In most cases, there seem to be a neural substrate, particularly in the basal ganglia and the frontal lobe, as well as memetic (cultural/ideational) component. Memes are neural connections representing ideas, which undergo Darwinian selection in the brain (Leigh 2010, 2012).

An evolutionarily important event was the development of romantic love, which serves as an example of preoccupation, obsession, and compulsion, usually but not always within normal range (Leigh 2010). Helen Fisher studied romantic love extensively. She states, "The sex drive evolved to motivate individuals to seek a range of mating partners; attraction evolved to motivate individuals to prefer and pursue specific partners; and attachment evolved to motivate individuals to remain together long enough to complete species-specific parenting duties. These three behavioral repertoires appear to be based on brain systems that are largely distinct yet interrelated, and they interact in specific ways to orchestrate reproduction, using both hormones and monoamines. Romantic attraction in humans and its antecedent in other mammalian species play a primary role: this neural mechanism motivates individuals to focus their courtship energy on specific others, thereby conserving valuable time and metabolic energy, and facilitating mate choice" (Fisher et al. 2006).

The neural circuit underlying romantic love involves the right ventral tegmental area of the brain stem and right posterodorsal body of the caudate nucleus. The dopaminergic reward and motivation pathways contribute to aspects of romantic love.

The complex neurotransmitter network of the cortico-striatal-thalamo-cortical (CSTC) circuit involving dopamine, serotonin, glutamate, and gamma-amino butyric acid (GABA) may be dysfunctional in obsessive-compulsive syndrome (Harvey et al. 2001). The dysfunction in this loop may arise from an attenuation of feedback signal indicating reward which results in compulsive lever pressing in rats, which is further enhanced by lesions of the orbitofrontal cortex (Joel et al. 2005).

Compulsions may also develop from an operant conditioning paradigm as in compulsive gambling, which in turn may result in functional changes in the brain such as impairment of decision-making capacity (Fellows 2007; Hariri et al. 2006; Kalenscher et al. 2006).

Tourette's syndrome is an example of brain dysfunction that involves dysregulation of both ideational and motoric function illuminating the role of the basal ganglia in both. In this syndrome, there are simple and complex motor tics, vocal tics, and frequently obsessive-compulsive symptoms. Its onset occurs before the age of 21 and the course is waxing and waning. Tourette's syndrome occurs mainly in boys and is genetically transmitted with variable penetrance but it has also been associated with various infections and immunological conditions such as the PANDAS (pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection). The neuropathology seems to involve a disturbance of the dopaminergic system in the basal ganglia.

Gene–environment interaction involving the serotonin transporter promoter gene (5-HTTLPR) has also been reported in OCD, i.e., those with the *s*/*s* allele and childhood trauma were more likely to develop OCD with dissociative experiences (Lochner et al. 2007). Clearly, same gene–environment interaction may lead to multiple vulnerabilities in the CNS, including OCD, dissociation, anxiety, and depression.

Normal thinking process may become abnormal if stuck in a loop, as in preoccupations, obsessions, and compulsions. Preoccupations, obsessions, and compulsions may occur unwantedly and unexpectedly, depending on the state of the brain and the memetic nature of the thought. In the obsessive-compulsive disorder (OCD), there may be a primary dysfunction of the cortico-striatal-thalamo-cortical network involving dopamine and serotonin discussed above. Symptoms of OCD may also occur when an idea becomes particularly reinforced in the brain because it is fed by energies from related preexisting ideas (memes) in the brain. For example, a suicide idea may be introduced by a film to a depressed brain that has many preexisting self-punishment and guilt ideas, thus the suicide idea may gain strength, proliferate, and recruit the

motor neurons to carry out suicide. Other memes, like earworms which are unwanted melodies or sounds that keep on occurring in the mind, may replicate because of the strength of their vehicles (the rhythm, melody, form of presentation, color, smell, texture, etc.). Some such memes may represent "supernormal stimulus," the kinds of stimuli that are evolutionarily determined to elicit strong preferences, or results of early imprinting (Burkhardt 2005).

The diagnosis of obsessive-compulsive and related disorders is made on the basis of the severity of the phenomena and the degree of distress. Earworms are nuisances but not necessarily distressing, ego-alien obsessions can be very distressing, and compulsions may be disabling.

In this chapter, we will discuss first OCD and the related disorders—hoarding disorder, trichotillomania, skin-picking disorder, substance/medication-induced OCD, and then body dysmorphic disorder separately as it is of particular importance in certain areas of consultation-liaison psychiatry.

24.3 Obsessive-Compulsive Disorder (OCD)

The characteristic feature of this disorder is recurrent obsessive thoughts or compulsive acts. Obsessive thoughts are ideas, images, or impulses that enter the individual's mind again and again in a stereotyped form. They are almost invariably distressing (ego-dystonic) as they are violent or obscene or senseless, and the patient often tries to resist them—to no avail. These recurrent thoughts are recognized as the patient's own thoughts. Compulsive acts or rituals are stereotyped, repeated behaviors. They are neither inherently enjoyable nor result in the completion of inherently useful tasks. The patient often views them as preventing some objectively unlikely event. Patients usually recognize the compulsive acts to be pointless, and repeated attempts are made to resist them. If the individual is unable to perform the compulsive act, or resists it, unbearable anxiety may build up.

Onset is usually in childhood or early adulthood. OCD tends to be familial, and about 1–3 % of the population is affected (Arco 2008; Grados et al. 2003). It occurs equally in men and women and often develops in individuals who have obsessive-compulsive (anankastic) personality traits.

The perseverative responding seen in OCD may be attributable to a disinhibition of the prefrontal lobe, but there is also basal ganglia, particularly striatal, contribution.

Anxiety may be a prime trigger of OCD (Rachman and Hodgson 1980). Avoidance behavior in animals is well known to be very persistent as it so rarely has the opportunity for extinction—and drugs such as D-amphetamine exacerbate this perseverative tendency. Stereotyped behavior may arise as a coping response to reduce stress. Habit-learning in the rat seems to be mediated by specific sectors of the rat striatum and habit-learning in the striatum can be influenced by prefrontal cortical mechanisms.

In OCD, there may be a counterbalancing between impulsive and compulsive responding and an over-active "checking" mechanism that compares intended actions with their outcomes; if the hypothetical comparator is constantly detecting mismatches, this will continuously engage the "checking" mechanism possibly dependent on anterior cingulate influences (Boulougouris et al. 2009). Orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), basal ganglia, and thalamus are central to OCD pathophysiology and treatment response (Greenberg et al. 2010).

Patients with OCD often have depressive symptoms, and patients suffering from depression often develop obsessive thoughts during depressive episodes. In severe cases OCD may be crippling, as the patient may be unable to leave home without performing endlessly repetitive compulsive acts such as rearranging furniture and checking the locks. It is important to note that in the CL setting, the stress of the medical condition or the delirium or dementia associated with the medical condition or treatment may exaggerate a patient's obsessive-compulsive personality traits. For example, the

development of OCD following brain injury is well documented (Coetzer 2004; Hofer et al. 2012). Such OCD symptoms may resolve once the underlying delirium or stress is resolved.

The stress of illness and hospitalization and the cognitive deficits associated with head injury, medications, and mild delirium can accentuate personality traits such as obsessiveness. Uncertainties regarding diagnosis or proposed treatment may render a person to appear obsessive-compulsive. As it is rare for patients to develop OCD de novo in a hospital, every effort should be made to reduce the situational anxiety or the cognitive deficit accompanying the behavior.

24.4 Hoarding Disorder

A new diagnostic entity in DSM-5, hoarding disorder is characterized by persistent difficulty in parting with or discarding possessions regardless of their actual value, because of a need to save the items and distress in discarding them. This results in an accumulation of items that clutter the living space and compromises their intended use, and causes clinically significant distress or impairment in social, occupational, and other areas including maintaining a safe environment for self and others.

The prevalence of this disorder seems about 2–6 %, and it occurs in both males and females. The prevalence seems higher in older age, though it may appear in teenage, and there is often comorbidity with physical and mental illness (APA 2013; Ivanov et al. 2013).

According to DSM-5, hoarding behavior is familial; 50 % have relatives likewise affected, and twin studies reveal that 50 % of variability of hoarding behavior is attributable to additive genetic factors.

24.5 Trichotillomania (Hair-Pulling Disorder)

This is characterized by recurrent hair pulling resulting in hair loss. There are repeated attempts to stop or decrease hair-pulling to no avail, and the hair-pulling causes significant distress or impairment in social, occupational, or other important areas.

The prevalence seems to be 1–2 % in the general population according to DSM-5. Female to male ratio is 10:1. There is often comorbidity with other mental disorders, often OCD and depression.

24.6 Excoriation (Skin-Picking) Disorder

Synonyms include dermatillomania, neurotic excoriation, acne excoriee, pathologic skin picking, compulsory skin picking, and psychogenic excoriation. In this disorder, there is recurrent picking of one's own skin resulting in skin lesions in spite of repeated attempts to decrease or stop the picking. This causes clinically significant impairment in social, occupational, and other areas of functioning. According to DSM-5, the prevalence is 1.4 % or somewhat higher and 75 % are female. The condition often begins in adolescence and often begins with a dermatologic condition such as acne. Comorbidity with OCD and trichotillomania is common, as well as with depression.

24.7 Substance/Medication-Induced Obsessive-Compulsive and Related Disorder

All OCD-related disorders may be secondary to substances (both intoxication and withdrawal), particularly cocaine, amphetamines, and opiates.

24.8 Treatment of OCD and Related Disorders (BDD is Discussed Separately Below)

24.8.1 Pharmacotherapy

In patients with diagnosed OCD, the treatment of choice is an SSRI, increased gradually to a very high dose (e.g., fluoxetine 80 mg per day)

(Soomro et al. 2008). Antipsychotics may also be effectively used for augmentation of SSRI (Dold et al. 2013). Olanzapine has been used effectively in excoriation disorder (Gupta and Gupta 2000, 2001). The tricyclic, clomipramine, may also be effective in OCD (Marazziti et al. 2012).

For trichotillomania, *N*-acetylcysteine 1,200–2,400 mg per day may be effective (Bloch 2009; Bloch et al. 2013; Grant et al. 2009; Rodrigues-Barata et al. 2012; Rothbart et al. 2013).

24.8.2 Stereotactic Neurosurgery

Bilateral stereotactic cingulotomy and bilateral capsulotomy have been effective in severe treatment-resistant OCD (Sheth et al. 2013; van Vliet et al. 2013; Zhang et al. 2013).

24.8.3 Psychotherapy

Cognitive-behavioral therapy has been shown to be effective (Olatunji et al. 2013). In CBT for OCD, patients are taught that their intrusive thoughts are not indicative of anything important, but that a problem arises if such thoughts are perceived as unacceptable or threatening.

Exposure and response-prevention (ERP) is another psychotherapeutic modality which has been shown to be effective (Abramowitz et al. 2013). Through this technique, patients confront their fears and discontinue their escape response, facilitating extinction of the classically (Pavlovian) conditioned fear response. ERP can be carried out effectively with minimal face-to-face contact between the therapist and the subject as through the internet (Wootton et al. 2011).

Simultaneous administration of D-cycloserine may substantially improve effectiveness of exposure and response prevention (Wilhelm et al. 2008).

For trichotillomania, in addition to CBT, acceptance and commitment therapy (ACT) may be effective as well as dialectical behavioral therapy (DBT) (Trichotillomania-Learning-Center 1991). Physical barriers such as gloves may also be useful.

For excoriation disorder, in addition to CBT and ERP, hypnosis as well as physical barriers may be effective (Paley et al. 2010; Shenefelt 2000, 2004).

24.9 Body Dysmorphic Disorder (BDD)

This syndrome is characterized by a distressing or impairing preoccupation with slight or imagined defect(s) in one's physical appearance. BDD has been reported in various parts of the world. Also called "dysmorphophobia," it was described by Emil Kraepelin and Pierre Janet among others, and numerous case studies have been reported from around the world. The skin seems to be the most common area of concern (73 %), followed by hair (56 %), and nose (37 %) (Phillips and Diaz 1997; Phillips et al. 2006).

BDD appears to be relatively common. The point prevalence has been reported to be 0.7–2.4 % in the general population, which makes BDD more common than disorders such as anorexia nervosa or schizophrenia. In adult student samples, prevalence rates of 2–13 % have been reported (Bjornsson et al. 2010).

In clinical settings, the prevalence BDD has been reported to be as high as 9–12 % in dermatology settings, 3–53 % in cosmetic surgery settings, 8–37 % in individuals with OCD, 11–13 % in social phobia, 26 % in trichotillomania, and 14–42 % in atypical major depressive disorder (MDD).

Among psychiatric inpatients, 13–16 % of patients have been reported to have BDD. A study of adolescent inpatients found that 4.8 % of patients had BDD (Dyl et al. 2006).

Contrary to common expectation, males seem to be equally affected with BDD as females, or only slightly less (Phillips and Diaz 1997; Phillips et al. 2006).

About two-thirds of BDD patients have past or current ideas or *delusions of reference*, i.e., the belief that other people take special notice of them negatively or are mocking or ridiculing them because of how they look (Phillips et al. 1994).

Nearly everyone with BDD is reported to engage in specific behaviors, such as mirror

checking and skin picking. The relationship between thoughts and behaviors in BDD resemble the relationship between obsessions and compulsions in OCD, i.e., the compulsive behaviors arise in response to the obsessive thoughts about appearance, and are designed to reduce anxiety and other painful emotions associated with them, and as in OCD, these behaviors are not pleasurable. These compulsive behaviors are repetitive, time-consuming (about half of BDD patients spend 3 or more hours per day engaged in them), and hard to control and resist. Some behaviors, such as camouflaging disliked body parts (e.g., with a hat, makeup, sunglasses), are called *safety behaviors*, because their function is to reduce or avoid painful emotions or prevent something bad from happening, such as being humiliated or embarrassed. Most BDD patients perform multiple compulsive behaviors. They often compare themselves to other people, and about 90 % of BDD patients repeatedly look at themselves in the mirror, with the hopes of feeling they look acceptable, but usually feeling worse afterwards (Bjornsson et al. 2010).

BDD usually begins during adolescence, with two studies reporting a mean age at onset of 16 and a mode of 13 (Gunstad and Phillips 2003; Phillips et al. 2005). BDD appears to have a chronic course.

Rates of suicidal ideation, suicide attempts, and completed suicide appear markedly elevated. Approximately 80 % of individuals with BDD report past or current suicidal ideation, and about one-quarter have attempted suicide (Phillips 2007; Phillips and Menard 2006).

About one-third of people with BDD report violent behavior related to BDD symptoms. This may be related to anger about being deformed and /or inability to fix the deformity as well as delusions of reference (i.e., other people mocking them) (Phillips 2009).

According to one survey, 12 % of plastic surgeons reported that they had been threatened physically by a dissatisfied BDD patient (Sarwer 2002). BDD is often associated with alcohol or drug abuse.

Comorbidity is quite common with BDD, the most common being major depression (75 % lifetime prevlance), followed by substance-use disorders (30–48.9 %), social phobia (37–39 %), and OCD (32–33 %) (Bjornsson et al. 2010).

BDD patients may overfocus on details of visual stimuli rather than global aspects, i.e., they overfocus on minor details of their appearance, which may in turn fuel preoccupation with minor appearance flaws. An fMRI study of facial processing found a bias among BDD subjects for using strategies to encode details of stimuli rather than use of holistic visual processing (Feusner et al. 2007).

24.10 Treatment of Body Dysmorphic Disorder

24.10.1 Cosmetic Treatment in BDD Patients

A majority of individuals with BDD seek (71–76 %) and receive (64–66 %) cosmetic treatment (e.g., surgical, dermatologic, or dental) for their perceived appearance flaws (Crerand et al. 2005; Phillips et al. 2001). However, only rarely does such treatment seem to improve overall BDD symptoms. In one study, subjects retrospectively reported that only 3.6 % of all treatments resulted in overall improvement in BDD (Crerand et al. 2010). Surgical treatments were more likely than other cosmetic procedures to decrease preoccupation with the treated body part; however, overall BDD severity improved with only 2.3 % of treatments (Crerand et al. 2010). In a survey of cosmetic surgeons, 40 % of respondents indicated that dissatisfied BDD patients had threatened them physically or legally (Sarwer 2002).

24.10.2 PsychiatricTreatment of BDD

Selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy (CBT) are currently recommended as first-line treatments and they appear to be effective for a majority of patients. Twelve to 14 weeks of SSRI treatment is often needed before a response is seen, and

relatively high SSRI doses (higher than typically used for depression) often appear to be needed. If an SSRI is not adequately effective, augmentation with another medication, e.g., aripiprazole, or switching to another SSRI, may be effective (Phillips 2005; Phillips and Hollander 2008).

Cognitive behavioral therapy (CBT), including exposure and response prevention (ERP) to reduce avoidance and compulsive and safety behaviors, seems effective in BDD (Bjornsson et al. 2010; Phillips et al. 2008). CBT helps patients focus less on minor details of their appearance and take a more holistic view of their body.

Interpersonal therapy (IPT) may be effective by enabling patients to develop more effective strategies to reduce interpersonal distress, poor self-esteem, and depressed mood, which are hypothesized to maintain body image concerns (Klerman 1994).

Many patients with BDD lack insight into their illness and therefore are insufficiently motivated for treatment. Motivational interviewing may be useful for some of these patients (Miller and Rollnick 2013; Phillips et al. 2008).

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The Patient's Personality, Personality Types, Traits, and Disorders in the CL Setting

25

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25.1 Vignettes

1. A 34-year-old woman was admitted to the hospital after cutting her abdomen with a steak knife. She had methodically cut her skin, abdominal muscles, fasciae, peritoneum, and omentum, and pulled out her small intestine. She was in a pool of blood when her roommate came home and called the ambulance. Upon admission to the hospital, the patient denied suicidal intent; rather, she said she just had to cut herself and see blood to relieve the tension. She had seen visions of herself cutting before she actually cut herself. She felt no pain. Her abdomen was covered with scars from previous lacerations. This was her 18th hospitalization for cutting herself. The CL psychiatrist called a multidisciplinary conference concerning this patient. During the meeting, the surgical staff expressed considerable consternation and puzzlement over this patient. The CL psychiatrist empathized with the surgical staff about the frustration of having to deal with repeated self-mutilation. He then explained to the staff the nature of Borderline Personality Disorder, that the cutting behavior seems to have occurred in a dissociative state, and cutting often relieves unbearable tension in these patients. The staff's anger was visibly lessened following this conference, and they were able to treat the patient as another very sick patient.

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2. A psychiatric consultation was requested on a patient who was admitted to the hospital with back pain. A spinal mass was discovered on imaging and further diagnostic workup was in progress. The patient seemed to the staff to be depressed, just staring at the ceiling, and not sleeping or eating. The patient was an accountant, and was concerned about his business while he was in the hospital. The consultant was impressed with the detailed, exacting description he gave of his symptoms and signs, as well as descriptions of his job and other concerns. When asked, the patient admitted that what made him most anxious was not knowing what was going on in the hospital, what each procedure was, and what the diagnosis and prognosis were. The consultant arranged a meeting among the patient, the resident responsible for the patient, and, at his request, the patient's wife. During the meeting, the resident explained in detail the diagnostic and therapeutic plans for the patient utilizing printouts of web pages. The patient's seeming depression immediately lifted, and he began to cooperate with the treatment plans.

25.2 Concepts of Personality

Personality refers to the totality of attributes of a person including intelligence; cognitive, perceptual, and behavioral traits; and habitual coping styles. *Character*, in the psychodynamic sense, refers to an individual's typical ways of dealing with reality and stress determined by unconscious defense mechanisms such as denial and projection.

25.3 What Contributes to Personality?

Personality is formed by the interaction of genetic predisposition with early environment and the accumulation of experiences and learning, much of which is influenced by cultural and socioeconomic factors.

25.3.1 Genetic Contributions

Obviously, temperament and disposition of individuals are largely genetically determined. Some examples of genetic contribution to personality traits follow.

The short allele of the serotonin transporter promoter gene *5HTTLPR* may underlie an anxious trait that in interaction with experience may give rise to increased neuroticism and anxious or borderline personality traits (see Chap. 7).

Some personality traits, including novelty seeking, are good predictors of vulnerability to stress-related mood and personality disorders in both humans and rodents. High-novelty-seeking rats [high responders (HRs)] are vulnerable to the induction of depressive-like symptoms by social defeat stress, low-novelty-seeking rats [low responders (LRs)] are not. While LR animals exhibited an increase in hippocampal BDNF levels following social defeat, HR individuals did not. This difference in hippocampal BDNF expression promoted the vulnerability of HR and the resilience of LR rats. Preventing activation of BDNF signaling by infusing the BDNF scavenger TrkB-Fc into the dentate gyrus of the hippocampus of LR rats led to social defeat-induced social avoidance, whereas its activation in HR rats by the TrkB agonist 7,8-dihydroxyflavone promoted social approach. Along with the changes in BDNF expression following defeat, there was in LR animals a downregulation of the inactive BDNF receptor but not in HR animals. The BDNF upregulation in LR involved an epigenetically controlled transcription of a specific area of BDNF (bdnf exon VI). Thus, hippocampal BDNF regulation seems to be a critical regulator of stress resilience, and underscores the importance of epigenetic factors in mediating stress-induced adaptive and maladaptive responses in different individuals (Duclot and Kabbaj 2013).

Mounting evidence from animal studies show that the mesolimbic dopaminergic pathways are modulated by the brain-derived neurotrophic factor (BDNF). The personality traits of Novelty Seeking and Harm Avoidance, are mediated, in

part, through dopaminergic mesolimbic circuitry. In one human study, carriers of the 66Met+/A1+ BDNF gene variant scored lowest on Novelty Seeking and highest on Harm Avoidance, compared to all other genotype groups. These participants are characterized by a relatively low D(2) receptor density in the striatum and an impaired activity-dependent secretion of BDNF (Montag et al. 2010). The long allele of the dopamine DRD4 genes has also been implicated in the Novelty Seeking personality trait (Okuyama et al. 2000; Ono et al. 1997).

A "risk halotype" of tryptophan-hydroxylase 2 (TPH2) gene has been identified for borderline personality diagnosis, impulsive aggression, affective lability, and suicidal/parasuicidal behaviors (Perez-Rodriguez et al. 2010).

Monoamine oxidase A gene, in interaction with childhood abuse, has been implicated in the development of the antisocial personality disorder. The stress of medical illness and hospitalization often causes a regression in the patient's personality; that is, the patient retreats to a more immature, child-like state with an exaggeration of the personality traits. By understanding a patient's personality, the physician can then determine how it influences the patient's ways of perceiving the world. This understanding leads to an approach to the patient that would result in better a physician–patient relationship and increased patient cooperation.

These are only some of the known genetic influences in certain personality traits and possibly disorders.

25.3.2 Experiential Factors

It is well known that normal development involves psychosexual (e.g., Freudian) and psychosocial development (e.g., Erikson's stages), and that each developmental stage may contribute to individual differences in personality.

Of particular importance in the development of psychiatric, and personality *disorders*, is the experience of childhood trauma and abuse.

In one study, there were independent relationships between: physical abuse and antisocial personality disorder traits; emotional abuse and anxious and fearful (Cluster C) personality disorder traits; and maternal neglect and odd, eccentric (Cluster A) personality disorder traits. Furthermore, physical abuse was independently and positively associated with narcissistic and paranoid traits and negatively associated with Cluster C traits (Cohen et al. 2013).

Childhood maltreatment and temperamental traits play a role in the development of Borderline Personality Disorder (BPD). In one recent study, approximately 70 % of borderline personality disorder reported some form of abuse or neglect. Childhood maltreatment inversely correlated with sociability. The regression model showed that neuroticism-anxiety and aggression-hostility traits, as well as emotional abuse, were risk factors independently associated with the severity of BPD. Sexual abuse was not associated with the severity of the disorder. The interaction between high neuroticism-anxiety traits and the presence of severe emotional abuse was associated with BPD severity. Thus, the interaction between temperamental traits and childhood emotional abuse may have an influence not only on the development but also on the severity of BPD (Martin-Blanco et al. 2013; Newnham and Janca 2014).

Early parent–child relationships moderate the future developmental trajectory. In one study, diminished tense discomfort predicted more antisocial outcomes, but only in insecure or unresponsive relationships. That risk was defused in secure or responsive relationships. The links between diminished tense discomfort and future antisocial behavior in insecure parent–child dyads were mediated by stronger discipline pressure from parents (Kim et al. 2013).

Children with conduct disorder often have psychopathic traits. Psychopathic traits consist of a callous-unemotional component and an impulsive-antisocial component, which are associated with two core impairments. The first is a reduced empathic response to the distress of other individuals, which primarily reflects reduced amygdala responsiveness to distress cues; the second is deficits in decision making and in reinforcement learning, which reflects dysfunction in the ventromedial prefrontal cortex

and striatum. Genetic and prenatal factors contribute to the abnormal development of these neural systems, and social-environmental variables that affect motivation influence the probability that antisocial behavior will be subsequently displayed (Blair 2013).

25.4 Brain Mechanisms of Personality Disorder

In a study of emotional habituation, unlike normal population, neither borderline nor avoidant personality disorder patients showed increased activity in the dorsal anterior cingulate cortex when viewing repeated versus novel pictures. This lack of an increase in dorsal anterior cingulate activity was associated with greater affective instability in borderline patients. In addition, borderline and avoidant patients exhibited smaller increases in insula-amygdala functional connectivity than healthy subjects and, unlike healthy subjects, did not show habituation in ratings of the emotional intensity of the images. Borderline patients differed from avoidant patients in insula-ventral anterior cingulate functional connectivity during habituation. Unlike healthy subjects, borderline patients fail to habituate to negative pictures, and they differ from both healthy subjects and avoidant patients in neural activity during habituation. A failure to effectively engage emotional habituation processes may contribute to affective instability in borderline patients (Koenigsberg et al. 2013).

Borderline patients tend to attribute resentment and aggression to others (Barnow et al. 2009) and are more likely to ascribe anger to ambiguous facial expressions (Domes et al. 2008). A bias toward negative or threatening information in borderline patients is also reflected in brain imaging data of increased and prolonged amygdala responses (Bertsch et al. 2013a; Hazlett et al. 2012).

The neuropeptide oxytocin is involved in social behavior across species. In healthy individuals, the intranasal administration of oxytocin reduces anxiety and stress in social situations, enhances the recognition of facial expressions, and shifts attention from negative to positive information, although individual differences and situational factors seem to play an important role (Bartz et al. 2011; Olff et al. 2013). Neuroimaging and animal studies indicate that oxytocinergic modulation of social behavior is related to its effects on the amygdala (Knobloch et al. 2012).

Bertsch and colleagues found, in a facial emotion classification experiment, borderline patients exhibited more and faster initial fixation to the eyes of angry faces combined with increased amygdala activation in response to angry faces compared with the control group. These abnormal behavioral and neural patterns were normalized after intranasal oxytocin administration. They conclude that borderline patients exhibit a hypersensitivity to social threat in early, reflexive stages of information processing.

Oxytocin may decrease social threat hypersensitivity and thus reduce anger and aggressive behavior in borderline personality disorder or other psychiatric disorders with enhanced threat-driven reactive aggression (Bertsch et al. 2013a). Reduced oxytocin levels have also been found in female borderline patients (Bertsch et al. 2013b).

25.5 DSM Personality Disorders (PD)

DSM I and II defined personality disorders by narrative paragraphs providing a general description and clinical conceptualization for each disorder. If a person fits the description, that person could be diagnosed with the disorder regardless of the impact of symptoms on daily life. While these were descriptions, these diagnoses were based on prevailing psychodynamic theory of personality development.

Beginning with DSM–III (1980) and the adoption of the multiaxial system, pesonality disorders, together with developmental disorders, became Axis II and explicit criteria were specified for each. This categorical model continued to be used for diagnosing PDs, but the distinction between normal and abnormal personality traits

appeared for the first time—a person must surpass a certain number of identified personality symptoms that define a specific disorder in order to meet the necessary conditions for a diagnosis.

In the planning stages of DSM-5, major changes were proposed in personality diagnosis including the elimination of Axis II, elimination of the three clusters, and reducing the number of personality disorders from 10 to 6. Above all, a more dimensional approach was to be incorporated.

It also proposed replacing the 79 *DSM–IV* personality disorder criteria with 25 personality trait facets (from five higher-order trait domains: negative affect, detachment, antagonism, disinhibition, and psychoticism), with each of the personality disorder types defined by different combinations of these traits; assessing five severity levels of personality functioning based on impairment in core self-personal and interpersonal capacities; new criteria for the general personality disorder diagnosis based on a combination of core deficits and specified pathological traits. These changes were not adopted, however, and DSM_IV criteria have remained unchanged.

Behavior genetics tend to favor dimensional conceptualizations of personality pathology. Biometric modeling generally assumes multiple gene systems, or quantitative trait loci, underlying complex behavioral phenotypes (Butcher et al. 2008; Butcher and Plomin 2008; Larsson et al. 2008; Meaburn et al. 2008; Ronald et al. 2008; Viding et al. 2008; Wardle et al. 2008) Risk alleles for personality pathology are distributed throughout the population, with some people having very few, some have a moderate amount, and some having many, thus creating a dimension of risk.

Most behavior genetic modeling of personality disorder assumes a dimensional, spectrum model of disorder (South and DeYoung 2013a, b).

There is considerable evidence that all personality disorders have some heritable biological basis (Torgersen 2005; Torgersen et al. 2008; Torgersen et al. 2012). In a national Norwegian sample of adult twins, Torgersen et al., reported heritability estimates from 28 % (paranoid, avoidant) to 77 % (narcissistic, obsessive–compulsive). A twin study using parental ratings in a sample of children and adolescents found relatively high-heritability estimates: from .50 (paranoid) to .81 (dependent, schizotypal), with a median heritability of .75 (Coolidge et al. 2001).

In the NIPHTP community twin sample, schizotypal personality disorder had the strongest loading on the genetic and environmental factors and appeared to be the strongest marker of the genetic and nonshared environmental liability to Cluster A pathology (Kendler et al. 2006) Among Cluster B disorders, one genetic factor influenced all four disorders, but a second genetic and nonshared environmental factor was also needed to account for influence on antisocial and borderline PDs (Torgersen et al. 2008). A common factor accounted for 83 % and 48 % of the variance in avoidant and dependent personality disorders, respectively, but most of the genetic influence on obsessive-compulsive personality was disorder-specific (Reichborn-Kjennerud et al. 2007a; Reichborn-Kjennerud et al. 2007b). Thus, obsessive-compulsive personality disorder appears to be etiologically distinct from avoidant and dependent personality disorder; in fact the clusters did not appear to hold up genetically and was proposed to be disbanded in DSM-5 (Kendler et al. 2008).

Using the NIPHTP sample, Kendler et al. (2008) found three genetic factors that did not directly correspond to the *DSM* cluster structure. The first genetic factor included loadings on paranoid, histrionic, borderline, narcissistic, dependent, and obsessive–compulsive PDs; the second had loadings on borderline and antisocial PDs; and the third had loadings on schizoid and avoidant PDs. These three genetic factors captured only a modest proportion of the total genetic variance, with 6 of the 10 PDs demonstrating substantial disorder-specific genetic effects. In contrast, the three unique environmental factors corresponded well to the *DSM* cluster structure, although as with genetic influences, all disorders (with the exception of schizotypal) demonstrated

substantial disorder-specific unique environmental influences. The authors concluded that the three genetic factors reflect (a) a broad tendency toward personality pathology or negative emotionality, (b) genetic risk for a factor of "impulsive aggression," and (c) a factor of low extraversion or inhibition. Further, they posited that the pattern of findings for genetic and environmental influences have implications for the comorbidities commonly found among personality disorders, i.e., antisocial and borderline PDs may be highly comorbid because they share the same genetic influences. Other Cluster B personality disorders may be comorbid because the same environmental influences (i.e., those not shared in common with other family members) lead to a "final common pathway" of Cluster B-type pathology (Kendler et al. 2008; South and DeYoung 2013a).

Neuroticism is a heritable common feature of both internalizing disorders and externalizing disorders, and that novelty seeking is a heritable broad-band specific factor that distinguishes anxiety disorders from externalizing disorders.

When broadly defined according to various measures of antisocial behavior, it appears to demonstrate substantial *shared* environmental effects (Hink et al. 2013; Rhee and Waldman 2002). Disregard for others in toddlerhood was a strong predictor of antisocial personality later (Rhee et al. 2013).

The proposal to radically change the personality disorders section of DSM-5 resulted in much controversy, finally resulting in maintaining all DSM-IV personality disorder diagnoses, but relegating future development as a research area in Section III. Emerging Models and Measures.

Definition DSM-5 defines personality disorder as an *enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment* (APA 2013).

DSM-5 presents two different models of personality disorders, a dimensional model that is presented in an unofficial Section III, and a categorical model that is a carry-over of DSM III/IV, in Section II, which is the official diagnosis.

25.5.1 General Personality Disorder

Nevertheless, a dimensional model is presented as General Personality Disorder, with the diagnostic criteria of: (1) An enduring pattern of inner experience or behavior that deviates markedly from the expectations of the individual's culture, which is manifested in at least two of the following: (a) cognition, (b) affectivity, (c) interpersonal functioning, and d) impulse control.

The enduring pattern must be inflexible and pervasive across a broad range of personal and social situations, and it leads to clinically significant distress or impairment in social, occupational, or other important areas of functioning, and the pattern is stable and long duration, and its onset can be traced back to adolescence or childhood.

DSM-5 recognizes *personality traits* as enduring patterns of perceiving, relating to, and thinking about oneself. Only when the traits become inflexible and maladaptive enough to cause significant disruption would a personality disorder diagnosis be justified.

DSM-5 still maintains the three clusters of personality disorders which are based largely on phenomenology and not genetics or pathophysiology.

A listing of personality disorders in DSM-5 follows. Each personality disorder, when appropriate, will be discussed in Sect. 25.7.

25.5.2 Cluster A Personality Disorders

Paranoid PD, Schizoid PD, and Schizotypal PD.

25.5.3 Cluster B Personality Disorders

Antisocial PD, Borderline PD, Histrionic PD, and Narcissitic PD.

25.5.4 Cluster C Personality Disorders

Avoidant PD, Dependent PD, and Obsessive-Compulsive PD.

25.5.5 Other Personality Disorders

Personality Change due to Another Medical Condition, Other Specified and Unspecified Personality Disorder.

25.6 Classification of Personality Types

Prominent aspects of personality may be classified loosely into types. The Myers-Briggs Personality Inventory, based on Carl Jung's work, is an example that is used commonly. This typology contains the following dimensions: Introversion (I)–Extraversion (E), Sensing (S)–Intuition (N), Thinking (T)–Feeling (F), Judging (J)–Perceiving (P). Based on the predominance of these dimensions, a person's typology may be, for example, Introverted, Intuitive, Thinking, and Perceiving type (INTP). Eysenck's personality test measures three dimensions: *extroversion* as a measure of cortical activation (extroverts being underaroused, introverts being overaroused), *neuroticism* as a measure of activation thresholds of limbic or sympathetic system (minor stresses activate them in neurotics), and *psychoticism*, a tendency toward psychotic breaks and aggression (see Chap. 7 for a discussion of how personality traits may be predispositions for major psychiatric syndromes).

If everyone has a personality, and normal persons can be classified by personality type, what is a *personality disorder*? In our view, there is a continuum between normality and disorder. The only demarcation line is whether patients feel consistently distressed or their function is persistently impaired because of the personality characteristics.

Borderline personality disorder patients are often severely distressed and nonfunctional, and they often suffer from comorbid major psychiatric syndromes such as major depression and substance use.

The consultation-liaison (CL) psychiatrist must understand the interaction of personality types with the sick role that patients must assume in the general hospital setting (Bibring and Kahana 1968; Kahana and Bibring 1964; Leigh and Reiser 1980). Thus it is important for the CL psychiatrist to recognize the personality characteristics of the patient (i.e., personality type). We seldom, however, make the diagnosis of a personality disorder in the CL setting because such diagnoses in the medical record have little therapeutic value and often leads to stigma. The two exceptions are borderline personality disorder and antisocial personality disorder, which do have treatment implications.

25.7 Personality Types, the Sick Role, and Management Strategies

Many normal patients who are hospitalized will show transient exaggerations of their personality traits as a result of the stress of illness, hospitalization, and treatment. This section describes the types of traits, their interaction with the sick role (for further discussion of the sick role, see Chap. 10), and management strategies based on the personality needs.

We will here discuss the commonly encountered personality types in the CL setting. We will use the DSM-5 classification and nomenclature for personality disorders but we use the term personality types for those patients who do not meet the criteria for personality disorders (a majority of our patients), and some of the personality types discussed in this chapter are not DSM-5 personality disorders at all. Most patients discussed here are not candidates for treatment for their personality disorders per se in the medical setting—in fact, personality disorders are very difficult to treat even in long-term psychiatric outpatient therapy. As stated above, the goal of treatment in the general hospital and other medical settings is to take into account the personality needs of the patient in providing optimal medical care.

25.7.1 Cluster A: Odd and Eccentric Personalities

25.7.1.1 Guarded, Suspicious Patients (Paranoid Personality and Disorder)

Patients with this personality type are always watchful and concerned about the possibility that harm might be done to them, intentionally or unintentionally. They are quite fearful of being exploited or taken advantage of. They are quite sensitive to the possibility of criticism. They are prone to wonder about ulterior motives concerning any suggestions or remarks made by the health-care personnel, especially if they are ambiguous. These patients are also likely to misinterpret statements and actions and read something ominous or threatening into them. This is especially true in the presence of great anxiety, as in being hospitalized, and in states of reduced cerebral function that impair the integration of sensory input.

Such patients also tend to blame others for their illness. For example, a patient may claim that he developed a heart attack because his employer did not provide air conditioning for his work area and "poisoned the air" with carbon dioxide exhaled by so many others.

These patients, obviously, do not enjoy being in the sick role. The dependency on health care personnel increases their feelings of vulnerability, and with that comes the fear that persons in powerful positions will do harm to them or take advantage of them. Although they see the ill state as an undesirable one, they cannot trust the physician enough to cooperate fully.

A good management strategy for these patients is to assume a relatively neutral attitude concerning their suspicions, criticisms, and other manifestations of hostility without becoming provoked by them or arguing with them. A helpful statement is, "I understand how you feel under the circumstances." Identifying their suspiciousness as "sensitivity" is also helpful. Occasionally, agreeing with the patients about the inconveniences that they are suspicious about and then putting the blame on impersonal things like hospital regulations can diffuse their feelings of anger from being directed toward the health care personnel.

Above all, it is important to provide as little cause for suspicion as possible. This involves consistency on the part of health care personnel in terms of the information imparted to the patient. It is also necessary to explain, in as much detail as feasible, the nature of the patient's illness and plans for treatment. This will tend not only to minimize the suspiciousness but also to reduce the likelihood of litigation in case of complications, since this type of patient is likely to be litigious as well. When a procedure is recommended to the patient, it is best to present it as objectively as possible, so as not to arouse the suspicion that the doctor is trying to "manipulate" the patient for ulterior motives.

In severe cases, small doses of antipsychotic medications may help to reduce the degree of suspiciousness and accompanying anxiety during the hospitalization, for example, quetiapine 25 mg hs or risperidone 0.5 mg hs or b.i.d. po.

25.7.1.2 Seclusive, Aloof Patients (Schizoid Personality and Disorder)

This is the type of patient who seems to be remote, detached, and not in need of interpersonal contact. These patients usually prefer to be in private rooms and seldom speak or relate to other patients or staff. They like to be involved in solitary activities, such as reading or listening to music. They appear shy and uninvolved. Nurses are sometimes so disturbed by the aloofness and lack of personal response that they suspect depression, and thus bring the patient to the attention of the physician. Some patients with this personality might also appear to be eccentric, with affinities for activities associated with countercultures, such as unusual foods and quasi-religious sects.

The main concern of these patients is a desire not to be intruded on by others; they wish to maintain a sense of tranquility by being absorbed in themselves and things familiar to them. Any attempt at socialization by others may be seen as an intrusion threatening their fragile tranquility.

Illness is seen as a threat to this self-absorption and tranquility. These patients, therefore, have difficulty in adjusting to the sick role, with its

expectation of dependency on and cooperation with health care personnel. The patients come to terms with the role expectations through noninvolvement at a personal level while allowing the medical process to go on. Thus, a patient with this personality may appear to be strikingly unconcerned about illnesses and procedures that would normally be expected to arouse much anxiety. Of course, many patients with this personality delay seeking help because of their aversion to the intrusion into their privacy that is necessary in receiving medical care. On the other hand, some patients with this personality may use the sick role as an excuse to develop interpersonal relationships but without true intimacy. In managing such patients, it is important to recognize and respect their need for privacy. Although socialization and sharing are important to most people, these patients need to protect their privacy and tranquility. Some of these patients, however, may be able to form some relationship with one or two members of the hospital staff. These staff members can then serve as "translators" for these aloof patients.

25.7.1.3 Odd, Eccentric Patients with Schizophrenia-Like Tendencies (Schizotypal Personality and Disorder)

These are patients who seem odd and eccentric, have limited interpersonal contact, and have unusual experiences such as derealization and depersonalization, and they may manifest magical thinking, odd beliefs, paranoia, and other tendencies that approximate schizophrenia. Such patients may have peculiar beliefs and perceptions concerning illness that may conflict with the views of the medical profession. Health care professionals may be alarmed or turned off by the odd and eccentric behavior of such patients. Sick role expectations are often not shared by such patients. Managing patients who are odd and eccentric requires an understanding that the attributes are of long standing, and that the patient cannot really help being odd. Accepting and respecting such patients' individuality will allow a reduction of anxiety and perhaps paranoia so that medical treatment can be optimal. If the patient has a psychosis-like experience, perhaps precipitated by the stress of hospitalization and medical illness, small doses of antipsychotic medication may be helpful, for example, quetiapine 25 mg hs, risperidone 0.5 mg hs, b.i.d. po., or perphenazine 2 mg hs or b.i.d.

25.7.2 Cluster B: Colorful, Dramatic, Emotional, or Erratic Personalities

25.7.2.1 Patients with Repeated Legal Difficulties and Behavioral Problems (Antisocial Personality Traits)

Antisocial traits consist of a pattern of failure to conform to social norms, repeated lying, and deceiving others for profit or pleasure. Patients with these traits are often impulsive and aggressive, resulting in repeated fights. They tend to show personal and financial irresponsibility and to lack remorse, showing indifference to others' feelings. There is often a history of conduct difficulty before the age of 15, and these patients are unable to learn from experience, especially from punishment. It is therefore unrealistic to expect such patients to adhere without difficulty to the sick role expectations. These patients are often unreliable, demanding, uncooperative, impulsive, and aggressive. Managing such patients requires a firm and nonjudgmental attitude and explicit explanations as to how cooperation can result in specific benefit for the patient. Unreasonable demands should be declined based on explicit reasons or rules. Breach of rules and unlawful activity, if present, should be reported to the appropriate authorities. It is important for the health care personnel to realize that such patients naturally evoke angry feelings in others but that such provocations are part of their personality deficit.

25.7.2.1.1 Antisocial Personality Disorder

DSM-5 states the essential feature of this disorder is a pervasive pattern of disregard for, and violation of, the rights of others that begins in childhood or early adolescence and continues

into adulthood. For this diagnosis to be given, the person must be at least age 18 and must have had some symptoms of conduct disorder before age 15 years. Conduct disorder involves a repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated, i.e., aggression to people or animals, destruction of property, deceitfulness or theft, or serious violation or rules (APA 2013).

The prevalence is considered to be 0.2–3.3 %. Higher prevalence is among males with alcohol use disorder and from substance use clinics or prisons.

There is no conclusively successful treatment for antisocial personality disorder at this time (Gibbon et al. 2010; Khalifa et al. 2010).

25.7.2.2 Patients with Intense, Unstable Relationships (Borderline Personality and Traits)

Borderline traits consist of a pattern of unstable and intense interpersonal relationships, unstable self-image, and marked impulsivity that are self-damaging, such as substance abuse, compulsive sexual activity, and binge eating. Patients with these traits often suffer from chronic feelings of emptiness, and may have transient stress-related dissociative symptoms. These patients arouse very strong feelings among the hospital staff members, because such patients tend to see them as either all good or all bad (splitting). Consequently, some staff members feel very positively about these patients while others feel exactly the opposite. Such patients regress easily, and may act out impulsively if they feel uncared for. Their demands for care, affection, and, often, special treatment may escalate if they feel that the staff is accommodating. The basic difficulty with these patients is that almost all relationships become stormy, such that the doctor who was "perfect" 1 day may become a persecuting monster the next day because of a perceived mistreatment or imperfection.

25.7.2.2.1 Management in the CL Setting

Patients who attempted suicide (which may be the reason for psychiatric consultation) or demonstrated serious suicidal ideation may require psychiatric hospitalization. In the general medical setting, the approach should be caring but, above all, consistent, with explicit expectations on the part of both the patient and the staff. The caregiver must recognize that these patients invariably produce intense feelings as a part of their personality makeup, but that he or she must provide a consistent, evenhanded, and caring approach to them. Sometimes, a multidisciplinary conference about a borderline patient may help (See Vignette 1). In such meetings, staff's feelings about the patient may be expressed and empathized with. At times, splitting may be evident in such a meeting, which can be discussed as a part of the patient's personality pathology. Such a meeting can facilitate the staff being able to assume a more objective, caring approach toward such patients.

25.7.2.2.2 Borderline Personality Disorder (BPD)

In more severe cases, the patients are diagnosed as having the borderline personality disorder, which often also includes the features of suicide attempts, unstable sense of self, negative affect (anger, bitterness, demandingness, sadness), brief psychotic experiences, impulsivity, and low achievement (Gunderson and Singer 1975). They often engage in substance abuse and demonstrate eating disorders. Borderline personality disorder requires psychotherapy combined with pharmacotherapy for depression, anxiety, or psychosis if present—see next section (Gunderson 1986; Koerner and Linehan 2000; Linehan et al. 2008). Borderline personality disorder patients often engage in cutting behaviors for tension relief rather than with suicidal intent (as in Vignette 1 at the beginning of the chapter).

The term, borderline, derives from "borderline schizophrenia" and "borderline state," the notion that patients with this disorder were at one time considered to have been on the border between schizophrenia and neurosis. Other old terms referring to this disorder or subsets of its patients include pseudoneurotic schizophrenia, psychotic character, and "as if" personality (Gunderson 2009). Now it is generally recognized that BPD is a syndrome independent of schizophrenia, though it can be comorbid with it. Many of the

clinical features of BPD are shared with bipolar disorder as well as with posttraumatic stress disorder, with which BPD has a 30 % comorbidity (Gunderson 2009).

According to DSM-5, the essential feature of borderline personality disorder is a pervasive pattern of instability in interpersonal relationships, self-image, and affects, and marked impulsivity that begins by early adulthood and is present in various contexts.

Persons with this disorder make frantic efforts to avoid real or imagined abandonment. The individuals are exquisitely sensitive to environmental circumstances. They have a pattern of intense and unstable relationships. There is often identity disturbance—unstable self-image or sense of self. They display impulsivity in at least two areas that are potentially self-damaging; gambling, spending money irresponsibly, binging, substance abuse, unsafe sex, or reckless driving. They engage in recurrent suicidal behavior, gestures, or threats, as well as attempts. Completed suicide occurs in 8–10 % of these patients. Self-mutilation such as cutting and burning are common, and may occur during a dissociative episode. Such behavior is often accompanied with relief.

Many patients experience marked reactivity in mood such as intense episodic dysphoria, irritability, and anxiety. They often experience chronic feelings of emptiness, as well as episodes of intense anger, panic, or despair. They are often easily bored. During periods of extreme stress, transient paranoid ideation or dissociative symptoms may occur.

Prevalence in the general population is 1.6–5.9 %, about 6 % in primary care settings, and about 10 % in outpatient mental clinics, and about 20 % among psychiatric inpatients (DSM-5).

25.7.2.2.3 Treatment of Borderline Personality Disorder

BPD is the only major psychiatric syndrome for which psychosocial interventions remain the primary treatment (Gunderson 2009). There are two specific psychotherapeutic modalities specifically developed for BPD—*Dialectical Behavioral Therapy and Mentalization Therapy. Schema Therapy* has recently been shown to be cost effective and more effective than transference-based psychotherapy, clarification-oriented psychotherapy, and treatment as usual, in BPD as well as in cluster C, paranoid, histrionic, or narcissistic personality disorders (Bamelis et al. 2013; Bamelis et al. 2011).

25.7.2.2.3.1 Dialectical Behavioral Therapy (DBT)

DBT was developed by Marsha Linehan at University of Washington in Seattle. It was introduced as a carefully manualized 1-year outpatient therapy consisting of integrated group and individual-therapy components (Linehan 1993a, b). It specifically targets the parasuicidal behaviors of BPD by outpatient therapists through emotional validation, constant availability, and not reinforcing self-harm through hospitalization, and utilizes social skills training and mindfulness training. The basic tenet of DBT is as follows:

BPD patients exhibit emotional vulnerability to stimuli, i.e., excessive arousal of negative emotions, and tend to blame others for the distress. On the other hand, they have internalized the invalidating environment and show self-invalidation, i.e., have unrealistic and excessive expectations of themselves and develop self-blame and guilt when they are not met. Emotional vulnerability and self-invalidation are the first pair of "dialectical dilemmas." Borderline patients frequently experience a series of relentless crises, often contributed to by their own dysfunctional lifestyle and tendency for emotional overreaction. Because of their inability to modulate emotions, such patients have difficulty in facing the emotions associated with loss and grief, and thus suppress negative emotions. The unrelenting crises and inhibited grieving represent the second set of dialectical dilemmas. The final set of dilemmas consist of "active passivity," i.e., they are active in finding others to help them solve problems but are passive in helping themselves and "apparent competence," i.e., they have developed the appearance of competence in the face of invalidating environment without actually achieving a generalizable competence. A pattern of self-destructive behavior often results due to the excessive painful emotions and helplessness.

DBT uses the dialectical use of acceptance on the one hand and change on the other. The philosophical concept of dialectics involves the juxtaposition of thesis and antithesis, resulting in a resolution of the opposites through synthesis. In DBT, there are individual and group sessions that consist of four training modules—*mindfulness*, *interpersonal effectiveness*, *distress tolerance*, *and emotion regulation*. Through mindfulness training derived from Buddhist meditation, the patients learn to accept the here and now free from worries and thoughts. Through interpersonal effectiveness training that incorporates assertiveness training, patients learn to develop more satisfying ways of dealing with others. DBT identifies the triggers for distress and regulates the reaction to them and uses behavioral principles in reinforcing healthful behavior and not reinforcing self-destructive behaviors (Chen et al. 2008; Crowell et al. 2009; Linehan 1993b; Linehan 1987, 1993c, 1995; Shearin and Linehan 1994).

The therapist in DBT assumes the role of a "coach" for the patient (Rizvi et al. 2011).

DBT has been shown to be particularly effective for parasuicidal behaviors in general, as well as for a variety of conditions including BPD, PTSD, binge eating, etc. (Bohus et al. 2004; Chen et al. 2008; Crowell et al. 2009; Harned et al. 2012; Linehan et al. 2006; Linehan et al. 2008; Neacsiu et al. 2010).

25.7.2.2.3.2 Mentalization-Based Treatment

Mentalization-based treatment was developed by Fonagy in England specifically for BPD, and has been shown to be effective (Bateman and Fonagy 2009, 2010; Higgitt and Fonagy 1992; Sharp et al. 2011). Fonagy postulated that caretakers' failure to accurately mirror (validate) a child's mental states was responsible for difficulties in knowing one's self and in empathizing with others—an inability to mentalize, a concept similar to *theory of mind* (*TOM*) in psychological literature. It was designed to correct the borderline patient's underlying handicaps in mentalizing by adopting a noninterpretive, "not-knowing," inquisitive stance intended to facilitate the accurate recognition and acceptance of one's own and others' mental states (including the therapist's).

25.7.2.2.3.3 Schema Therapy

Schema therapy integrates elements of cognitive therapy, behavior therapy, object relations, and gestalt therapy into one unified, systematic approach to treatment.

Schema Therapy, developed by Jeffrey Young, is based on identification and management of Early Maladaptive Schemas (or just "schemas"), Coping Styles, Modes, and basic emotional needs (Young 1990; Young et al. 2003).

Schemas are defined as self-defeating life patterns of perception, emotion, and physical sensation. For instance, a person with an Abandonment schema could be hypersensitive to their perceived value to others, which in turn could make them feel fearful in relationships. Coping styles are our behavioral responses to the schemas in hopes of making things better, but in fact they very often wind up reinforcing the schema. For example, someone with an avoidance coping style might behave in ways to limit the closeness in the relationship in order to try to protect themselves from being abandoned. The resulting loneliness or even actual loss of the relationship could reinforce the person's Abandonment schema.

Modes are mind states that one can shift into that combine schemas and coping styles into a temporary "way of being." (Young et al. 2003) For example, a Vulnerable Child Mode might be a state of mind encompassing schemas of Abandonment, Defectiveness, Mistrust/Abuse and a coping style of Surrendering (to the schemas).

If basic emotional needs are not met in childhood, schemas, coping styles, and modes can result. Some basic needs that have been identified are: connection, mutuality, reciprocity, flow, and autonomy.

The goal of Schema Therapy is to help patients get their core emotional needs met. Schema therapy utilizes various techniques including limited reparenting, imagery, rescripting, flashcards, diaries, etc.(Bamelis et al. 2012; Bamelis et al. 2013; Rafaeli et al. 2010; Young et al. 2003) Mindfulness meditation may also be blended into schema therapy (Amaro et al. 2010; Ball 1998).

Medications may be used to treat symptoms of depression, anxiety, and micropsychotic episodes. For micropsychotic episodes and for very

strong urges to self-mutilate, small doses of antipsychotics may be indicated on an as needed basis, e.g., perphenazine 2 mg or quetiapine 25 mg, up to three times a day PO PRN.

Medications should be used in conjunction with psychotherapy for comorbid conditions such as PTSD, bipolar disorder, major depression, and schizophrenia.

25.7.2.3 Dramatizing, Emotional Patients (Histrionic Personality and Disorder)

Patients with this personality type tend to come across as being rather charming and fun to talk with. They have a certain dramatic flair when giving accounts of their lives and are often quite amusing. Their histories tend to be more impressionistic and diffuse than precise. They may be overtly seductive: female patients wearing provocative negligees and "parading around" in the hospital; male patients making sexually seductive comments to nurses and female physicians. There is a tendency for these patients to consider their relationship with the doctor as special, with sexual overtones. The medical staff often finds itself split around these patients, some liking them very much and others feeling angry with them. The patients themselves have usually unwittingly provoked these split reactions.

A major concern underlying such behavior is the need to be attractive and desirable to others, to prove their masculinity or femininity over and over again and to gain care and support. An underlying fear that they might not be found attractive and desirable is accentuated by illness, with its threat to the integrity of the body. As patients, persons of this type have an exaggerated need to be reassured that they are still attractive and will not be deserted.

The sick role may or may not be compatible with this type of personality. On the one hand, the dependency and social perquisites inherent in the sick role afford some of these patients an acceptable opportunity to exhibit and "flirt" with authority figures in a situation that sets limits. Patients with extreme forms of this personality, despite their overtly sexually provocative behavior, tend to be rather inhibited in actual sexual encounters. For them, the hospital and medical treatment may be exactly the type of setting they find most comfortable for seductive behavior without danger of actual sexual activity. On the other hand, some patients become extremely frustrated by the confinement and limitations of the sick role, especially if they had been accustomed to active, exhibitionistic, and gratifying lifestyles. For example, a man who had been accustomed to a "Don Juan" lifestyle may find the restriction of sexual activity in the hospital most unbearable.

These patients do best when the doctor responds amiably and engages them within set boundaries and limits. However, this should not be overdone, since these patients also tend to be frightened if their characterological seductiveness seems to lead to unexpected intimacy. Showing some warmth and personal concern is usually all that is needed. When there seems to be a split in staff feelings, these should be openly discussed and resolved in staff meetings. It may also be necessary to set firm limits with these patients, at the same time indicating concern and willingness to continue to take care of them. Repeated reassurances are often necessary. With this group of patients, unlike the orderly, controlling personalities, the doctor's personal manner and attitudes are relatively more important in providing reassurance than factual content, such as discussion of objective findings and test results.

25.7.2.4 Superior and Special Patients (Narcissistic Personality and Disorder)

These are patients who behave like VIPs, whether or not they are. Such patients have a tendency to appear snobbish, self-confident, and sometimes grandiose. They are often quite proud of their bodies and their physical abilities. This basic style might be partially covered up by exaggerated, artificial humility. There is a sense of arrogance and disdain when they are in contact with other people. Though these patients may seek the most prestigious medical centers and the most eminent physicians when ill, there is often an air of tentativeness in their responses when the physician explains anything to them. They may display an arrogant attitude, especially toward persons on the lower strata of the hospital hierarchy, such as

house officers, student clerks, and nurse's aides. They are likely to threaten to notify the chief of service or the director of the hospital of any inconveniences they suffer. They also use "name-dropping" to try to impress health care personnel.

Many patients with this personality style have idealized body images, and illness represents a threat to the maintenance of this body image. Many neurotic patients with overvaluation of physical prowess, stamina, and fitness were found to have developed the neurosis after illness or injury, often of a minor nature, e.g., the "athlete's neurosis" (Little 1969).

The patients with superiority feelings naturally do not find the sick role agreeable. Their need to see themselves as being perfect and invulnerable is contradictory to the notion that they "cannot help themselves" and are in need of more competent help. Although they may submit to this unpleasant situation, they often attempt to find weaknesses and faults in the physicians, as though to cut them down to size in order to still feel superior to them.

Needless to say, health care personnel often resent this type of attitude. The result is often a battle between the care giving staff and the patient, each attempting to cut the other down!

Successful management of these patients involves a certain degree of magnanimity on the part of health care personnel, allowing these patients to boast of their strengths. When this is done, the patients may feel secure enough to identify the caring persons with the self as being almost perfect. It is, however, a mistake to be unnecessarily humble in relation to these patients. An attitude of security about one's professional competence, while recognizing the worth of the patient, is important to ward off insecure feelings on the patients' part that they might not be in the best hands after all.

25.7.2.5 Impulsive Patients with a Tendency to Act Out (Impulsive Personality—Not a DSM-5 Diagnosis)

These are the patients who keep on doing things they did not "mean" to do, usually on the basis of some impulse. These patients may appear to be rational and well controlled, until an impulsive action occurs. Usually, however, they have a history of being involved in interpersonal or legal difficulties because of some maladaptive acting-out behavior. The characteristic feature is a lack of deliberation, with decisions being reached on the spur of the moment. Patients with this character style seem to lack tolerance for sustained thinking and for frustration. They often say that they acted "without thinking" or "could not help" what they did and often are quite remorseful afterward. In the health care system, these impulsive actions usually involve some aggressive acts against health care personnel or ill-advised decisions such as signing out against medical advice despite having a serious illness.

These patients seem to feel an overwhelming sense of impotence in the presence of relatively minor frustrations and appear to be unable to delay gratification or to feel gratified by anticipatory cognitive processes such as planning.

Patients with an impulsive personality style are likely to seek help for relatively minor symptoms based on the immediate pain or discomfort experienced, and they are likely to demand immediate relief from the discomfort. If immediate relief is not produced, they are prone to acting out by such aggressive acts as cursing at the physician or kicking an article of equipment in the treatment room. Such patients, although wanting immediate relief from symptoms, often have difficulty in tolerating the treatment process, especially when it also involves some discomfort, such as a nasogastric tube. Although these patients may appear to have understood the necessity of such a procedure, they are as likely to curse and attempt to sign out in the midst of the procedure when discomfort occurs. Thus, cooperation with the physician (a sick-role expectation) is difficult for these patients.

Medical professionals, trained to be always deliberate and objective, tend to dislike patients with this personality type. They see these patients as being defective and childish. In fact, this style may be a manifestation of a defect in the integrative functions of the brain rather than a primarily developmental personality style. In fact, it is well known that brain-damaged patients frequently exhibit impulsive behavior. It is important, therefore, for

health care personnel to deal with it as a defect, just as they have to recognize and deal with a diabetic patient's metabolic defect. The management strategy, thus, would involve preventing situations in which the defect would be of major consequence and compensating for it when it is unavoidable.

For example, tranquilizers may be utilized more freely for these patients as a partial preventive measure against outbursts of aggression. Benzodiazepines such as lorazepam 1–2 mg may be used 30 min before a procedure. First generation antipsychotics (e.g., perphenazine 2–4 mg b.i.d. p.o.) may be used for their neuroleptic effect so as to decrease the patient's stimulus-bound immediate response to discomfort. Second-generation antipsychotics (e.g., risperidone, olanzapine, aripiprazole) and mood stabilizers (e.g., valproic acid) in small doses may also be considered.

Pain should be treated especially vigorously. Firm limit-setting is also necessary to establish some external control over these patients' acting-out behavior. In fact, these patients feel reassured by firm limit-setting, which also gives them a sense of external control and caring. Whenever possible, persons familiar to the patient, such as friends and relatives, should be mobilized to support and control the patient.

25.7.2.6 Patients with Mood Swings (Cyclothymia and Cyclothymic Disorder)

These patients characteristically have "ups and downs," that is, periods of relative euphoria and hyperactivity followed by periods of depressed feelings and lack of energy. Although most people have some periods characterized by euphoric or depressive moods, persons who have this personality trait exhibit such mood swings consistently. During the "up" periods, they feel optimistic, ambitious, and usually physically well. During the "down" periods, feelings of pessimism and a sense of malaise predominate. If these changes are exaggerated so as to cause major problems in function, the psychiatric diagnosis of bipolar disorder or cyclothymic disorder should be considered (see Chap. 15).

The importance of recognizing this personality trait lies in that, depending on the mood in which these patients find themselves, the reaction to illness and to the medical treatment may vary. When an illness occurs during an up period, patients may not even recognize the presence of the symptoms, or even if the patients do recognize them, they may brush them aside as being of no consequence. If patients happen to be in a down phase, however, they may feel quite pessimistic about the symptoms and attach all kinds of grave implications to them. In fact, they may be convinced, even before they see a physician, that they have a terminal illness for which there is no hope. In addition, because of the feelings of malaise and lack of energy experienced during the down phase, these patients may experience exaggerated discomfort that may be caused by minor dysfunctions.

Patients with this personality trait might be more prone to developing severe depression in the presence of major stress such as a serious medical illness. If a patient who has this pattern develops evidence of serious depression, including feelings of hopelessness, guilt, and lowered self-esteem, coupled with weight loss, anorexia, sleep disturbances, and, perhaps, suicidal thoughts, the diagnosis of major depression should be made, and definitive treatment instituted (See Chap. 15).

25.7.2.6.1 Cyclothymic Disorder

This is the more serious form of cyclothymia, and DSM-5 includes this disorder in the section of *Bipolar and Related Disorders* rather than in the personality disorders section because of its proximity to the extreme form, *Bipolar Disorder*.

DSM-5 defines cyclothymic disorder as a chronic, fluctuating mood disturbance involving numerous episodes of hypomanic symptoms and periods of depressive symptoms that are distinct from each other. The hypomanic symptoms and depressive symptoms must be insufficient in number, severity, pervasiveness, or duration to meet the full criteria for the hypomanic episode and major depressive episode, respectively (See Chap. 15) (APA 2013).

25.7.3 Cluster C: Shy, Anxious, and Fearful Personalities

25.7.3.1 Shy, Anxious, Rejection-Sensitive Patients (Avoidant Personality and Disorder)

These patients do not reach out to people for fear of rejection—that they are not likable, socially inept, and likely to be criticized. Thus, they tend to avoid activities that are likely to involve interpersonal contact. Hospitalization would be especially stressful for these patients because of the necessity to deal with new sets of people, both health care professionals and other patients, who might all dislike them, criticize them, and reject them. Managing such patients involves understanding their fear of criticism and rejection. A good approach to these patients entails a friendly and caring attitude and patiently explaining the procedures and treatments, as these patients are very much in need of feeling accepted by others.

25.7.3.2 Dependent, Demanding Patients (Dependent Personality and Disorder)

It is said that one can detect this type of personality by noting the amount of luggage the patient brings to the hospital. An exaggerated caricature form of this personality is indeed seen in the patients who come into the hospital as though they were prepared to stay for months, if not years. Patients of this type have a need for a great deal of reassurance and often want special attention from health care personnel. They tend to become dependent on the doctor and others who are involved in their care and often make frequent, inappropriately urgent calls to nurses and doctors. When their (excessive) demands are not met fully, they tend to feel angry and rejected.

The underlying dynamic for this type of personality is considered to be a regressive wish to be cared for as though by an idealized, nurturing mother. The fear of being rejected, left out in the cold, and neglected tends to exaggerate the need for reassurance and care. The sick role may be considered to be a temptation for these patients to return to a state of infantile dependency, and they may consider the illness to be a result of a lack of protection and concern by others.

The incessant demands of a patient of this type, coupled with relative comfort in the dependent position, may be regarded by others, especially doctors and nurses, as "enjoying" being sick, counter to the sick role expectation that the patient should consider being ill an undesirable state and try to get better by seeking and cooperating with medical care.

When excessive demands for attention are not met, the patient may become hostile, in turn provoking anger and conflict. The nurses, for example, may feel that the patient wants too much attention, while the patient feels that the nurses are cold and uncaring.

There is a flip side to this coin as well. A patient of this type was referred to the psychiatrist by an alarmed surgeon because he too eagerly consented to an amputation the first time it was discussed as a possibility. In this instance, it was learned that the doctor had been overly indulgent with the patient, allowing special privileges and giving an inordinate amount of care and attention. The patient, before long, regarded the doctor as an omnipotent, mothering figure and wanted to go along with anything that the doctor suggested might be good for him.

25.7.3.3 Orderly, Controlling Patients (Obsessive-Compulsive Personality and Disorder)

Such patients tend not to show feelings and generally experience illness without outward signals of emotional reaction. Their descriptions of symptoms are complete, precise, and dispassionate.

This personality style is motivated by a desire to control external as well as internal states. Behind the desire to control may be fear of loss of control or being helpless.

The sick role is obviously difficult for patients with these personality characteristics. Removal from normal responsibilities and daily routine may be experienced as disruptive. Being unable or not permitted to help themselves may be an alien experience for them. Needing to seek advice and help from a professional may generate concerns about who will control whom, and they

may feel deeply threatened by the control that doctors and nurses must assume over their lives and their bodies in order to administer the necessary medical care.

In response to these threats, they may become contentious, complaining, and accusatory. Usually quite conscious of time and details, such as medication schedules, they may become incensed and critical if the nurse brings a pill a few minutes late.

Such patients do not respond favorably to blanket reassurances. They are likely to wonder if the physician is competent when reassurances are given without firm foundation in facts. The doctor's explanation of one hopeful laboratory finding may be far more reassuring to this type of patient than many impressionistic but unsupported optimistic statements.

A rule of thumb in dealing with this type of personality is to attempt to recruit the patient to be a part of a therapeutic team effort against the illness. This enables patients to feel that the physician respects their autonomy enough to ask them to cooperate in the common endeavor. Detailed explanations of the diagnosis, the physical and laboratory findings, and treatment plans are helpful, especially for more educated patients (as in Vignette 2 above). Sometimes it is useful to the patients to help the treatment team by keeping a diary of symptoms or by recording some of their clinical data, such as the volume of water drunk and urine voided.

Case History: A chemistry technician with diabetes mellitus was admitted for treatment of leg ulcers. Within days after admission, he complained of the "sloppiness" of the doctors and nurses, and their lack of punctuality in bringing his medications. Successful management involved the physician's acknowledging the patient as someone related to the medical profession ("As a chemist, you would understand the mechanism of diabetes mellitus. Now, we want to treat this with diet and insulin, and we will follow the course with blood glucose levels."). In addition to giving the patient credit for his knowledge of chemistry, the doctor taught him to change his own medicated dressings (he could do it "much better than any nurse") and to keep track of his medications to be sure that they were taken on time.

25.7.3.4 Long-Suffering, Self-Sacrificing Patients (Masochistic Personality—Not a DSM-5 Diagnosis)

Some experienced physicians say that this personality type can be diagnosed by the pitch and tone of the patient's first utterance at first contact with the doctor. Such patients often speak in a wailing, complaining voice, and usually the history involves a long list of hard luck and disasters: surgical operations followed by complications, trusted persons turning out to be untrustworthy, promised cures for a symptom bringing on more symptoms and side effects than relief, and other complaints. They almost always have endured protracted pain and suffering, and this "present illness" represents an additional suffering for a patient who seems to have been "born to suffer."

When listening to patients with this type of personality, one usually finds that they have taken care of someone else despite their own suffering and misery. They take much pride in relating how this feat was achieved in the presence of so much suffering and so many misfortunes. Often, that someone else is a child, a spouse, or a parent.

A major underlying dynamic in these patients is considered to involve strong feelings of guilt that do not allow them to enjoy life for themselves. With a "need" to suffer in order to expiate the guilt feelings, altruistic activities (such as caring for others) in the presence of physical or emotional pain may allow them some covert gratification (claim to happiness). Thus, these patients appear as though they are "exhibiting" their misfortunes, sufferings, and altruistic acts.

Another underlying dynamic in such patients is the use of pain and suffering as a lifestyle, as a means of maintaining interpersonal relationships. These are patients who might be "addicted" to the sick role (see Chap. 10). The sick role is taken on from time to time throughout their lifetimes, although they also feel proud of having taken care of others despite the sick-role restrictions. A closer

scrutiny reveals that the sick role is assumed as a way of meeting their needs indirectly through suffering and through ongoing contact with the physician. Many patients diagnosed as "hypochondriacs" have this personality type (see Chap. 23).

Patients with this type of personality often become severe problems for health care personnel. Typically, they tend to *react negatively to reassurances*, totally frustrating the doctors. When the physician prescribes a medication and offers the reassurance that it will relieve the pain, these patients are likely to return complaining of more rather than less pain, which may now be felt in areas that were previously free of pain! In addition, they may have nausea and dizziness. They may even overtly blame the physician for their added troubles, but most often this is attributed to bad luck. The physician, nevertheless, is often made to feel guilty by these patients. This frequently results in a rejection of the patient by the physician, which adds to the patient's feeling of being mistreated. Thus, these patients commonly have a history of repeated rejection or transfer from doctor to doctor.

If not quite reaching the degree of pathology of factitious disorder (Munchausen syndrome, See Chap. 21), the long-suffering personalities are often addicted to the sick role, and thus appear to the health care personnel not to consider being sick an undesirable state and pay only lip service to wanting to get well.

Patients with this personality type are best managed when the physician gives "credit" to their suffering and expresses appreciation for their courage and perseverance in the face of protracted pain and hardship. It is a mistake to promise such patients complete relief from pain and suffering. In fact, since they need to expiate guilt and maintain relationships, such a promise may provide a powerful reason for the patients' "refusal to improve." Taking away the symptoms and suffering would leave them exposed and helpless, without any means of relating to others.

Recognition of this pattern also helps the physician to recognize the necessity to accept and set limited goals for the treatment in order to avoid later frustration, feelings of helplessness, and reactive anger. This can prevent or postpone the development of disruptive tension in the relationship with the patient. It is often helpful for the physician to approach this type of patient with some degree of pessimism, such as, "Although we cannot take away the pain completely, this medication may take the edge off the pain somewhat," or "It is remarkable that you can tolerate this discomfort as much as you do!"

Attempts to mobilize altruistic tendencies may also be helpful. For example, a patient may be persuaded to seek proper treatment to alleviate crippling pain so that she might be better able to care for her children.

One has to differentiate this type of personality from patients who experience protracted suffering due to actual complications from treatment. Patients suffering from chronic illnesses without this character style do not show the self-sacrificing element, and although they may feel rather cynical about the prolonged illness, they do not show the tendency to "refuse to improve."

25.7.3.5 Other Personality Disorders

25.7.3.6 Personality Change Due to Another Medical Condition

Many medical conditions, particularly head trauma, neurodegenerative diseases, infections, metabolic/endocrine diseases, nutritional deficiencies, poisoning, can cause personality change. Exaggeration of preexisting personality characteristics with brain injury is well known (Gunter et al. 2013; Laborey et al. 2013; Sela-Kaufman et al. 2013; Sinha et al. 2013).

DSM-5 lists a number of types of personality change—labile, disinhibited, aggressive, apathetic, paranoid, other, combined, and unspecified types.

Personality change, especially lability, impulsivity and paranoia occur frequently as a symptom of delirium.

Recognition that the personality change is due to the underlying medical condition is usually reassuring both to the patient and the family. Treatment should be geared to the underlying medical condition, with symptomatic treatment if indicated, such as mood stabilizers or antipsychotics.

25.8 From Types to Individuals

As should be clear from our discussion, the various characteristics of personality types are not mutually exclusive but tend to coexist in varying combinations. One of our most gratifying experiences is to hear our students complain to us, after a discussion of personality types, that they could not actually categorize a single patient neatly into any single type. The personality types described here are like caricatures. In real life, it is the rule rather than the exception to see patients with characteristics belonging to several personality types. For example, one patient may be orderly and controlling *and* guarded and suspicious, or another may be dependent and demanding *and* also have mood swings. Once an individual is recognized as being unique, with certain characteristics from several different personality types, then the management of such a patient can be truly individualized.

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Acute Settings and Conditions: Intensive Care Unit, Heart Disease, Stroke, Seizures

26

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26.1 Vignettes

1. A 24-year-old woman with subarachnoid hemorrhage due to rupture of a berry aneurysm was admitted to the intensive care unit (ICU). A psychiatric consultation was requested as the patient seemed to be depressed. The consultant found that the patient felt sad about not being able to see her 2-year-old son, as children were not allowed in the ICU. She was afraid that she might die without being able to say goodbye to him. The consultant was able to obtain special permission from the administration for her husband to bring the child once a day. She recovered fully from her hemorrhage.
2. A 17-year-old girl was admitted to the ICU after ingestion of 50 acetaminophen tablets in a suicide attempt. The patient's liver enzymes were elevated, and she was being treated with acetylcysteine. A psychiatric consultation was requested for the suicide attempt. The consultant found that the patient had symptoms of increasing depression over the past 3 months, with serious suicidal plans and termination behavior, such as giving her iPad to her closest friend and writing a goodbye letter to her parents and boyfriend. She was sorry that she did not die, and saw no point in continuing to live. The consultant decided to transfer her to a psychiatric inpatient facility when her medical condition stabilized. The consultant ruled out the use of

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an antidepressant at present because of the patient's compromised liver condition, but antidepressant therapy would be started upon transfer to a psychiatric hospital.

26.2 Delirium and Psychosis in the Intensive Care Unit

Acute illness is usually accompanied by acute stress. Altered states of consciousness, particularly delirium, are common in patients with acute illness, especially in the intensive care settings. Acute stress often induces dissociation in predisposed individuals, and medications used to treat the medical symptoms, such as narcotic pain medications and steroids, can contribute to confusion and delirium. The confusing sensory overload and deprivation common in ICU settings where night and day may be indistinguishable also contribute to delirium. Delirium with psychotic features such as visual hallucinations, paranoid delusions, and agitation has been called "ICU psychosis" (McKegney 1966; Eisendrath 1980).

Facilitating acute medical treatment is the primary goal of psychiatric intervention in the acutely medically ill patient. While treatment of delirium, particularly with psychotic symptoms, is desirable, the patient may be in need of the medications that may be responsible for the delirium/psychosis, such as steroids, for maintaining life. Under such acute conditions, the consultant may recommend further sedation, even to the point of keeping the patient asleep during the acute phase of treatment, or antipsychotic drugs to control the psychotic symptoms while continuing the medical drug. On the other hand, medications that require time to work, such as antidepressants, and drugs that may further complicate medical conditions, such as liver function or cardiac function (e.g., thioridazine, ziprasidone, citalopram, that may prolong the QT_c interval), may be best withheld during the intensive care stay. With ICU psychosis, transfer out of the ICU is indicated as soon as feasible. See Chap. 12 for further discussion on delirium.

26.3 Stress, and the Role of Psychological Defense Mechanisms, Coping Styles, and Personality

Acute medical illness, especially severe enough to require ICU admission, is a stressful event. In addition to the acute symptoms that may be painful and frightening, patients have the added stress of uncertainty about whether or not they will survive or be disabled and about how long they will be hospitalized, as well as concerns about family, job, pets, and so on. There should be routine inquiry about the particular concerns each patient has regarding acute hospitalization. In an acute setting, certain accommodations to alleviate the patient's stress may be necessary, such as allowing a child to visit (as in Vignette 1). The medical staff should always maintain a channel of communication with the patient and family, and discuss any new developments in the diagnostic process and treatment plan and allow them to ask questions. An important aspect of stress management is information and strategic planning that brings a sense of mastery to an uncertain situation.

The physical setting of the ICU may have a unique meaning to the patient that can only be understood by communicating with the patient (as in Vignette 1 in Chap. 14). A common reason for ICU psychiatric consultation is a serious suicide attempt, which may be the result of a serious untreated depressive syndrome (as in Vignette 2). Even when a severe depressive syndrome is present, the consultant should exercise caution in considering the use of antidepressants as the patient's metabolic function may be altered (e.g., liver damage with acetaminophen overdose). It is generally judicious to wait until the patient is transferred out of the acute ICU before starting antidepressant drugs.

The acute stress associated with an acute medical illness naturally recruits the patient's psychological resources, which include defense mechanisms, coping mechanisms, and an exaggeration of the personality traits. Psychological defense mechanisms, such as denial and

repression, refer to unconscious, automatic mechanisms the individual uses in the face of anxiety-provoking situations. Coping mechanisms refer to conscious, deliberate ways of dealing with stress, such as getting information about the disease or procedure, or seeking diversion, such as relaxation techniques. Personality style (see Chap. 25) is usually exaggerated in the face of stress.

Denial as a defense mechanism has been shown to be adaptive during the acute phase of myocardial infarction in the CCU (Hackett et al. 1968), but maladaptive in seeking help and during the recovery phase (Levine et al. 1987). During the recovery phase, patients who use denial tend not to undertake the lifestyle modifications necessary to prevent recurrence of the disease. Intellectualization in the form of reading about the disease and discussing it with the health care professionals can be an effective way of reducing anxiety and gaining a sense of mastery.

In general, patients' defense mechanisms should not be challenged during the acute phase of an illness, but rather respected. Frontal challenge of a defense mechanism is likely to result in an uncontrolled anxiety or a rupture in the relationship between the patient and the health care professional. Coping mechanisms should be respected and enhanced, including teaching new coping mechanisms such as relaxation training.

As stress accentuates personality traits, someone who tends to be usually vigilant may appear to be paranoid, someone who is exacting may seem to be obsessive-compulsive, and someone who tends to be expressive may come across as being histrionic. The health care professional should recognize the role of stress in exaggerating such personality traits, and not rush in labeling the patient as having a personality disorder. With relief of the stress and anxiety, their personality will return to baseline.

26.4 Heart Disease

26.4.1 Anxiety

There is a close reciprocal relationship between heart disease and both anxiety and depression. The Normative Aging Study, a longitudinal prospective study of older men in Boston, found a significant association between baseline increased anxiety and sudden cardiac death at follow-up, and a dose-dependent relationship between the degree of depression at baseline and coronary artery disease at follow-up (Kawachi et al.. 1994; Sesso et al. 1998).

About 50 % of patients with an acute coronary syndrome exhibit symptoms of anxiety and about 25 % experience as much anxiety as an average inpatient in a psychiatric unit. Patients with increased anxiety in the hospital usually continue to experience anxiety at least 1-year posthospitalization (Cassem and Hackett 1971; Billing et al. 1980; Crowe et al. 1996).

Panic disorder is particularly associated with cardiac symptoms. Approximately 20 % of patients who come to the emergency room with chest pain meet the criteria for panic disorder and patients with coronary artery disease are four times as likely to have panic disorder as the general population (Huffman et al. 2002; Huffman and Pollack 2003).

26.4.1.1 Treatment of Anxiety in Cardiac Patients

Patients who suffer an acute coronary event often feel anxious because they feel out of control. They often feel reassured by the calm and competent demeanor of the health care professionals who show an interest in the welfare of the patients. Frequent visits by the physicians and nursing staff and inquiring about patients' needs can be highly anxiolytic. Discussion of such behavioral preventive measures as exercise, diet, and smoking cessation provides a sense of control over the illness. Teaching relaxation techniques can also be helpful.

Benzodiazepines are useful in treating acute anxiety. Lorazepam 0.5–1 mg po every 6 h PRN is commonly used. Scheduled doses of longer acting benzodiazepines, such as clonazepam 0.5 mg twice a day may prevent unnecessary anxiety.

SSRIs may be used to treat anxiety and depression in cardiac patients (see Sect. 26.4.3 below).

26.4.2 Posttraumatic Stress Disorder

Posttraumatic Stress Disorder develops in about 8–16 % of patients following a myocardial

infarction or coronary artery bypass graft (CABG) (Doerfler et al. 1994, 2005; Stoll et al. 2000; Shemesh et al. 2001).

Antipsychotics can be used for severe anxiety and psychotic features associated with delirium, but they should be used cautiously and in small doses (e.g. haloperidol 0.5 mg PO BID) due to the QTc prolongation side effects.

26.4.3 Depression

26.4.3.1 Depression as a Risk Factor in Heart Disease

About 15–20 % of patients with coronary disease have depression (Hance et al. 1996; Kessler et al. 2003) and depression is a major predictor of subsequent mortality (Lesperance and Frasure-Smith 2000; Frasure-Smith et al. 2009).

A metaanalysis of 28 epidemiologic studies with nearly 80,000 patients shown depression to be an independent risk factor for cardiovascular disease (Van der Kooy et al. 2007). The relative risk of developing heart disease in depressed but healthy people is 1.64, which is less than that in active smokers (2.5) but more than that in passive smokers (1.25) (Wulsin and Singal 2003).

Major depression (MDD) during the year preceding baseline assessment increased the risk of dying from ischemic heart disease by 2.7 times in the follow-up period (Ishihara-Paul et al. 2008; Surtees et al. 2008a, b).

The prevalence of depression is three times greater in post-MI patients and post-MI depression is associated with 2 to 2.6-fold increased risk of all-cause mortality, cardiovascular mortality, and cardiovascular events in a metaanalysis of 22 prospective studies (Barth et al. 2004).

In *ESCAPE* study (Epidemiological Study of Acute Coronary Syndromes and the Pathophysiology of Emotions), 804 patients were assessed 2 months after acute coronary syndrome (ACS). MDD more than doubled the risk of cardiac death, MI, cardiac arrest, and nonelective revascularization within 2 years (Frasure-Smith and Lesperance 2008; Thombs et al. 2008). Lesperance et al., reported that the higher the Beck Depression Inventory score at the time of hospital admission in post-MI patient, the higher the 5-year mortality rate (Lesperance et al. 2002; Frasure-Smith et al. 2009). Pre-MI MDD was associated with immediate post-MI in-hospital complications such as ventricular arrhythmias, congestive heart failure, and reinfarction (Huffman et al. 2008).

The characteristics of depression affecting morbidity and mortality in MI include first-episode depression around the time of MI and depression within 1 month after ACS.

Severity of MDD in first few weeks of hospitalization for ACS or failure of MDD to improve during the 6 months following ACS predicted more than a doubling of mortality over 6.7 years of follow-up (Glassman et al. 2009).

Forty percent of CHF patients suffer from comorbid depression and is associated with decline in health status and increased rates of rehospitalization . Depression increases cardiovascular mortality and arrhythmic death despite optimized treatment. Depression is associated with longer hospital stay and higher 60–90 day postdischarge mortality (Albert et al. 2009).

INTERHEART study, involving 52 countries, explored attributable risk in the development of myocardial infarction. They found that psychosocial factors including stress, low generalized locus of control (the perceived inability to control one's life), and depression accounted for 32.5 % of the attributable risk for MI, which is slightly less than smoking but greater than hypertension and obesity (Rosengren et al. 2004).

Heart and Soul Study by Whooley et al., was a longitudinal study of more than 1,000 stable coronary heart disease patients recruited from outpatient clinics in the San Francisco Bay Area, 10 % of patients with moderate to severe depressive symptoms had a heart attack, stroke or angina, compared to 6.7 % of patients who were not depressed. Whooley found that depressed patients were in essence less likely to take care of themselves. They were especially unlikely to keep up with any sort of exercise regimen, a factor that was most associated with cardiac events. While people who are depressed may lack the motivation to exercise, a gradually growing number of research studies suggest that aerobic exercise can relieve depression.

Depression was associated with elevated levels of norepinephrine, more inflammation, and lower blood levels of omega-3 fatty acids. But when exercise and other health behaviors were factored in, these physiologic changes did not account for the link between depression and heart disease—only exercise and health behavior mattered (Duivis et al. 2013a, b; Martens et al. 2010; Ruo et al. 2003, 2004; Whooley et al. 2008; Schenker et al. 2009).

This study also found an association between the serotonin transporter promoter gene (SERT or 5-HTTLPR) and several aspects of heart disease. The short allele of this gene has been shown to interact with stressful life events to predict depression in otherwise healthy individuals. Among patients with chronic heart disease, carriers of the s allele of 5-HTTLPR were more vulnerable to depression, perceived stress, and high norepinephrine secretion. These factors may contribute to worse cardiovascular outcomes in these patients (Otte et al. 2007). They also found hopelessness was a risk factor for mortality in cardiac disease even after accounting for severity of depression, and that patients with the short allele of the 5-HTTLPR gene had a higher rate of hopelessness among men but not in women (Kangelaris et al. 2010).

Depression may increase cardiac mortality through the following mechanisms:

1. Increased catecholamine which may lead to increased cardiac activity and oxygen demand as well as increased blood pressure activity (Jewitt et al. 1969; Bouzinova et al. 2012).
2. Changes in autonomic nervous system activity as manifested by decreased heart rate variability, often associated with increased C-reactive protein, may lead to susceptibility to ventricular arrhythmias (Stein et al. 2000; Carney et al. 2001, 2005; von Kanel et al. 2011).
3. Increased tendency for platelet aggregation in patients with coronary disease, which may increase the risk of acute coronary event (Mendelson 2000; Delle Chiaie et al. 2013)
4. Noncompliance to cardiac health regimen—depressed patients tend to be less adherent to medication regimen and to modifications in diet, exercise, and smoking cessation (Bernard et al. 2013; Eze-Nliam et al. 2010; Hitsman et al. 2013; Weinberger et al. 2013; Khawaja et al. 2009; McGrady et al. 2009; Thorndike and Rigotti 2009). Statin use has been associated with decreased risk of depression in coronary disease patients (Otte et al. 2012).

Social support seems to play a protective role for cardiac patients with depression, probably through mitigation of the depressive symptoms (Frasure-Smith et al. 2000). In outpatients with chronic coronary heart disease, depressive symptoms were associated with perceived deficits in doctor–patient communication, while medical comorbidities and disease severity were not, suggesting that patient reports of doctor–patient communication may partly reflect the depressive psychological state of the patient (Schenker et al. 2009).

26.4.3.2 Treatment of Depression in Cardiac Disease

In view of the adverse effects of depression in cardiac outcome, treatment of depression is important in cardiac patients, although just how effective antidepressant treatment remains unclear.

Several prospective studies have been performed concerning psychiatric syndromes including depression and cardiac disease.

SADHART (Sertraline Antidepressant Heart Attack Trial) by Glassman et al., was a multicenter, double-blind, placebo-controlled, randomized clinical trial comparing the safety and antidepressant efficacy of sertraline vs. placebo in 369 patients with acute coronary syndrome and major depression. The results showed that sertraline is a safe drug for these patients, and that it may help prevent recurrent cardiac events, but patients treated with sertraline did not show a significant improvement in depression compared to placebo-treated patients. A 7-year follow-up showed that the severity of depression within a few weeks of hospitalization for acute coronary syndrome or failure of depression to improve during the 6 months following the cardiac event predicted more than a doubling of mortality at

follow-up. Furthermore, marked improvement in depression was associated with improved adherence to sertraline (Glassman et al. 2002, 2009). In a SADHART substudy, depressed MI patients treated with sertraline had substantially less platelet and endothelial biomarker release (Serebruany et al. 2003, 2005). Treatment with sertraline compared with placebo did not provide greater reduction in depression or improved cardiovascular status among patients with CHF and depression (O'Connor et al. 2010).

ENRICHD (ENhancing Recovery In Coronary Heart Disease patients) was a multicenter, randomized-controlled clinical trial. A total of 2,481 patients, average age 61 years, were recruited from eight clinical centers in the United States. Participants in the study had to be in a recovery state after an acute MI (screened during the first 28 days since the MI). They also had to fulfill the DSM-IV criteria of major depression, minor depression with a history of major depression, or dysthymia and the ENRICHD criteria for Low Perceived Social Support (LPSS). The study included women (44 %) and minorities (34 %). 1,238 patients were randomly allocated to CBT intervention with adjunctive pharmacotherapy if needed, and 1,243 to usual medical care. CBT, which aims to modify thought patterns that are associated with patients' symptoms and facilitate change in patients' habits, was given for 6 months. The primary end-points of the study were reduction in all-cause mortality or recurring nonfatal MI. The mean follow-up was 41 months. Although the intervention treatment program significantly reduced depression and significantly increased the level of social support in comparison to the usual care group, it did not lower mortality or the recurrence of MI. Death was recorded in 303 (24.4 %) of the intervention treatment group and 299 (24.2 %) of the usual care group (Investigators 2001; Louis et al. 2002; Berkman et al. 2003; Froelicher et al. 2003; Sheps et al. 2003; Trockel et al. 2008). Many factors are probably responsible for the disappointing results, but it is possible that the usual care given may have been quite effective in preventing mortality or recurrence of MI in this population.

MIND-IT (*Myocardial Infarction and Depression-Intervention Trial*) involved 2,140 patients admitted for MI screened for depressive symptoms at 0, 3, 6, 9, and 12 months after MI . The first-choice treatment was a placebo-controlled treatment with mirtazapine, with alternative open treatment with citalopram for nonresponders. There was no significant difference in depression outcome or new cardiac events when evaluated at 18 months postmyocardial infarction. Mirtazapine responders showed significant increase in tumor necrosis factor compared to nonresponders (Denollet et al. 2009; Tulner et al. 2011).

CREATE (*The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy*) evaluated the efficacy of citalopram and interpersonal therapy (IPT) in reducing depressive symptoms in patients with stable coronary artery disease and major depression. Participants underwent two separate randomizations: (1) 12 weekly sessions of IPT plus clinical management ($n=142$) or clinical management only ($n=142$) and (2) 12 weeks of citalopram, 20–40 mg/d ($n=142$), or matching placebo ($n=142$). Clinical management consisted of 20–25 min sessions on psychoeducation, reassurance, and compliance adherence. Citalopram was superior to placebo in reducing 12-week Hamilton Depression Rating Scale scores. There was no benefit of IPT over clinical management (Lesperance et al. 2007). Citalopram was not associated with decrease in platelet activation markers but it significantly increased production of nitric oxide (van Zyl et al. 2009)

A metaanalysis of SADHART, CREATE, ENRICHD, MIND-IT, and randomized-controlled trials of fluoxetine and mirtazapine showed that treatment of depression with medication or CBT resulted in modest reductions in depressive symptoms but no evidence that depression treatment improved cardiac outcomes (Thombs et al. 2008).

Cardiac Rehabilitation including exercise training, education on heart healthy living, and counseling to reduce stress and help to return to an active life has been shown to have an impact

on depressed cardiac patients. 522 post-acute cardiac events patients with depression who completed cardiac rehabilitation and 179 patients who dropped out within 2 weeks of the start were studied. Depressive symptoms decreased 63 % following rehabilitation, from 17 to 6 % in the intervention group and depressed patients who completed rehabilitation had a 73 % lower mortality (8 % vs. 30 %) compared with control depressed patients who did not complete rehabilitation (Milani and Lavie 2007).

26.4.3.3 Conclusions

Depression is a significant risk factor for new heart disease and increases morbidity and mortality in established heart disease. Mechanisms linking depression and heart disease include serotonergic pathway and platelet dysfunction, inflammation, autonomic nervous system and hypothalamic-pituitary-adrenal axis imbalance, and psychosocial factors.

Drug therapy and psychotherapy have been shown to improve depression but not clearly shown to decrease cardiac morbidity and mortality.

Given these findings, it seems SSRIs are safe and potentially helpful in reducing both depression and cardiac events, probably also owing to their antiplatelet agglutination effect as well as antidepressant effect. Health-promoting behaviors including exercise and smoking cessation are helpful in depressed cardiac patients. Cognitive Behavioral Therapy has been shown to be effective in treating the depression in cardiac patients. In addition to SSRIs, the SNRI, duloxetine, and mirtazapine can be used effectively in cardiac patients (Montgomery 1995; Hudson et al. 2005; Thase et al. 2005; Wohlreich et al. 2007). On the other hand, another SNRI, venlafaxine should rarely be used in cardiac patients due to its dose-dependent increase in blood pressure, QTc prolongation, and other cardiac toxicity (Feighner 1995; Blythe and Hackett 1999; Combes et al. 2001; Letsas et al. 2006; Martinez et al. 2010).

Bupropion is also effective and may help smoking cessation as well, but it lowers seizure threshold and can prolong QTc (Isbister and Balit 2003; Tonstad et al. 2003). Tricyclics, while effective, have strong anticholinergic action and should be used cautiously. They also have more QTc prolonging side effect, as does the SSRI, citalopram (Rasmussen et al. 1999; Catalano et al. 2001; Kanjanauthai et al. 2008).

In addition to drug therapy, cardiac rehabilitation, smoking cessation, exercise, diet, and other life style changes can be effective both in reducing depression and reducing cardiac morbidity/mortality in heart disease patients.

26.5 Acute Neurologic Conditions

26.5.1 Stroke

Some 40–50 % of poststroke patients have depression within 5 years of stroke, and about 30 % have depression 10 years after stroke. The rate of recovery from depression among patients depressed a few months after stroke range from 15 to 57 % 1 year after stroke. Major predictors of depression are disability, depression pre-stroke, cognitive impairment, stroke severity, and anxiety. Lower quality of life, mortality, and disability are independent outcomes of depression after stroke (Lincoln et al. 2012; Ayerbe et al. 2013a, b).

Escitalopram and duloxetine have been shown to be effective in preventing poststroke depression and reducing cognitive impairment (Espinera et al. 2013; Jorge et al. 2010; Zhang et al. 2013; Zittel et al. 2008; Gusev and Bogolepova 2009).

Pathological laughing and crying is seen in 20 % of poststroke patients, and may respond to antidepressants (Andersen 1995).

Disinhibition syndromes, ranging from mildly inappropriate social behavior to full blown mania, may result from lesions of prefrontal cortices, and orbitofrontal and basotemporal cortices of the right hemisphere. (Starkstein and Robinson 1997; Zamboni et al. 2008)

Lesions of the left hemisphere, particularly closer to the left frontal lobe, seem to be particularly associated with depression (Parikh et al. 1987; Tiller 1992; Barker-Collo 2007). Right hemispheric lesions are often associated with agnosias of various kinds including anosognosia (unawareness of deficit) and prosopagnosia (face-blindness)

(Palmerini and Bogousslavsky 2012; De Renzi et al. 1994; Ellis 1994; Beis et al. 2007). Gerstman's syndrome consisting of finger agnosia, right-left disorientation, agraphia, and acalculia, often arises from lesions of the left parietal lobe (angular gyrus and supramarginal gyrus) near the junction with temporal lobe (Jung et al. 2001).

26.5.2 Seizures

At least 50–60 % of patients with epilepsy have psychiatric symptoms, particularly of mood, anxiety, and psychotic disorders (Marsh and Rao 2002). Psychiatric symptoms are particularly common in partial complex seizures, which commonly arise from the mesial temporal lobe, particularly the amygdala, hippocampus, and neocortical regions (Trescher and Lescher 2000). The aura may include such emotions as fear and euphoria, and déjà vu, jamais vu, or depersonalization. There may also be visual disturbance, such as tunnel vision and micropsia or macropsia. Once consciousness is impaired, the patient may display automatisms such as lip smacking, chewing, or swallowing. There may also be amnesia surrounding the seizure event.

Initial assessment should determine whether the psychiatric symptoms are direct expressions of the epileptic seizure (i.e., the ictal state), or features of a periictal state, i.e., postictal or preictal/prodromal phases that are temporally associated with seizures, but are not manifestations of epileptic seizures, or manifestations of chronic nonictal conditions present during the interictal period. Symptoms associated with ictal and periictal states are transient and accompanied by other features of a typical seizure. Nonictal psychiatric conditions tend to persist, and are sometimes chronic. Some patients have more than one disturbance, with different psychiatric symptoms during each phase of the seizure.

26.5.2.1 Ictal Phase

The key features of ictal psychiatric disturbances are the characteristics of a typical seizure—the events are stereotyped, begin suddenly and without provocation, are brief (<1–3 min), and end abruptly. With complex partial seizures, consciousness will be altered, though impairment or confusion may be subtle. There may also be staring, motor or oral automatisms, simple utterances or nonsensical speech, and undirected pacing. Such behaviors or emotions during the seizure will be out of context for the situation and unresponsive to interventions. EEG abnormalities and a postictal elevation in prolactin support the diagnosis of epilepsy (Marsh and Rao 2002).

It is important to note, however, that psychological stress can precipitate epileptic seizures (Fenwick 1991b).

Nonconvulsive partial status epilepticus can manifest as prolonged states of fear, mood changes, automatisms, or psychosis that resemble an acute schizophrenic or manic episode (Trimble 1991). While usually confused, such patients can usually respond to simple commands and questions. *Absence* status epilepticus may be associated with fluctuating states of arousal, blinking, staring, and myoclonic jerks. An EEG may be necessary to confirm the diagnosis of status epilepticus, especially when there is concomitant interictal psychopathology or in nonepileptic psychiatric patients on medications that lower the seizure threshold (Abend and Marsh 2009).

Ictal Anxiety is quite common in epileptic patients. Ictal fear, an extreme feeling of unprovoked terror or panic as a discrete manifestation of epileptiform activity, is often described as 'unnatural'. It may be associated with visual or auditory hallucinations and autonomic phenomena such as hyperventilation, tachycardia, flushing, gastrointestinal upset, or sweating (Betts 1981)

Ictal Depression is less common than ictal anxiety; it was reported to be a part of the aura in 1 % of one large sample of epilepsy patients, and was most common with temporal foci (Marsh and Rao 2002). When ictal dysphoria is reported, the mood state tends to come on suddenly, without environmental precipitants and has a prolonged duration relative to the usual aura or postictal state. Depressed moods can also predominate during status epilepticus.

Ictal Psychosis may be manifest with olfactory and gustatory hallucinations. Ictal visual or

auditory hallucinations typically involve poorly defined shapes or sounds. Paranoid or grandiose thoughts also occur and may be frightening or lead to inappropriate behaviors.

Treatment of Ictal Psychiatric Symptoms should be geared toward the seizure disorder with antiepileptic medications and/or surgery. Psychotropic drugs other than benzodiazepines should be avoided because of their seizure threshold lowering effect.

26.5.2.2 Periictal Psychiatric Manifestations

Preictal (*or prodromal, aura*) disturbances are common, and include irritability, apprehension, mood swings, depression, psychosis, and aggression lasting for several minutes, several hours, or days before a seizure (Blanchet and Frommer 1986). Olfactory hallucinations such as the smell of burning rubber are common aura of seizures. The preictal symptoms can wax and wane, but generally escalate up to the time of the seizure, which relieves the prodromal symptoms (Fenwick 1991a, b).

26.5.2.3 Postictal Psychiatric Conditions

Postictal psychiatric disturbances include diverse motor, somatosensory, autonomic, and cognitive deficits as well as psychosis, and vary in their duration. Some patients return to baseline immediately or within seconds to minutes, even after severe generalized or partial seizures. Others experience significant disability, and may not recover for several hours, days, or even weeks. Postictal psychiatric disturbances may occur either associated with delirium or in clear consciousness. The latter tend to resemble acute interictal psychiatric syndromes, but with a shorter duration, and sometimes a delayed onset following a lucid interval, especially in cases of postictal psychosis. Postictal syndromes tend to remit spontaneously, although antipsychotic medications may be necessary to control symptoms. After recovering from the postictal event, some patients become extremely distressed and worried that the psychiatric symptoms will persist (Kanner et al. 1996; Marsh and Rao 2002).

Postictal psychosis occurs in up to 10 % of patients (Lancman 1999; Marsh and Rao 2002) and tends to develop several hours to a few days after a seizure. The symptoms may include delusions, hallucinations, thought disorder, or manic or depressive mood. Recognition is critical since threatening delusions or hallucinations can result in aggressive or self-destructive behaviors. Relative to interictal psychosis or postictal confusion, there is greater potential for well-directed violent behavior or suicidality. The known risk factors for postictal psychosis include bilateral interictal epileptiform discharges, an aura of ictal fear, a long duration of epilepsy before the onset of postictal psychosis, and the presence of gross structural lesions (Marsh and Krauss 2000; Marsh and Rao 2002).

26.5.2.4 Interictal Psychiatric Conditions

There is an overall higher rate of psychiatric disorders in epilepsy patients compared with the general population (Jones et al. 2011). While more psychiatric disturbances are associated with temporal lobe epilepsy, they can occur in any type of epilepsy. Many factors including the severity of the seizure disorder, cognitive function, and medications including seizure medications may affect the psychiatric symptoms. (Schwartz and Marsh 2000).

Interictal Mood Disorders range from transient episodes of low or elevated mood to persistent mood disorders associated with neurovegetative signs and symptoms such as changes in sleep, appetite, energy, and concentration. *Depression* is quite common in epilepsy patients, especially in temporal lobe epilepsy (Sanchez-Gistau et al. 2010). Depression is also common following surgery for epilepsy, especially in patients with preexisting depression. However, de novo depression following surgery has been reported in about 20–25 % of patients (Foong and Flugel 2007; Garcia 2012). Suicide rate is also increased in patients with seizure disorder (Hesdorffer et al. 2012).

Anxiety symptoms are more common in seizure patients than in general population.

Psychosis may be present in about 7 % of interictal patients (Marsh and Rao 2002).

Reported risks include bilateral temporal foci, seizure clustering, a relative absence of past febrile convulsions and structural imaging abnormalities. Persistent interictal psychoses often involve delusions, usually paranoid or religious in nature, and visual and auditory hallucinations. There is extensive overlap in the phenomenology of nonepileptic schizophrenic syndromes and chronic interictal psychosis (Marsh and Rao 2002).

26.5.2.5 Psychiatric Complications of Antiepileptic Drugs

Antiepileptic drugs may be associated with psychiatric side effects, which may be both negative and positive. Among the older drugs, there seems to be a link between barbiturates and depression, whereas carbamazepine and valproates have mood stabilizing and antimanic effects. Among the newer drugs, vigabatrin, tiagabine, and topiramate have been linked to treatment-emergent depressive symptoms, whereas levetiracetam has been associated with psychosis, dysphoria and mood lability. There is controversial evidence that there may be an increased risk of suicide and suicidal ideation in patients receiving seizure medications (Mula et al. 2013).

Treatment emergent psychiatric conditions associated with antiepileptic drugs
Depression
Barbiturates
Tiagabine
Topiramate
Vigabatrin
Zonisamide
Psychosis
Ethosuximide
Levetiracetam
Phenytoin (toxic levels)
Topiramate
Vigabatrin
Zonisamide
Irritability/emotional lability
Felbamate
Lamotrigine
Levetiracetam

(Based on Mula et al. 2013).

26.5.2.6 Treatment of Psychiatric Syndromes in Epileptic Patients

Drug treatment of epileptic patients should take into account the potential lowering of seizure threshold of the psychotropic medication. Among *antidepressants*, the highest relative risk for seizures occurs with high therapeutic doses of buproprion, clomipramine, and maprotiline and the lowest relative risk occurs with the SSRIs and mirtazapine. *Antipsychotic* agents are associated with a 1 % risk for seizures (Lancman 1999). Among first generation antipsychotics, high potency agents such as haloperidol have a lower risk than low potency drugs such as chlorpromazine. *Clozapine* may cause epileptiform EEG abnormalities and is associated with a dose-related higher risk for seizures. Valproate is commonly used to treat clozapine-induced seizures in nonepileptic schizophrenic patients.(Marsh and Rao 2002)

Carbamazepine should not be used together with clozapine because both have potential risk of agranulocytosis. Recently, the USA FDA has made a labeling change to the drug information contained in carbamazepine. Owing to recent data implicating the HLA allele B*1502 as a marker for carbamazepine-induced *Stevens-Johnson syndrome* and toxic epidermal necrolysis in Han Chinese, the FDA recommends genotyping all Asians for the allele (Ferrell and McLeod 2008). This allele is also found in Europeans in up to 5 % of the population (McCormack et al. 2011).

Newer second generation antipsychotics, such as aripiprazole, risperidone, olanzapine, quetiapine, and ziprasidone are less likely to reduce the seizure threshold (Marsh and Rao 2002; Swainston Harrison and Perry 2004).

Benzodiazepines are used to treat anxiety and they reduce the likelihood of seizure activity. Buspirone lowers seizure threshold in animals and is contraindicated in epileptic patients in British formularies (Marsh and Rao 2002).

Psychotherapy may effectively deal with the anxieties and stigma associated with seizure disorder, and to enhance coping abilities of patients. Cognitive-behavioral therapy, supportive therapy, and group therapy can be useful for anxiety,

depression, and demoralization associated with epilepsy (Dorwart 1984; Cobb 1985; Taube and Calman 1992). Stress management and diet (e.g., modified Atkins diet) may also be effective in reducing the frequency and severity of seizure disorders (Panjwani et al. 1995; Dilorio et al. 1997; McPherson and McEneny 2011; Sharma et al. 2013). Psychoeducation, particularly for epileptic children and families, may be helpful (Aliasgharpour et al. 2012; Brabcova et al. 2012; Noble et al. 2012).

26.5.2.7 Psychogenic Nonepileptic Seizures (PNES)

Consultation-liaison psychiatrists are often asked to evaluate and treat patients suspected of having psychogenic nonepileptic seizure (PNES). PNES often occurs in patients who have history of somatization and under psychologically stressful conditions. Stress may also trigger epileptic seizures and in a recent study. Video EEG monitoring is a definitive diagnostic tool for PNES, but in a recent study, 17 % of patients with PNES also had comorbid epileptic seizures (Asadi-Pooya and Emami 2013). Once PNES is diagnosed, informing the patient of its nature, and providing stress management may drastically reduce recurrence of episodes (Reuber et al. 2005; Arain et al. 2007; Razvi et al. 2011).

26.6 Communication with Patients Who Are Unable to Speak

In the ICU and other acute care settings, psychiatric consultation may be requested for patients who are intubated, heavily sedated, or have other difficulties in communicating. In patients who are heavily sedated or delirious, the extent of sedation/delirium/coma should be ascertained, but a definitive consultation should be postponed until the patient's mental status improves. One important consideration about patients who have communication difficulty (including delirium, stupor, and coma) is that they are likely to be able to hear (and mishear) what others say, although they may not be able to respond or ask questions. One should choose one's words carefully, and not say things the one would not wish the patient to hear.

With an intubated patient, or patients with severe dysarthria, communication may be achievable through writing, or pointing to letters on an alphabet board or keyboard. Specialized computerized communication devices for intubated patients may be available (Etchels, Macaulay et al. 2000). A signal may be agreed upon at the outset of the interview, such as nodding, raising a finger, or blinking, to indicate yes and no, and the consultant may ask leading questions to obtain basic information, such as, "Are you in pain?" "Are you in a hospital?" "A hotel?" "Are you feeling depressed?"

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Chronic Conditions, Lung Disease, Cancer, the Palliative Care Settings, and the Dying Patient

27

Hoyle Leigh

Contents

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27.1 Vignettes

1. A 50-year-old man was referred for psychiatric consultation because he refused a surgical procedure. He also had visual hallucinations of old friends and angels that were comforting for him. The patient was a homeless man who was brought in by the police after he was found on the street lying in a puddle of blood. He was bleeding from the rectum, was found to have a large rectal mass with extensive involvement of other pelvic structures. A hemicorpectomy was proposed, which the patient refused. The psychiatric consultant determined that the patient understood the nature, benefits, and risks of the proposed operation. As the hallucinations were comforting rather than frightening, no antipsychotic drugs were administered. Sufficient pain relief was recommended. The patient died in his sleep several days later.
2. An 84-year-old man who was recently placed in a nursing home was found with a plastic bag over his head in a suicide attempt. He was brought to a psychiatric facility, and then transferred to the general hospital as he was bedbound. His medical history revealed metastatic prostate cancer. The general hospital medically cleared him, as no immediate treatment for the carcinoma was planned. The nursing home refused to take the patient back because of his suicidal ideation. He was depressed, felt hopeless, and wished to die.

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The psychiatric consultant interviewed his wife, who told her that the patient was a self-made man, who was always independent, and she wanted nature to take its course. She was willing to have her husband at home, but had problems with constantly changing caregivers; also the bathroom door was too narrow to accommodate the patient's wheelchair. The consultant arranged a meeting with family, the responsible physician, and the social worker, in which arrangements were made for the patient to be cared for at home with a more reliable caregiver, and to provide a commode at the bedside. He was prescribed methylphenidate 5 mg in the a.m. and fluoxetine 20 mg in the a.m. The patient felt relieved when hearing these plans, and at follow-up a month later he was quite energetic with no symptoms of depression.

3. A 35-year-old woman was admitted for an overdose of sedatives in a suicide attempt. The patient was diagnosed with metastatic breast cancer about a year previously, and as she was experiencing increasing bone pain, she decided to take her "exit pills." As she survived the suicide attempt, she was interested in discussing the meaning of her cancer with the psychiatric consultant. Eventually, the patient became an outpatient of the consultant, who, at the patient's request, did a weekly exploratory psychotherapy. She gained insight concerning the meaning of the cancer in view of her own personal history, and died in about a year's time, feeling more in control with herself during the dying process.

27.2 The Chronically Ill and Disabled Patient

Chronic patients, patients with permanent disability, with chronic diseases such as obstructive lung disease, and the terminal patients all have in common the fact that their medical condition cannot usually be reversed. Such patients often engender a feeling of helplessness in the physician.

Physicians are trained to seek out the cause of the illness and cure it, and patients who do not fit this model are frustrating indeed. The physician must recognize that there is a need for a role adjustment, from that of an active fighter against disease to that of a comforter, in dealing with chronic and palliative care patients. This involves accepting that the patient's condition is not reversible, and, in terminal patients, letting go while providing maximum pain relief and comfort. Many physicians feel uncomfortable with this role adjustment, and may unconsciously tend to avoid or neglect such patients, or use heroic measures to "save" the patient (as in the first vignette above). The role of the consultant, then, is to help reduce the discomfort on the physician's part so that optimal medical care can occur.

27.3 Demoralization Syndrome

A term first coined by Jerome Frank (Frank 1961; Frank and Frank 1991) is often seen in chronic or palliative care settings, and is characterized by hopelessness, loss of meaning, and existential distress. It is associated with chronic medical illness, disability, bodily disfigurement, fear of loss of dignity, social isolation, feelings of dependency on others, and the fear of being a burden. Because of the sense of impotence or helplessness, many with the syndrome predictably progress to a desire to die or to commit suicide (Clarke and Kissane 2002; Clarke et al. 2005; Kissane et al. 2001). Demoralization syndrome is not an official DSM diagnosis and has many features of depression but it occurs in the context of medical disease and it is not usually accompanied with anhedonia, and patients with this syndrome may still feel hopeful and experience positive emotions if aspects of the disease, such as pain, are effectively treated. The physician can validate the patient's experience through empathic listening and enhance the patient's coping skills and resilience (Jacobsen et al. 2007). Stimulants such as methylphenidate or dextroamphetamine may be effective for patients with demoralization syndrome and provide some boost of energy as well as better appetite and sleep. (as in Vignette 2 above) (see Chaps. 8 and 15).

Psychiatric consultation may be requested on chronically ill and disabled patients for evaluation of comorbid psychiatric illness per se, psychological reactions to the chronicity, or disability such as demoralization and depression, for issues concerning possible addiction to pain or antianxiety medications, noncompliance with a chronic regimen (such as insulin self-administration), and suspicion that the patient is unwilling to get better. Any comorbid psychiatric conditions, if diagnosed, should be treated appropriately with psychopharmacologic agents when indicated, keeping in mind possible drug interactions with the medical condition.

Psychotherapeutic approaches for adjustment to chronic illness and disability include support groups, supportive psychotherapy and problem solving, and cognitive-behavioral therapy. Physical therapy is often an excellent psychotherapeutic tool as it instills a sense of hope and expectation for improvement or recovery. Web sites are available for most chronic illnesses and disabilities and can provide excellent educational material as well as information about support groups.

The issue of possible addiction to pain medication is discussed in Chap. 22. As for addiction to antianxiety agents, particularly benzodiazepines, the consultation liaison psychiatrist often encounters patients who have withdrawal symptoms in the hospital setting when they were receiving much higher doses chronically prior to admission (Fontaine et al. 1984). Such withdrawal symptoms may be seen by the medical staff as excessive anxiety. Caution is needed in elderly patients because benzodiazepines may cause sedation, disinhibition, delirium, and falls. Interactions with narcotic analgesics and alcohol should be kept in mind.

For chronic patients with liver, kidney, and HIV, see respective chapters on these topics.

27.4 Lung Disease

27.4.1 Asthma

The prevalence of asthma appears to be increasing, and about 300 million persons in the world suffer from it (Masoli et al. 2004).

While the notion that psychological factors are etiologic in bronchial asthma as one of the "classical psychosomatic diseases" is no longer accepted, psychological stress is well known to predispose to and trigger acute asthmatic attacks (Humeniuk et al. 2003; Iamandescu and Mihailescu 2008; Joachim et al. 2003).

Depression has been reported in as much as 50 % of patients with bronchial asthma (Mancuso et al. 2000). Depression in asthmatic patients may be associated with an increased risk for sudden death (Zielinski et al. 2000). Suicidal ideation was found to be increased in the asthmatic population compared to general population (Goodwin and Marusic 2004). Depression and anxiety tend to adversely affect both asthma control and quality of life and thus treating these conditions may improve both asthma and their quality of life (Urrutia et al. 2012).

Anxiety symptoms such as chest tightness and choking sensations are common in patients with both anxiety and asthma. Anxiety disorders in general, including generalized anxiety and panic disorder are more common among asthmatics than in general population (Goodwin et al. 2003). The close relationship between anxiety and asthma may be related to hyperventilatory panic attacks arising from an innate emotional response to severe breathlessness (dypenea-fear theory) (Ley 1989). Stress may also trigger vasoconstriction through vagal stimulation in certain individuals (Lehrer et al. 1993).

The mental health of children, as well as that of their caregivers, was closely associated with predicting morbidity in children with asthma (Weil et al. 1999).

Treatment of depression and anxiety should include psychosocial modalities such as stress management, relaxation training, psychoeducation, cognitive behavioral therapy, as well as phamacotherapy. Beta-blockers such as propranolol are generally contraindicated in bronchial asthma patients. Antidepressants such as bupropion, mirtazapine, SSRIs, and SNRIs have been used widely in asthma patients (Brown et al. 2007; Krommydas et al. 2005). There have been reports, however, of overdose of SSRI resulting in serotonin syndrome precipitating an asthmatic attack (Carson et al. 2000). Antianxiety agents such as

benzodiazepines may be used to control acute anxiety symptoms in asthmatic patients (DeVane et al. 1998). There is one report of clonazepam relieving myoclonus caused by hypoxia due to prolonged asthmatic attack (Chee and Poh 1983).

27.4.2 Chronic Obstructive Lung Disease (COPD)

COPD is an essentially irreversible and progressive disease of air flow limitation in the lung caused by small airway disease and parenchymal destruction. COPD develops most often in long-term smokers, and is currently the 4th leading cause of death in the United States, afflicting about 14 % of adult population, and is expected to be the third leading cause of death globally by 2020 (Rabe et al. 2007). Depression, anxiety, and psychosis are significant factors in the morbidity and mortality of COPD, and COPD itself is a significant risk factor for psychiatric symptoms.

27.4.2.1 Depression

The life-time risk for depression in COPD patients is considered to be about 40 %, rising to about 60 % in severe COPD patients, and among patients who recently recovered from an acute exacerbation of COPD, the prevalence ranges from 19 to 50 %.

There is a bidirectional relationship between depression and COPD. As with schizophrenia, the higher rates of smoking seen in patients with depression could lead to the higher prevalence rate of COPD in depressed patients (Jain and Lolak 2009).

COPD may also be a risk factor for depression; chronic hypoxemia in COPD may lead to disruptions of noradrenergic and dopaminergic synthesis, release, and restoration that may ultimately lead to depression. Chronic hypoxemia may also lead to poor oxygenation in the periventricular and subcortical regions of the brain, which are vulnerable regions to hypoperfusion, and lead to similar brain changes as seen in patients with depression (Norwood 2006). The lower quality of life and decreased functioning capacity of COPD patients may also lead to depression.

27.4.2.2 Anxiety

As with depression, there is a bidirectional relationship between COPD and anxiety. As in depression, smoking plays a significant role in patients with anxiety. Panic disorder is a significant risk factor for nicotine dependence, and is associated with negative thoughts related to the illness, such as perceiving it to be long lasting, having a greater impact on daily life, and having worse consequences (Howard et al. 2009; Sartor et al. 2008). There may also be common pathophysiology between COPD and anxiety, such explanatory models include hyperventilation model, carbon dioxide hypersensitivity model, and cognitive-behavioral model (Mikkelsen et al. 2004).

27.4.2.3 Schizophrenia

Patients with schizophrenia may be more likely to have COPD (Carney et al. 2006). The increased COPD rate may be attributed to the increased smoking rates among schizophrenics, suggesting a "self-medication" hypothesis that stimulation of central nervous system (CNS) nicotinic cholinergic receptors may improve the negative symptoms of schizophrenia as well as overcome the dopamine-blocking effects of antipsychotics causing anhedonia (Dalack et al. 1998). Thus, second generation antipsychotics that have less D2 blocker activity, and especially aripiprazole which has a partial dopamine agonist action, may reduce nicotine dependence in schizophrenic patients (Brown et al. 2012; Kim et al. 2010; Ramaswamy and Bhatia 2006).

27.4.2.4 Treatment of Psychiatric Syndromes in COPD

Antidepressants including bupropion, SSRI, SNRI, and mirtazapine seem to be well tolerated in COPD patients. Drugs with strong anticholinergic side effects such as tricyclic antidepressants should be used with caution in COPD patients due to their mucus drying as well as potential cardiotoxic effect.

Cognitive behavioral therapy (CBT) has also been used effectively to treat depression in COPD patients (Hynninen et al. 2010).

Antianxiety agents are often necessary in treating anxiety associated with COPD but

benzodiazepines are often avoided as first-line therapy in COPD because of their potential respiratory drive depressive effects. Clinically, this is primarily a concern in patients who have COPD, who retain carbon dioxide (CO_2). Buspirone, which does not have the sedating effect may be effective in relieving anxiety in some patients. SSRIs are considered to be first-line therapies for anxiety disorders (Shanmugam et al. 2007).

Pulmonary rehabilitation can improve anxiety, health status, exercise tolerance, dyspnea intensity, and quality of life in COPD patients. Such a rehabilitation program is relatively inexpensive and well tolerated by patients (Guell et al. 2006; Kayahan et al. 2006).

27.5 Cancer

Until relatively recently, the diagnosis of cancer was almost tantamount to the diagnosis of a terminal disease. With recent advances in cancer detection and effective treatment modalities, however, many cancers are now considered to be either curable or, even in metastatic cases, chronic diseases with varying prognosis. Over two-thirds of some 11.4 million cancer patients in the United States can expect long-term survival (Irwin et al. 2013). In spite of this, many patients and their families still have the notion that cancer means death. Thus, an important role of the psychiatric consultant for the cancer patient is to ascertain the degree of information the patient and family have about the disease, the effectiveness of communication between the patient and the health care team, and the educational needs of the patient and family in relation to treatment and prognosis concerning the disease.

Clinical depression and anxiety are the most common causes of distress in cancer patients. Estimates of prevalence range between 5 and 50 %, depending on the screening method, diagnostic criteria used, and timing of assessment. In one study, 30 to 40 % of oncology, hematology, and palliative care patients experienced some combination of mood disorder, including depression, anxiety, adjustment disorder, or dysthymia. The results did not differ between the palliative and nonpalliative setting, and there were no consistent effects of age or gender, reinforcing the importance of vigilance for mood symptoms in all patients and at all stages of treatment (Artherholt and Fann 2011).

27.5.1 Anxiety

In a large-scale study of adult outpatients at a tertiary cancer center, 34 % endorsed clinically significant anxiety symptoms (Brintzenhofe-Szoc et al. 2009). Anxiety can range from mild to severe and fluctuate at critical points, such as before or after receipt of test results. If anxiety is both excessive, distressing, and impairs function significantly, an anxiety disorder should be considered. In one study of cancer care settings, adjustment disorders were present in about 20 %, and anxiety disorders in 10 % (Mitchell et al. 2011).

27.5.2 Depression

The estimated prevalence of depression was, in one metaanalysis, 5 to 16 % in outpatients, 4 to 14 % in inpatients, 4 to 11 % in mixed outpatient and inpatient samples, and 7 to 49 % in palliative care. Studies which used expert interviewers (psychiatrists or clinical psychologists) reported lower prevalence estimates (Walker et al. 2012).

Prevalence of depression varies based on the type of cancer involved, with depression rates generally reported to be highest for pancreatic, oropharyngeal, and breast carcinomas and lowest for lymphoma, leukemia, and gastric cancers. As with medical illnesses in general, rates of depression in cancer patients increase as disease severity intensifies (Raison and Miller 2003).

Symptoms of depression, including low mood, loss of interest in usually pleasurable activities, feelings of hopelessness or guilt, or suicidal ideation, are particularly important in recognizing depression in cancer patients. Neurovegetative symptoms such as fatigue, anorexia, weight loss, and sleep difficulty may be less reliable indicators of depression in cancer patients, as these

symptoms may be directly associated with cancer or its treatment such as chemotherapy.

Depression may be particularly prevalent in palliative settings. Risk factors for depression include younger age, antidepressant use at baseline, lower self-esteem, hopelessness, physical illness burden, and proximity to death. Approximately 15 % of palliative cancer patients have major depression (Rayner et al. 2011). Depression symptoms were three times more common in the final 3 months of life compared with a year or more before death (Lo et al. 2010).

Recent data on risk of *suicide* in cancer patients revealed that the prevalence of suicidal ideation may be comparable to that of the general population but that prevalence of completed suicide is elevated in patients with cancer. Based on a large retrospective analysis of Surveillance, Epidemiology, and End Results (SEER) data, the risk of suicide may be highest in the first year, and particularly high in the first month, after cancer diagnosis. Risk factors for suicide include clinical depression, demographic factors such as older age and lack of social support, and factors related to the patient's illness, e.g., disease progression (Artherholt and Fann 2011).

27.5.3 Cytokines, Sickness Behavior, and Depression

In addition to the psychological stress of being diagnosed with cancer and of the unpleasant effects of cancer treatment, certain biochemical substances associated with cancer may contribute to depression.

Proinflammatory cytokines released during tissue damage and inflammation have been shown to affect neurotransmitter function, neuroendocrine function, and behavior (Dunn et al. 1999). The cytokine-related behavioral changes, called *sickness behavior*, include many features that overlap with major depression including anhedonia, fatigue, anorexia, weight loss, sleep disturbance, cognitive disturbance, social isolation, and decreased libido.

Thus, the cytokines released by the neoplastic process, as well as in treating the cancer, may contribute to the symptoms of depression in cancer patients. At least in one study, pretreatment with an SSRI resulted in a reduction in the occurrence of serious depression in melanoma patients receiving interferon-alpha therapy (Musselman et al. 2001).

27.5.4 Treatment of Anxiety and Depression in Cancer Patients

Interdisciplinary rehabilitation programs that include relaxation training, exercise, and individual and group psychotherapy have been shown to be effective in reducing emotional stress and improving the quality of life in cancer survivors (Braam et al. 2013; McClellan 2013; Walker et al. 2013). Hypnosis has been used effectively in treating nausea and vomiting in chemotherapy patients (Richardson et al. 2007).

27.5.4.1 Drug Therapy

There is conflicting evidence concerning whether antidepressants such as SSRIs and tricyclics have either detrimental or beneficial effects in cancer. A recent review suggests that antidepressants, particularly fluoxetine, may activate the immune system and induce apoptosis in tumor cells (Frick and Rapanelli 2013).

According to a recent survey of cancer survivors, antidepressants are most commonly used in cancer patients (14 %), followed by antianxiety agents (6 %), and antipsychotics (2 %). Stimulants were used in about 1 % of patients (Punekar et al. 2011).

An important consideration in the drug therapy of anxiety and depression in cancer patients is that relief of contributing physical factors such as pain and discomfort with appropriate pain medications. This may be as important as treating the psychiatric symptoms per se.

In treating cancer patients with psychotropic medications, the physician should be mindful of possible interactions of the drug with anticancer drugs, as well as adverse side effects such as sedation, gastrointestinal side effects such as nausea, vomiting, and diarrhea, anticholinergic

effects, and sedation/respiratory depression. For example, in breast cancer patients who receive tamoxifen, a prodrug that becomes active only when metabolized, drugs that inhibit cytochrome p450 2D6 such as fluoxetine, paroxetine, bupropion, and duloxetine should be avoided. Drugs that do not inhibit 2D6, such as mirtazapine, sertraline, escitalopram, and venlafaxine may be used (Andrade 2012).

On the other hand, some side effects may be beneficial. For example, antihistaminic side effects of olanzapine and mirtazapine reduce nausea and increase appetite, as well as enhance sleep, and are effective in cancer chemotherapy patients (Kast and Foley 2007). Duloxetine has been shown to be effective for neuropathic pain in cancer patients (Matsuoka et al. 2012; Torta et al. 2011; Yang et al. 2012).

Bupropion may be helpful in treating fatigue and sexual dysfunction of cancer patients (Breitbart and Alici-Evcimen 2007; Mathias et al. 2006; Moss et al. 2006).

Psychostimulants such as methylphenidate, amphetamine, and modanafil may be useful in increasing energy and improve cognitive function in cancer patients with fatigue (Breitbart and Alici 2010; Joly et al. 2011; Minton et al. 2011).

27.6 The Dying Patient and Palliative Care

Health care professionals are naturally reluctant to disclose to their patients that they are dying—that the professional is powerless to prevent the inevitable. In this information era, however, health care professionals are ethically and legally required to disclose all important medical information to the patient. In making these disclosures, the ethical principle of beneficence suggests that physicians should disclose information in a way that benefits and does not harm patients (see Chap. 10). Surveys of terminally ill patients show that most patients do want to know the truth about their illness (Kelly and Friesen 1950; Noone et al. 2000; Seo et al. 2000).

For the terminally ill patient, the most important *approach* for the consultant to keep in mind is that, from the patient's perspective, here-and-now comfort, relief of pain, and small pleasures including not having to think about his or her terminality are the important concerns. Elisabeth Kübler-Ross (1969) proposed that there are five stages of psychological adaptation to dying: denial and isolation, anger, bargaining, depression, and acceptance. Though these stages are useful in understanding dying patients who show one or more of the characteristics of these stages, the health care professional should be aware that these stages do not necessarily occur in sequence, and, in fact, many patients may never undergo some of the stages, such as bargaining or acceptance. Some patients may adaptively fight to the end, even by engaging in an exploratory psychotherapy (as in vignette 3) (Leigh 1974).

For some patients, having the option or means of suicide, such as consulting the book *Final Exit* (Humphry 2002), gives a sense of mastery and control so that they gain the courage to live for today in spite of pain and discomfort. Thus, the possession or acquisition of a lethal medicine or weapon is not ipso facto evidence of immediate suicide risk requiring psychiatric certification. Executing an advance directive, appointing a durable power of attorney, and drawing up a will all provide a sense of mastery and autonomy for the terminal patient. Pleasurable activities and any distraction from illness should be encouraged for the terminally ill patient.

Patients' individual coping strategies should be respected and supported. Thus, one patient may choose to avoid discussing the disease and prognosis entirely, while another may read voluminously about the disease and become an expert in it, and another may find solace in philosophy or literature. Patients should be asked about whether they would like visits by clergy.

There is controversial evidence that psychotherapy may prolong survival of metastatic cancer patients (Chow et al. 2004; Goodwin et al. 2001; Spiegel et al. 2002), but there is a consensus that psychotherapy and psychoeducation can reduce the pain and depression associated with terminal cancer (Boesen and Johansen 2008, Daniels and Kissane 2008, Kissane 2009).

Many terminal patients feel comforted by simply being with another human being. For dying patients with no relatives or friends, volunteers can provide needed support and nonprofessional human contact. Where applicable, pets can also provide comfort and companionship, as well as a sense of usefulness for the patient.

For further discussion of psychotherapeutic (particularly "narrative") approaches for seriously ill patients, see Psychosocial Treatments Relevant to Consultation-Liaison Psychiatry in Chap. 29.

Hospice care, either as an inpatient or as an outpatient, may be particularly helpful for the terminally ill patient as it can provide expert care and support for both the patient and the family.

Pharmacologically, immediate comfort and pain relief is the utmost goal of treatment, even if there is attendant risk of delirium, respiratory depression, and other consequences. Narcotic analgesics, which are also good antianxiety agents, should be administered liberally, as well as antianxiety and antidepressant drugs as needed. Historically, the Brompton cocktail, consisting of morphine, cocaine, and alcohol, had been used in Great Britain for treatment of pain in terminal cancer patients (also used in modified form in many hospices). As one oncologist remarked, "There is no drug test at the pearly gate to Heaven."

27.7 Care of the Caregivers

The caregivers of seriously chronically ill and dying patients suffer from as much, if not greater, stress as the patients themselves. Epel et al. (2004) showed that healthy mothers who cared for chronically ill children showed premature cellular aging (telomere shortening) in proportion to the number of years of such caring, and cellular aging also correlated with the amount of perceived stress.

A recent study showed that depression among the caregivers of terminal cancer patients was high—63 % percent of females and 38 % of males had depression. Factors independently associated with mood disorders included emotional burden, problems in social involvement, and nonattendance of meeting places; help and assistance from public local services (for patients) decreased the risk of mood disorders in caregivers. Females, compared to males, were found to use emotional-oriented coping strategies more frequently (Mazzotti et al. 2012).

Psychiatric symptoms are common in caregivers of asthmatic children. Approximately 50 % of caregivers of inner-city children who have asthma have significant psychiatric symptom severity. Depression and anxiety disorders were much more common among asthma caregivers than in the general public. Additionally, depression in the caregiver was associated with a 58 % increase in unscheduled clinic visits by the child, and an anxiety disorder in the caregiver was associated with a 31 % increase in asthma-related hospitalizations for the child (Wade et al. 1997). Treatment of the depressed caregivers with antidepressants (sequential response dependent series of escitalopram, bupropion, and mirtazapine) resulted in significant reduction in the self-reported depression ratings of the caregivers as well as significant correlations between improvement in caregiver depression scores and quality of life in the caregiver as well as objective measurement of asthma-related symptoms and lung functioning in the child (Brown et al. 2008).

Psychological support should be provided for the caregivers of chronic and/or terminal patients, which may include support groups, classes, and scheduled holidays (with someone else taking over the caring). Enhancing a sense of coherence of the caregiver family member by the nursing staff may also be helpful in reducing or preventing depression and distress (Tang et al. 2012).

A recent review concerning the care of cancer caregivers (Applebaum and Breitbart 2012) showed that psychoeducation had positive impacts on caregivers' knowledge base and ability to provide care, and also led to improvements in psychological correlates of burden (i.e., depressive and anxious symptomatology) and patient functioning, even when patients were not the direct recipients of the intervention. Problem solving/skills building interventions were also largely successful in improving caregivers'

ability (and confidence in these abilities) to provide care, including the ability to assess and manage patients' symptoms, identify solutions to problems that arose during caregiving, and enhance their overall ability to cope with this role. Overall, the family and couples interventions led to clinically significant improvements in caregiver functioning, in addition to the functioning of the couple or family unit as a whole. CBT and IPT were also effective in reducing psychological distress in caregivers and patients. Combining elements of psychoeducation and support or communication skills training conferred multiple benefits for caregivers.

Respite care, which entails hospitalization of the patient for a short period during which the caregiver can rest and recoup, or day care for the patient, may be essential, especially for caregivers of patients with advanced dementia (Payne 2006; Miyashita et al. 2008; Ryan et al. 2008).

In one study, differences were found between the perceived needs of staff caring for terminal cancer patients and dementia patients. For caregivers of terminal cancer patients, listening to the family member, being available, creating a sense of security, and supporting the family after the patients' death were rated higher while for dementia, forming support groups for families, offering respite care, educating families, and relieving the family's feeling of guilt was rated to be more important (Albinsson and Strang 2003).

For the caregivers of patients with dementia, the issue of placement of the patient in a nursing home can bring much psychological conflict, guilt feelings, and indecision that may call for professional counseling. The psychiatric consultant, as well as the responsible physician, neurologist, or a member of the nursing home staff, can provide such counseling by discussing various options, what can be expected in the nursing home, and reassuring the caregivers that psychological conflicts and guilt feelings are universal in such situations, and that patients with advanced dementia are usually better cared for by professionals who are accustomed to meeting their specific needs.

Hospice care, either as an inpatient or as an outpatient, may be particularly helpful for the terminally ill patient as it can provide expert care and support for both the patient and the family.

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The Renal Dialysis and Kidney Transplant Patient

28

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Contents

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28.1 Introduction

Kidney disease is widespread and endemic. It is estimated in its latest available statistics that 27 million people in the US have chronic kidney disease (United States Renal Data System 2012). Its extreme form, renal failure (ESRD) is diagnosed in 117,000 people in the US yearly.

There are 86,000 people in the US waiting for a kidney transplant and 355,000 on form for dialysis. Medicare is the major payer for treatment of renal failure in the US for which it spends $47.5 billion yearly. Therefore, the treatment of renal failure is a major part of American medicine. In order for the behaviorally trained professional to make any depth impact in the study and/or treatment of these patients, he/she must have a working relationship with the nephrology staff (Levenson and Olbrisch 1993). Contact starts at the top of the nephrology/transplant surgery chain of command. If the relationship is to be anything more than an outside specialist rendering judgment, it is essential that one be accepted by the director of nephrology/transplant surgery as a member of the team (Cohen et al. 2005a). If so, then there may be a possibility for a true liaison relationship to develop. If not, then the relationship is most likely constrained to a limited consolatory one. Lest one be too optimistic about entering such a relationship, one needs to be reminded that, in general, resistance and at times hostility toward a behavioral view surrounding

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physical illnesses and their treatments can and often are great among physicians (Reichsman and Levy 1972).

There is a good body of research and clinical experience about the behavioral aspects of dialysis and renal transplantation because the kidney is the first vital organ that has been transplanted and the first for which there is a mechanism for its artificial substitution by dialysis. Nevertheless there is still a dearth of systematic, mutlisite studies. With these shortcomings in mind, the authors of this chapter will endeavor to tell the reader what are their major stresses, their various forms of treatment, the psychological problems of these patients and how the behaviorally trained professional may help these patients.

28.2 Forms of Dialysis and Stresses and Their Treatment

There are two forms of dialysis, hemodialysis and peritoneal dialysis. In the former, the patient's blood is delivered into the dialysis machine and separated from dialysis fluid via a semipermeable membrane. The processes of dialysis is an osmotic one in which compounds flow through a semipermeable membrane from the higher concentration side into the side of the membrane with a lower concentration of those substances. For example, if the ionic concentration of potassium is lower in the dialysate fluid than in the patient's blood, potassium will flow from the blood through the membrane and into the dialysate fluid (Parker 1992). In peritoneal dialysis, dialysis fluid is delivered via an abdominal fistula directly into the peritoneal cavity and the peritoneum serves as the semipermeable membrane. Careful consideration is given to what constitutes dialysis fluid. Of course, water is its main constituent. The selection of substances in the water involves a molecular size small enough to go through the membrane and substances that need to be removed and others replaced.

Dialysis, more so than any other form of medical treatment requires dependency on a machine, a procedure, and to a group of professional personnel. The very independent patient may therefore have difficulty tolerating dialysis. On the other side of personality types, the very dependent patient may derive some sort of satisfaction in such dependency making his/her rehabilitation back to work, school, or home activity more difficult. The medical-psychiatric liaison professional may aid the nephrology team early on in selection of a modality of treatment for renal failure (Levy and Wynbrandt 1975). In general, independent people do better in situations of less dependency such as renal transplantation, continuous ambulatory peritoneal dialysis, or home hemodialysis.

28.3 Psychiatric Complications and Their Treatment

28.3.1 Delirium

As defined (DSM-5 2013), delirium is a disturbance in attention and cognition usually developed over a short period of time. It is one of the most overlooked/underdiagnosed syndromes in the medically ill, especially in people with renal failure. Its many causes include that produced by medication and that by a medical condition. Dialysis patients are prone to many medical complications such as anemia, fluid overabundance, secondary hyperparathyroidism and uremia. Concerning the latter and its treatment, people with renal failure before and often during treatment are uremic. We know that it is not the overabundance of urea that causes this problem. For example, if one injects urea into an experimental animal it will not produce what we consider to be a uremic state. Rather, it is an accumulation of various toxic substances that are removed by a normal kidney that gives rise to it. Unlike the person with normal 24/7 kidney function, the dialysis patient is intermittently uremic, due to intermittent kidney-like function. Also, the process of dialysis in relatively rapidly shifting electrolytes and fluids may give rise to what is termed "disequilibrium syndrome" which is not uncommonly seen during and after dialysis runs.

28.3.2 Depressive Disorders and Suicide

Depressive and anxiety disorders are common complications of medical and surgical illnesses (Levy 1989). Most often the depressive disorders are precipitated by a loss that is real, threatened, or fantasized.

Patients with renal failure, especially those on dialysis sustain many such losses. Most never return to the outside work, household, or school activities they had prior to suffering from kidney failure (Cukor et al. 2013). The loss of a job is a major event in that it not only results in a loss of money, but it usually is associated with a loss of self esteem as well as a loss of the sense of masculinity in men and femininity in women. Further, patients on dialysis have a loss of personal freedom, a loss of independence, a loss of life expectancy, and a loss in their healthy appearance (Rosenthal et al. 2012). The medical regimen of these patients involves a loss of the freedom to choose the foods they like to eat and restraint in fluid intake (Gressel et al. 2014). There is usually a loss in appearance. Patients on dialysis usually have a change in their complexion in which they appear almost sun tanned, but not of a healthy looking brown. Because the avenue of access to the circulatory system involves the surgical creation of arterio-venous fistulas, both the scars of these procedures as well as the often snake-like bulging caused by the arterialization of the venous system compromises their appearance.

From the earliest days of dialysis, it was noted that the incidence of suicide in these patients seemed to be higher than in the general population or in other chronic medical illnesses. The earliest systematic study of this observation was conducted by Abram and his colleagues (Abram et al. 2001). They sent out questionnaires to all of the existing hemodialysis centers in the US at that time. With about half of the questionnaires returned and poor statistics as to comparisons, they, nevertheless concluded that suicide in dialysis patients was 500 times greater than in the general population. Although this study is a flawed one, in its somewhat dramatic conclusion it brought attention to the subject of suicide in these patient populations. To the best of knowledge of the authors of this chapter, there has been no valid study to date of suicide in dialysis or renal failure patients. The problem here is in the accuracy of statistics concerning suicide. To illustrate, in 1961 when the Nobel Prize novelist, Ernest Hemmingway left treatment for depression at the Mayo clinic and went home to Ketchum, Indiana and shot himself in his mouth, the coroner in that town registered his death as due to natural causes. Less dramatically, is not voluntary withdrawal from dialysis, a self-death? There is also a large gray area in people not adhering to diet and fluid restriction. These and other methods of self-destructive behavior, whether conscious or not border on methods of self-death.

Interestingly, when one looks as who does the act of suicide, one is confronted with interesting conclusions. For example, each year more New York City policemen die from suicide than in the line of duty. For the past several years more US servicemen and servicewomen die due to self-injury than in battle. Although there are no credible statistics, most would agree than more members of health professions kill themselves than the general population. The obvious reason seems to be that if the individual has a means of suicide at hand, there is a greater chance that the individual will meet his/her death by that means. This is the case of the dialysis patient. In years past when the portal of delivery of hemodialysis was the external arterio-venous shunts, many patients died by their disconnecting the arterial portion of their shunt. Now, as then, a method of suicide is going on a high potassium diet and/or not showing up for a few hemodialysis runs.

The accepted ideal treatment of the depressive disorders is by the use of antidepressant medications and psychotherapy. Unfortunately, the ideal and the practical treatment often do not meet in this group of patients. It has been observed and initially described (Reichsman and Levy 1972) that people with kidney failure are among the most resistive toward a psychological view of their lives. It is often rationalized by, "If you had my illness, you would be as sad as I am". Nevertheless, the more insightful patient may be amenable to a talking therapy. Cukor and his

associates have done some groundbreaking studies on modified cognitive behavioral therapy (CBT) on dialysis patients (Cukor et al. 2013). They have shown that this form of therapy reduces depressive affect, improves quality of life, and promotes treatment adherence well within statistical significance. Medication, namely antidepressants are usually more acceptable than talk because they adhere to the traditional medical model of illness and are viewed by many as less spooky than talking therapy. A discussion of their use appears later in this chapter.

28.3.3 The Anxiety Disorders

Where there is depression there is often anxiety as well (Cukor et al. 2007). But it may also exist by itself because anxiety is the body's protective mechanism against threats to its integrity, again real, threatened, and/or fantasized. The patient treated for renal failure has many potential reasons to be anxious. For the person who has been transplanted, there is the continual fear of organ rejection. Dialysis invokes many potential fears. Since the procedure involves continual removal of blood into an apparatus and then its return, there is always the possibility of blood loss. As previously mentioned the relatively rapid removal of electrolytes and fluid often produces a transient disequilibrium syndrome, making the patient borderline delirious and possibly anxious. In center hemodialysis units it is not uncommon to see major medical problems among fellow patients including cardiac emergencies and occasionally death of patient being dialyzed. In addition, changes in staffing and waiting for medical procedures usually are associated with anxiety. Quality of life is materially affected by anxiety (De Sousa 2008).

28.3.4 The Noncompliant and Aggressive Patient

When consultation-liaison psychiatrists or other behavioral professionals are asked to speak to a group of nephrology professionals, more often than not, the subject will be "the noncompliant patient". That observation underscores the commonality of this problem for nephrology staff. As to its definition, "noncompliance" is a subjective conclusion and may vary from one observer to another. It is being used in this chapter not to include the patient who is just annoying, questioning staff, or requesting second opinions, but rather to include the very distressing, extremely demanding person including people who continually does not adhere to their medical regimen to the extreme degree.

Two factors need to be considered in studying this subject. First, renal failure patients do not represent the crosssection of society. They are heavily weighted in the direction of lower class, impoverished people, those who did not adhere to their medical regimen as hypertensives and diabetics, and people with addictive disorders. The antisocial person is overrepresented in this group of patients. Therefore, one can see why these patients, as a group may be different from the general population or other people with chronic medical illnesses in adherence to diet and other aspects of the medical regiment of renal failure. The second factor is understanding how different personality types adjust or fail to adjust to chronic medical illness. As previously mentioned the very independent or very dependent patient will respond differently to different forms of renal failure therapy. Once again, we wish to underscore the importance of the behaviorally trained professional to be involved in advising nephrology staff as the selection of a modality of treatment that compliments the personality type of the individual. Again, the very independent person should be steered in the direction of self-care or transplantation. Factors that may be helpful in the treatment of noncompliant persons include an understanding that failure to adhere to the medical regimens will result in possible hospitalizations and, more likely, a decrease in life expectancy. When noncompliance involves missing dialysis runs or aggressive behavior, it is important for staff to maintain minimal tolerance for it. Again, early on, it is important for the unit to make it clear any behavior that affects the safety of staff and patients will be treated as a police matter. Further, chronic offenders including

people who repeatedly miss dialysis runs should be transferred to other units if feasible.

Case Vignette
A 64-year-old man had been on maintenance dialysis 3 times weekly and an outpatient dialysis facility for 4 years. One day he did not show up for dialysis. He was phoned at the boarding home where he lived, and he stated he was not coming in for dialysis anymore. He gave no further explanation. The unit social worker asked the psychiatric consultant to join her for a home visit to evaluate the patient. The patient gradually revealed that he was hurt and angry because the staff nurses had been giving him relatively little attention lately in contrast to that given a new patient. He stated that he believed the nurses did not want him coming in anymore. He was reassured that he was an important member of the dialysis community. This staff nurses, who had been completely unaware of the patient's feelings, were happy to provide increased attention and socialization with the patient. For this patient the main source of social stimulation was in the dialysis unit which had essentially become a surrogate family for him.

28.3.5 Sexual Dysfunction

Many years ago Belding Scribner, an early pioneer in treating chronic renal failure observed that one-third of men on dialysis were totally impotent, one-third are partially impotent, and one-third have no impotence problem (Levy et al. 1974). This led to a few studies, most of which were conducted by questionnaires that showed that Scribner was almost correct. When women were asked about their sexual functions, a significant group, but less than men, said that they had issues of sexual dysfunction, in particular, a decrease in libido and decrease in orgasm. Renal transplant patients also have similar problems with sexual function, but at a far lesser degree than dialysis patients (Levy 1973).

There are several modalities of treatment of sexual problems in these patients. Since depression is often closely associated with sexual dysfunction, the relief of depression can reduce and even cure sexual problems in a significant group of these patients. Masters and Johnson techniques (Masters and Johnson 1970) have been used with success on selected patients. In men, the use of agents that increase the release of nitric oxide in the corpus cavernosum of the penis such as sildenafil (Viagra) and similar medications have been received as a gift to many patients.

28.4 Pharmacology of Renal Failure

In addition to its discussion in this part of this chapter, pharmacology will also be discussed later on.

Pharmacokinetics refers to the factors affecting the passage of pharmaceuticals from their entry into the body to their excretion (Callaghan et al. 1999). The five phases of pharmacokinetics are given below in bold print. *Drug absorption* is crucial because it encompasses how much of the medication actually enters the body, usually via the gastro-intestinal system. Except in rare cases of gastroparesis or GI edema, both of which are associated with slower absorption, patients with renal failure do not have any significant change compared to those with normal kidney function. *Drug distribution* refers to the concentration of that medication in body tissues. The distribution will be increased in the cachectic patient and decreased in the edematous. *Protein binding* refers to the ability of the body to bind the drug to body protein, in particular albumin. The free, unbound portion of the drug is that which is therapeutically active. Renal failure patients have a significantly diminished ability to bind pharmaceuticals to body protein, thereby making more of the drug available for both therapy and toxicity. Since virtually all medications with the exception of lithium that are used by psychiatrist have a high degree of protein binding, the general rule is that one should not prescribe for renal failure patients more than three-fifths of the maximum dose given to those with normal kidney function.

Since, the major organ for *drug metabolism,* is the liver (again, with the exception of lithium), which eliminates metabolites in bile, making drug *excretion* an issue only in those few drugs such as lithium that are excreted by the kidney in urine.

With few exceptions, most psychologically active medications are fat soluble, pass the blood-brain barrier, are metabolized by the liver, and excreted by the bowel. One should use a lower than maximum dose of every drug used in renal failure patients than those with normal renal function. This axiom should be kept in mind in the description of medications mentioned below.

When used judicially, antidepressants may be an important part of the treatment of these patients. One must keep in mind that the major handicap in the use of tricyclic medications is the potential issue of overdose in a population with a high incidence of suicide. Because of the issue of suicide and because tricyclic antidepressants are very anticholergic, the SSRI's are preferred.

Although there is less data on the use of antipsychotics in these patients, they may be used with caution. One should keep in mind the issue of QT prolongation as one would in patients with normal renal function. There is a host of potential side effects of clozapine including the more recent interest in relatively high incidence of pericarditis in those receiving this medication. The data released in the CATIE studies (Lieberman et al. 2005) indicate some advantage in the use of the older typical antipsychotics because they have a longer track record than the atypicals.

Benzodiaazepines are commonly used for the short-term treatment of anxiety, but risks may exceed benefits if used daily over the long term (see Chap. 20). Lorazepam, which is removed by the kidney in those with normal renal function, reverts to hepatic metabolism with excretion in bile in kidney failure, and therefore may be used in these patients (Lam et al., 1997).

Among the mood stabilizers, lithium is a unique medicine, especially in its use in patients with renal failure. It is dialyzable and thereby removed entirely by the artificial kidney. It may be given as a single dose after each dialysis run and will be maintained at about the same concentration in the body because its avenue of excretion, the kidney is blocked in renal failure. When the patient is dialyzed lithium's small molecule passes through the semipermeable membrane and is eliminated. There is less data concerning the use of the antiseizure medicines, chief of which is valproate. However, experience has shown that they may be used in patients with renal failure (Levy 2000).

28.5 Withdrawal from Dialysis

Consulting psychiatrists may be asked to provide perspective and advice to nephrologists when their patients wish to forego or to discontinue dialysis, particularly in cases in which the treating physician is not comfortable with a patient's decision. The willful rejection of life-prolonging treatment is an emotionally laden issue, and cognitive dissonance between patient and physician may manifest itself in assertions of patient psychopathology or in questions about the patient's capacity to make this decision in an informed manner.

It is important in such consultations to understand that they occur at a time of cultural change in the dialysis community. At its emergence in the 1960s, dialysis was a self-limiting, scarce resource. This has changed, and with availability of dialysis no longer limiting its employment, patients and caregivers have since been forced to confront the limitations and the individual, social, and ethical consequences of the treatment itself (Russ and Kaufman 2012; Russ et al. 2007). A struggle to set informed standards for the initiation and maintenance of dialysis has ensued and is reflected in the nephrology and broader medical literature of recent years. This struggle has occurred in the context of larger social dialogues centering on patient autonomy, emerging models of collaborative medical decision-making, and death with dignity.

The survival curve for ESRD (Chronic Kidney Disease Stage 5) patients on chronic dialysis is not encouraging, particularly for those with substantial comorbidities (Cohen et al. 2006; Schell et al. 2013). According to the USRDS 2009

Annual Data Report, adjusted rates of all-cause mortality are 6.3–8.2 times greater for dialysis patients than for the general population (USRDS 2010). Older age, peripheral vascular disease, major neurocognitive disorder, low albumin, and treating nephrologists' subjective impressions of survivability are significant variables in near-term mortality. The latter is according to a validated model for predicting 6-month mortality among hemodialysis patients developed by Cohen et al. (2010). The rate of dialysis withdrawal is higher among the elderly, older, and presumably more fragile patients. These patients have been a rapidly growing segment of the dialysis population. This includes the very elderly (80 years and above), whose rate of dialysis initiation increased by 57 % between 1996 and 2003, and whose subsequent 1-year mortality was a sobering 46 % (Kurella et al. 2007; Swidler 2013). Russ and Kaufman (2012) noted that the initiation of dialysis was often a matter of passive acquiescence to physician advice on the part of older patients, commenting that "older patients generally accept dialysis treatment but do not choose it." This, of course, is none too solid a footing for treatment with uncertain long-term benefits. It is in this context that the American Society of Nephrology places explicit emphasis on a shared decision-making process between patients, families and physicians in initiating dialysis (RPA; Williams et al. 2012).

For those initiating treatment, dialysis even under the best of circumstances exacts its own considerable price, and at least a fifth of patients do ultimately withdraw. Existing data point to a steady increase in this proportion, with withdrawal rate varying by age, sex, and race/ethnicity (Renal Physicians Association and American Society of Nephrology 2010; Cohen et al. 1997; Kurella et al. 2010). The stage of illness at which any particular patient reaches a threshold for discontinuing dialysis is highly individual, and is further influenced by culture, religion, and family.

Unfortunately, despite an increased awareness in the field of the limitations of dialysis in time and tolerability, and of the need for anticipatory discussions of treatment goals and end points, only a minority of ESRD patients complete advanced directives. This potentially leaves physicians and surrogates with little concrete guidance if substituted withdrawal decisions must be made (Kurella et al. 2010).

In early studies on ESRD, voluntary cessation of dialysis was indiscriminately labeled as being a type of suicide (Abram et al. 2001). While ESRD patients do in fact have an increased risk of suicide compared to the general population, withdrawal from dialysis before death occurs much more commonly, and a distinction in the psychiatric literature between pathologically-driven suicide and rational treatment termination in dialysis patients has since been recognized (Kurella et al. 2005). Rational motives for a patient to refuse dialysis are legion. If they are not transplant candidates, chronic dialysis patients suffer significant discomfort, inconvenience, and progressive functional disability, in return for which they may sometimes expect a limited extension of life on the edge of uremia. The duration of such extended life is particularly small in older and sicker patients (Chandna et al. 2011) for whom standard palliative measures offer incomplete relief of physical symptoms while adding their own side effects to the overall burden of care. Loss of autonomy and quality of life for the poor prognosis patient can reduce the effect of chronic dialysis to a prolongation of the dying process (Brown 2012). Under such circumstances, withdrawal from dialysis is appropriate and permits the facilitation of a "good death," with comfort, dignity, and brevity (Cohen et al. 2005b).

Patients may also refuse dialysis for reasons that are pathological. As elsewhere described there is an impressive array of psychiatric disorders found in the chronic dialysis/ESRD population including, most commonly, depressive and anxiety spectrum disorders, followed by delirium and major neurocognitive disorder; psychotic and substance abuse disorders are also well-represented (Kimmel et al. 1993, 2007; Halen et al. 2012; Cukor et al. 2007). Kurella et al. (2005), drawing on data from the United States Renal Data System (RDS) and the Centers for Disease Control and Prevention, have described a higher rate of reported deaths by suicide among ESRD patients as compared with the general

population. Independent predictors include advanced age, male gender, white or Asian race, geographic region, substance dependence, and recent admission for mental illness. Risk for suicide was found to be highest in the first 3 months after initiation of dialysis, subsiding thereafter. Dialysis-dependent patients can also more passively take their own lives by missing treatments and medications, engaging in dietary indiscretions, and ignoring fluid restrictions. Rosenthal et al. (2012) found depressive affect as measured by the Beck Depression Inventory to be a significant predictor of mortality in a cohort of 130 urban ESRD patients on hemodialysis, with a concurrent, strong association noted between depression and medication nonadherence. Consulting psychiatrists are commonly asked to help distinguish pathological from benign motives in patients refusing dialysis and to guide physicians struggling with the decision of whether to honor or challenge these refusals. In such a consultation, the most important initial decision made by the psychiatrist is how stringent a test to apply for capacity.

The setting of a situation-specific standard for capacity by the consultant is substantially influenced by the perceived risks and benefits of the proposed dialysis and by whether a refusal can be considered medically reasonable under the circumstances. The consulting psychiatrist should discuss these case-specific issues with the treating nephrologist and should be aware that the Renal Physicians Association (RPA) deems it appropriate to withhold or withdraw dialysis under a number of circumstances. These include the direct request of acute renal failure or ESRD patients with decision-making capacity; incapacitated patients who have previously refused dialysis in oral or written directives, or whose legal agents refuse dialysis in their behalf, patients with irreversible, profound neurological impairment lacking evidence of awareness, thought, sensation, and purposeful behavior (RPA 2010; Cohen et al. 1997, 2003; Moss 2001). In addition, the RPA recommends consideration of forgoing dialysis for patients with a very poor prognosis or for whom administration of dialysis is unsafe—including patients with advanced major neurocognitive disorder who are unable to cooperate with the procedure itself (RPA 2010). One potential pitfall in the nephrology recommendations should be noted. From the consulting psychiatrist's point of view, it is troublesome to uniformly assign a low capacity standard for dialysis refusal to those patients who are uncooperative or combative with the dialysis procedure, as they may include individuals with psychotic, neurodevelopmental, or mood disorders that are potentially treatable. Likewise, the consulting psychiatrist must tread carefully around the determination of irreversibility of neurological impairment, being aware that it is not unknown for renal failure to precipitate catatonia (Huang and Huang 2010; Carroll et al. 1994).

In setting capacity standards, it is also helpful to refer to the degree to which patients' decisions are culturally endorsed and supported by family and loved ones. This is not to say that an individual patient's decision must be popular. Rather, it is to say that to the degree a decision to terminate dialysis conflicts with a patient's traditional values and imperils social bonds, suspicion of a capacity-altering mental illness should be heightened. In such cases, a more exacting examination of the patient's information-processing and reasoning is appropriate.

In addition to setting an appropriate threshold for decision-making capacity, it is important to be cognizant of the fact that psychiatric illness in and of itself cannot be equated with incapacity to refuse dialysis.

The existential, spiritual or developmental struggles at the end of life should not be unnecessarily labeled as pathological. Ambivalence and even anguish about relinquishing life-prolonging treatment is to be expected, and may also be found in those parties most intimately involved in the patient's life and care. Nonetheless, severe psychiatric disorders can be incapacitating and should be ruled out in cases of life-threatening noncompliance and early dialysis termination. Major depressive disorder, particularly when complicated by psychosis can readily interfere with an individual's ability to retain, weigh, and cognitively process information and should be suspected in clinically suspect dialysis refusals (Cohen et al. 2003). There are instances in which

it is appropriate and necessary to defer dialysis discontinuation while treating comorbid psychiatric illnesses (Cohen et al. 2003).

As previously noted, the concept of "shared decision-making" is now emphasized in dialysis decisions (RPA 2010; Williams et al. 2012). Often the need for a capacity determination is itself an indication of failure in a shared process that should ideally build consensus among stakeholders, including patient, family, physicians, and other significant caregivers (Cohen et al. 2003). A number of potential sources of conflict are described in the RPA recommendations, including miscommunication or misunderstanding about the patient's prognosis, participant values, interpersonal, and individual issues. From the psychiatric perspective, reframing a capacity consultation to focus on restoring dialogue between participants may be a more helpful intervention than seemingly vindicating one or another party. Where a consensus cannot immediately be reached, RPA guidelines suggest considering a time-limited dialysis. In the event of emergent circumstances, the RPA recommendations suggest providing dialysis with the consent of the patient or legal designate while allowing conflict resolution to proceed. The psychiatric consultant may be called upon to provide an emergent, temporizing capacity determination if such consent is withheld. It should be reiterated, however, that while shared decision-making and stakeholder consensus is the ideal, patients with intact decision-making capacity have the right to unilaterally refuse dialysis.

Once a decision has been made to withhold or terminate dialysis, it can be anticipated that lethargy, coma, and death will ensue within a mean time of 8 days. The International Dialysis Outcomes and Practice Patterns (DOPPS) study found that 79.1 % of patients died within 10 days of withdrawal (Cohen et al. 2006; Fissell et al. 2005). It has been traditionally taught that uremic deaths are gentle. However, retrospective, family-derived data have described severe pain in a preponderance of dying ESRD patients during the last week of life (Cohen et al. 2005a). This highlights the fact that psychiatric consultation does not necessarily end with the withdrawal of dialysis. The termination of life-prolonging treatment provides an opportunity for the psychiatric consultant to help smooth the transition of the patient's care to a primary goal of palliation.

28.6 Palliative Care

Patients with ESRD are defined by clinical suitability for dialysis or transplantation. These patients are an at-risk population for vascular events, with increased risks of acute myocardial infarction, congestive heart failure, and cerebrovascular accidents/transient ischemia and with accompanying graded increases in mortality from these conditions with advancing kidney disease (United States Renal Data System 2012). These patients are increasingly elderly with multiple comorbidities, entering ESRD with a median age of 65 (Cohen et al. 2006) and with a mortality rate eight times that of the general Medicare population (Werb 2011).

Prognosis in ESRD is felt by the Renal Physicians Association (2010) to be particularly poor for patients with at least two of the following: age 75 years or greater, high comorbidity, marked functional impairment, and severe, chronic malnutrition. The RPA (2010) now recommends prognostic estimates be provided to patients with Acute Kidney Injury, Stage 5 Chronic Kidney Disease (ESRD). Proximal causes of death in patients with renal failure are for the most part related to cardiovascular events, but septicemia, dialysis withdrawal, stroke, sequelae of calciphylaxis, and complications of diabetes are also represented in ESRD deaths (Werb 2011).

In addition, psychiatric syndromes, anemia, and diseases of bone, skin, and joints are frequently found. To this substantial burden of illness is added the systemic and growing effect of uremia itself, along with symptoms referable to treatment. Chronic pain in hemodialysis and ESRD patients is common, significant, and often ineffectively managed (Davison 2003, 2005).

Taking mortality and illness burden into account, dialysis patients are often appropriate for consideration of palliative care (Werb 2011; Davison 2003, 2005). Unfortunately, ESRD care

in the United States tends to be fragmented and poorly reflective of patient goals and prognosis, with uneven and inadequate access to palliative care resources (Kurella and Meier 2013).

28.6.1 General Issues in Renal Palliative Care

End Stage Renal Disease patients live with protracted somatic discomfort. As a group, patients have been described as suffering an average of 10.5 symptoms at any given time, including most prominently fatigue, pruritis, pain, cramps, sleep disruption, anorexia, and constipation (Merkus et al. 1999; Valderrqabano et al. 2001; Weisbord et al. 2003). Sexual dysfunction is also common and is discussed elsewhere in this chapter. Remedies are available for most symptoms, but are limited in efficacy and tolerability. Issues of comfort and palliation have a direct impact on the course of intercurrent psychiatric conditions. Consulting psychiatrists should be aware of some common issues in renal palliative care and should tailor interventions to add to patient comfort during life-prolonging treatment as well as during the dying process.

Fatigue is common and multifactorial in etiology. Sleep disturbance, anemia, physical deconditioning, and depression may contribute, in addition to hyperparathyroidism, uremia, and effects of dialysis itself (Murtagh and Weisbord 2010). Exercise, cognitive interventions, and other nonpharmacological measures should be integrated into treatment where possible (Murtagh and Weisbord 2010). Other nonpsychiatric issues such as hypothyroidism should be ruled out, and treatment of kidney disease-related anemia with erythropoietin-stimulating agents considered (Murtagh and Weisbord 2010). Existing psychotropic medications should be reviewed in order to minimize those with potential for contributing to sedation, anergia, and abulia. A psychostimulant like methylphenidate may be used symptomatically (Cohen et al. 2006).

Pain is reported by 50–63 % of dialysis patients (Cohen et al. 2006; Merkus et al. 1999), and may be even more prevalent among those who are dying (Cohen et al. 2005a). Pain may be acute or chronic, nociceptive, somatoform, visceral, neuropathic, or complex regional in distribution. Like sleep disturbance, pain in ESRD patients may have multiple potential etiologies, including the primary renal disease itself, comorbid conditions, downstream complications, or dialysis treatment (Davison et al. 2010). The Renal Physicians Association refers practitioners to an evidence-based tool for pain management in dialysis patients developed by the Mid-Atlantic Renal Coalition (MARC) and the Kidney End-of Life Coalition (2009). The Clinical Algorithm & Preferred Medications to Treat Pain in Dialysis Patients (http://www.kidneyeol.org/painbrochure9.09.pdf) provides specific recommendations on the use of non-opioid and opioid agents in CKD/dialysis patients, with opioids employed at moderate to severe pain levels. In considering these recommendations and the comments below, it should be borne in mind by the consulting psychiatrist that the use of narcotic analgesics in chronic, nonmalignant pain remains clinically controversial and potentially problematic. The employment of opioids is most clearly appropriate in the palliative management of patients suffering from pain due to end stage, time limited disease. Analgesic therapy in ESRD relies on the "analgesic ladder" developed by the World Health Organization. It proceeds sequentially from nonopioid with or without adjuvant therapy to weak opioid and ultimately to strong opioid levels of analgesia, maximizing each level in turn before moving to the next, with nonopioids and adjuvants accessible at all levels (Davison et al. 2010). Opioid dosages are individualized by effect and tolerability, rather than by standard dosing. Weak opioids can have dose limitations due to compound formulation with nonopioid agents like acetaminophen or by disproportionate adverse side effects at high doses (Davison et al. 2010). The use of opioids requires an active collaboration between physician and patient, including patient education and consent, reassessment of target pain symptoms, assessment, and description of observed symptomatic and functional benefits. One should monitor and manage opioid-related side effects, with appropriate

documentation. There is extensive literature to guide the physician in the choice and dosing of particular opioid agents in context of renal failure (Davison et al. 2010). Morphine is avoided in this population due to accumulation of its neurotoxic 6-glucuronide metabolite, which can lead to prolonged coma and myoclonus (Werb 2011). Meperidine cannot be recommended, given its neurotoxic metabolite normeperidine, with its potential for precipitating agitation, delirium, psychosis, and seizures, and its accumulation in renal impairment (Davison et al. 2010). Methadone may also bear watching from the standpoint of the consulting psychiatrist, given its potential for QTc prolongation and attendant risk of Torsade de Pointes (Krantz et al. 2002; Sekine et al. 2007). Davison et al. (2010) consider hydromorphone and fentanyl to be better alternatives among the strong opioid medications. It should be noted that psychotomimetic potential has been noted with mixed agonist-antagonist analgesics (butorphanol, nalbuphine, pentazocine) and that *N*-methyl-D-asparate (NMDA) antagonists might in theory be effective in hyperalgesia or loss of opioid effect (Inturrisi 2002). Adjuvant psychotropics are often added for management of neuropathic pain, especially tricyclics like amitriptyline and anticonvulsants like gabapentin. Although enterically metabolized, the usual caveats apply about the use of tricyclics in elderly patients and in those vulnerable to delirium, constipation, and seizure. The common comorbidity of renal failure and cardiac disease is also something to consider when prescribing tricyclics as adjuvants in dialysis patients, as well as the potential for a lethal outcome of overdose in this at-risk population. It should be noted that among tricyclics, desipramine is 70 % renally excreted; the drug and its 2-hydroxy metabolite can accumulate in renal failure and are not removed by dialysis. About half of protriptyline's elimination is by a slow renal excretion; it is also nondialyzable. Gabapentin is commonly prescribed in neuropathies. It is excreted unchanged in the urine; dosage must be adjusted downward for creatinine clearance and supplemental posthemodialysis doses must be given. Blood levels of carbamazepine and valproic acid need to be monitored. Carbamazepine is substantially dependent on renal excretion. Despite limited dependence of the drug on renal elimination, free valproic acid levels can be elevated in renal failure. Among the SNRI antidepressants, duloxetine has come into play as a treatment for pain related to diabetic neuropathy, along with fibromyalgia and chronic musculoskeletal pain. However, it is dependent on renal elimination and is contraindicated in renal failure.

Sleep disruption is common among ESRD patients, with a prevalence far higher than among the general population, ranging from 20 to 83 % in studies of dialysis patients (Murtagh and Weisbord 2010) and a high incidence of formal sleep disorders, including restless legs syndrome, periodic leg movements disorder, and sleep apnea has been documented (Cohen et al. 2006; Kimmel et al. 1997). Obstructive sleep apnea may be particularly prevalent among ESRD and dialysis patients, with resultant psychiatric and systemic comorbidities (Murtagh and Weisbord 2010) Iliescu et al. (2003) have documented a relationship between poor sleep quality as measured by the Pittsburgh Sleep Quality Index and depression among hemodialysis patients. Other than the standard methods of sleep hygiene and treatment of primary sleep disorders, the efficacy of symptomatic treatments for insomnia in uremic patients is not clear (Pieta et al. 1998). There is also additional risk in uremic patients of precipitating neuropsychiatric side effects with medications (Pieta et al. 1998; Sloand et al. 2004). Short-term treatment of insomnia with sedative hypnotics can be considered if sleep apnea is not present. These may include low to standard doses of zolpidem, temazepam, flurazepam and trazodone. In dialysis patients, particularly those with cardiac disease, it is worth noting that trazodone may contribute to hypotension and that trazodone-associated arrhythmias have been reported (James and Mendelson 2004). Triazolam at low doses is also considered a renal hypnotic. Its potential for inducing rebound insomnia, anterograde amnesia, and behavioral disinhibition is likely no greater than that of other benzodiazepines (Rothschild 1992; Mendelson and Jain 1995). However, potential for contributing to delirium is significant.

Anorexia is found in 25–48 % of chronic dialysis patients (Merkus et al. 1999), and is potentially multifactorial in its etiology. Reversible, nonpsychiatric causes should be investigated and treated and nutritional support provided; adequacy of dialysis should be ensured (Murtagh and Weisbord 2010). Medications contributing to dry mouth and constipation, particularly those with anticholinergic properties should be reduced or eliminated if possible. Metoclopramide has been suggested (Murtagh and Weisbord 2010), but from the psychiatric perspective extrapyramidal side effects, abulia and depression would be concerns. Depressive disorders should be investigated in malnourished patients (Cohen et al. 2006) and treated if present. In the treatment of depressive disorders accompanied by anorexia, side effect profiles of psychotropic agents like mirtazapine can be used to advantage, if bowel motility and sensitivity to sedation allow.

28.6.2 Psychiatric Aspects of Renal Palliative Care

Palliative care should be initiated well in advance of actual dialysis withdrawal, and should be anticipatory in its approach to management (Davison et al. 2008). Psychiatric treatment is an essential aspect of this management both before and during hospice, and should attend to ongoing emotional needs as well as discrete end-of-life symptoms such as agitation. Psychotherapeutic interventions in the hospice setting are generally supportive, directed at helping the patient and loved ones make the best use of the remaining time before the advent of terminal uremia and loss of awareness. Life review, expressions of love and devotion, and the specific addressing of "unfinished business" between patient and family may all have necessary roles in the leave-taking process. As the patient's window of lucidity closes, the clinician at bedside will often direct increased attention to the bereaved survivors.

Patients will come to palliation with their own clinical histories and ongoing psychiatric issues. Psychiatric treatment begun in prepalliative phases of renal failure is dealt with elsewhere in this chapter. Among the decisions that need to be made as the patient's level of awareness declines and end of life approaches is at what point to taper maintenance psychotropic agents, including antidepressants and mood stabilizers. This will be a risk/benefit decision based on multiple factors including the perceived ongoing clinical benefit of maintenance agents, any history of rapid deterioration of them, evidence of their accumulation, and toxicity. Eventually, it can be expected that supervening lethargy will lead to a progressive streamlining of the patient's regimen.

In contrast to psychopharmacology begun in the advanced but stabilized renal failure patient, psychiatric pharmacotherapy initiated in the final week of life is shorter term and symptom-driven rather than syndrome-driven, targeting changes in mental status potentially disruptive to the comfort and dignity of the patient. When terminal delirium is accompanied by agitation, haloperidol is the mainstay psychotropic (Neely and Roxe 2000), as it is hepatically metabolized, and has inactive metabolites. It may be used at 0.5–1 mg po/SQ/IM/IV hourly, titrating to effect (Neely and Roxe 2000). Akathisia, dystonia and Parkinsonism can be dealt with by using diphenhydramine 25–50 mg IV q 4–6 h in the usual manner (Neely and Roxe 2000), although the use of this agent will likely hasten cognitive decline. Haloperidol and benzodiazepines can be employed in the short period of postdialysis palliation to quell intercurrent anxiety, affective lability, and sleep disturbance. As always, the consulting psychiatrist should be alert for paradoxical disinhibition and accelerated confusion when using benzodiazepines in the neuropsychiatrically compromised patient.

It should be noted that the postdialysis dying process involves role transition for the caregivers, as well as for the patient and loved ones. Doctors, nurses, and ancillary staff may be susceptible to feelings of helplessness and professional inadequacy in context of death, particularly if the relationship with the patient has deepened over time. Psychiatric consultation during this critical period also includes maintaining an awareness of distress experienced by members of the renal team and responding supportively to it.

28.7 Renal Transplantation

The selection process for potentially eligible patients and living donors includes psychosocial assessment, often employing instruments capable of highlighting those candidates meriting more complete examination by a transplant team psychiatrist (DeMartini et al. 2005). There are at least a couple of general transplant screening instruments available, including the Psychosocial Assessment of Candidates for Transplantation (PACT) and the Transplant Evaluation Rating Scale (TERS) (DeMartini et al. 2005; Olbrisch et al. 1989; Twillman et al. 1993).

The psychiatric consultant assesses potential donors and recipients with regard to their psychiatric histories, coping styles, available systems of support, motivations for candidacy, and decisional capacity (Cohen et al. 2006). The psychiatrist is asked to assure the team that candidates and donors are capable of informed consent to renal transplant and that organ donation itself is altruistic and not coerced. The consulting psychiatrist is also expected to identify behavioral "red flags" likely to impact on patient survival. When psychiatric problems affecting candidacy are identified, the consultant may be called upon to help the candidate stabilize sufficiently to become eligible.

Capacity may be affected by misunderstanding of the procedure and its probable results. Unrealistic expectations of return to a predisease state of health should be uncovered in the course of assessment, as should significant gaps in the patient's understanding of the posttransplant burden of care and the risks of noncompliance. Cognitive impairment from delirium or uremic dementia should be detected and its effect on the patient's decision-making capacity determined. In this respect, a pretransplant capacity evaluation should include a structured cognitive assessment tool, with or without formal neuropsychological testing. As an example, the Structured Interview for Renal Transplantation (SIRT) has been developed by Mori and colleagues as a comprehensive tool and clinical guideline for the pretransplant assessment of the renal patient. It collects information relevant to the transplant team's assessment and decision, including data on the patient's understanding of the illness, coping style, mental health history, and cognition (Mori et al. 2000).

It should be recognized that the presence of a psychiatric history itself does not preclude a patient from giving valid, informed consent to renal transplantation, particularly if the psychiatric illness has been responsive to treatment (Cohen et al. 2006). Even patients with prohibitive burdens of psychopathology, including psychosis and suicidality, can be treated and reevaluated for capacity when in remission.

Aside from the question of capacity, limited available data do not indicate that psychiatric disorders should be considered automatic contraindications to renal transplantation, particularly in the setting of good social supports (Carrasco et al. 2009). Pretransplant patients can suffer progressively increasing anxiety and depression while awaiting an organ (Corruble et al. 2010), while there is at least some data indicating that prevalence of anxiety and depression may diminish after transplantation (Lopes et al. 2011; Szeifert et al. 2010).

Available data do show renal transplant candidates to be less candid than the general C/L population about past psychiatric treatment history (Mori et al. 2000; Rundell and Hall 1997). This is problematic since survival of transplanted organ recipients is dependent on strict treatment compliance, which can be undercut by psychiatric disorders, including anxiety disorders, depressive disorders, and substance use disorders (DeMartini et al. 2005). In one longitudinal study, depression and age were the two most important predictors of survival in renal candidates (Mori et al. 2000; Levenson and Olbrisch 1993). Levy (1994) identifies as higher risk those patients who have become psychiatrically symptomatic in context of ESRD and dialysis. He also points out family history of psychiatric illness as a significant factor, and stresses the necessity of pretransplant education about the possible complications of immunosuppressant therapies as a buffer against unpleasant surprises (Levy 1994). Active substance abuse contraindicates transplantation, though patients with at least 6 months' abstinence can be reconsidered (Cohen et al. 2006),

particularly if active in treatment. Personality disorders are likely to pose a challenge to the patient's ability to work with the treatment team and to the team's ability to metabolize the patient's behavior. Personality-disordered patients are, when transplanted, likely to require a specialized behavioral treatment plan with close coordination among psychiatric and non-psychiatric team members. The consultant's pretransplant role with these patients includes helping the team to realistically gauge whether its program will be able to effectively contain the patient. As always, past history of treatment compliance is the most direct predictor of a candidate's future behavior. A pattern of missed dialysis sessions, dietary indiscretions, and medication noncompliance contraindicates renal transplantation (Cohen et al. 2006).

The capacity of candidate donors is subject to its own set of potential failings. Given that the procedure offers under the best of circumstances no benefit to the health of the donor, a high standard of capacity should be required in terms of retaining and understanding risks and potential consequences. Leo et al. (2003) identify chronic psychosis, severe affective disorders, suicidality, intellectual developmental disorder, unremitted substance use disorder, and severe personality disorder as conditions likely to preclude well-informed decisions about renal donation.

The consultant also needs to assess the individual donor's motivation. Inappropriate familial pressure or unfair external emotional leverage on a candidate donor may preclude exercise of a valid choice. Guilt, fear of retaliation, and expectations of reciprocal emotional commitment are additional examples of inappropriate donor motivations. Unexplored ambivalence may ultimately sabotage donor compliance with preoperative protocol (Leo et al. 2003), and Levy (1994) feels that "the potential donor with an ambivalent relationship with the recipient should not be encouraged to donate". Financial enticements of donors are both unethical and illegal. Leo et al. (2003) offer a useful guideline for the structured interview of prospective kidney donors. Baskin (2009) points out the ethical challenges inherent in evaluating unrelated prospective solid organ donors, and in attempting to more clearly understand motives presented as purely altruistic.

There is very limited psychiatric outcome data on donors posttransplantation. A recent modestly sized, prospective study based on a Symptom Checklist administered before and after donation indicated an overall increase in psychological symptoms over time, though not generally of clinical significance, and difficult to distinguish from fluctuations found in the general population (Timmerman et al. 2013). A retrospective review by Rowley et al. (2009) found that kidney donors with histories of psychiatric illness who underwent preoperative psychological evaluation and were cleared for donation tolerated the procedure and its aftermath without psychological deterioration. For the consulting psychiatrist this once again serves to highlight the importance of preoperative clinical screening of the prospective donor.

Postoperative psychiatric issues are not uncommon among renal transplant patients. Data from Fukunishi et al. (2001) show a peak prevalence of psychiatric disorders among adult living-related renal transplant recipients of 28 %, occurring 3 months after surgery and subsequently declining at 1 and 3 years. Delirium is the most common disorder during the early postoperative period, closely followed by major depressive disorder, persistent depressive disorder, and adjustment disorders. Brief psychotic disorder, somatic symptom disorder, substance-induced disorders, and posttraumatic stress disorder are also represented. There has been at least one documented case of hyperactive delirium followed by catatonia after liver and kidney transplantation (Kalivas and Bourgeois 2008).

Postoperative delirium in renal transplant patients can be precipitated by diverse factors, including narcotics, immunosuppressant, and glucocorticoid-induced neurotoxicity, infection, and residual uremia (Cohen et al. 2006). Patients with major neurocognitive disorders are at increased risk for delirium. As in all delirium management, identification and correction of precipitants is the primary approach, with adjunctive use of medications for symptomatic management of agitation, disorganization, disinhibited

behavior, hallucinosis, and delusions. Haloperidol, oral or parenteral, remains first-line medication for agitated delirium (Cohen et al. 2006). Atypical antipsychotics such as risperidone can be tried, although hypotension and reflex tachycardia are of concern. It should be noted that all antipsychotics commonly used in delirium carry the risk of QT interval prolongation with attendant arrhythmias.

Depression is the most common longer-term psychiatric problem afflicting renal transplant recipients, found in children and adolescent recipients as well as among adults (Ghanizadeh et al. 2009). Nowak et al. (2010) cite a prevalence rate of 22 % in an outpatient transplant center cohort. It should be recognized by the consultant and by the transplant team that in addition to attendant psychological suffering and suicide risk, depression may have a pernicious effect on posttransplant medication compliance and disease survival. Found a significant correlation between score on the Beck Depression Inventory-II and the likelihood of lapses in compliance with immunosuppressant medications in an urban kidney transplant population, with depression accounting for 18 % of variance in adherence scores. Data from a Netherlands cohort indicated that preexisting depression persisted after transplantation and that it was associated with cardiovascular and all-cause mortality (Zelle et al. 2012). In a prospective cohort study of outpatient kidney transplant recipients, Nowak et al. (2010) found that in a prospectively followed cohort of recipients depression, as measured by the Center for Epidemiologic Studies—Depression scale was significantly associated with 5-year mortality and was predictive of graft loss.

Etiologies and contributing factors to depression in transplant recipients are diverse, ranging from pharmacological to psychodynamic. Posttransplantation depression can be precipitated by immunosuppressant medications, including steroids (Levy 1994) and by graft rejection (Iwashige et al. 1990). Tsunoda and colleagues have identified social isolation (living alone) as a particularly strong demographic predictor of depression among patients following kidney transplantation (Tsunoda et al. 2010), while Zelle et al. (2012) have also identified associations of posttransplant depression with lower physical activity level, inability to work, proteinuria, and longer dialysis duration. A paradoxical depressive syndrome in the presence of successful transplantation has been described by Fukunishi et al. (2001) as occurring in 5 % of kidney recipients. They have felt it to be precipitated by guilt regarding the donor's sacrifice. A subsequent study by Sugawara et al. (2008) has identified 25 such cases among a cohort of 1,139 renal transplant recipients. They did not identify guilt as the prominent dynamic, but cited rather the mourning of an imagined past, irretrievably lost to chronic illness (Baines and Jindal 2002).

Transplanted patients are also vulnerable to anxiety caused by medications as well as by the chronic threat of rejection and organ failure. Psychological discomfort with the donated kidney can be an ongoing issue for the patient, with "internalization" of the foreign organ occurring only incrementally (Levy 1994; Muslin 1971). The psychiatric consultant should also be aware that tacrolimus itself can precipitate anxiety and akathisia—with clinical incidence related to plasma level (DeMartini et al. 1996).

Antidepressant management and anxiolysis in ESRD are discussed elsewhere in this chapter, with similar concerns for the transplant patient in the transitional postoperative period. Mania, including that produced by glucocorticoids can be treated with mood-stabilizers, with considerations attendant to renal management as elsewhere noted. Steroid-induced psychotic disorder should prompt treatment with antipsychotic medications.

It should be noted that altered pharmacokinetics in the setting of resolving renal failure continues to affect the selection and dosing of psychotropic medications in the posttransplant period. The consultant should also be aware that most maintenance psychotropic medications are held on the day of surgery. Since most of these medications are not dependent on renal metabolism, they should generally be restarted postoperatively. Medication withdrawal is of particular concern in patients maintained on

benzodiazepines, and perioperative institution of an equipotent dosage of parenteral lorazepam should be considered.

Pharmacotherapy after renal transplantation is complicated by the presence of immunosuppressants in the patient's regimen. The psychiatric consultant should be aware of the psychiatric effects of immunosuppressants commonly used in renal transplantation. As detailed by DeMartini et al. (2005), each immunosuppressant agent is associated with common, annoying side effects and with less common but more worrisome neurotoxic symptoms. Cyclosporine commonly causes headache, restlessness and tremor; a minority of patients can suffer delirium, medication-induced psychotic disorder, cortical blindness, seizures, loss of speech, and coma. Cyclosporine neurotoxicity can precipitate posterior reversible encephalopathy syndrome (PRES), can cause demyelination, may be likelier with higher doses and IV administration, and may be potentiated by hypocholesterolemia, hypertension, and hypomagnesemia (DeMartini et al. 2005; Kim et al. 2011). Tacrolimus commonly causes tremor, restlessness, insomnia, vivid dreams, hyperesthesias, and headache. It can also cause anxiety and akathisia. Neurotoxic states can manifest in agitation, dysarthria, delirium, seizures, hemiplegia, cortical blindness, posterior reversible encephalopathy syndrome (PRES), and coma. Tacrolimus neurotoxicity can be mediated by demyelination, is associated with higher plasma levels and with pathology that disrupts the blood-brain barrier (DeMartini et al. 2005; Kim et al. 2011). Demyelinating syndromes or PRES will require imaging, ideally magnetic resonance imaging (MRI), for diagnosis. Tacrolimus neurotoxicity can appear at substantial delay if blood level rises, as seen in a recently-reported case of medication-induced mania and psychosis occurring 17 years after kidney transplant (Bersani et al. 2013).

Azathioprine may precipitate depression, although reports are confounded by the presence of other possible culprit medications (DeMartini et al. 2005). Mycophenolate mofetil may also be associated with neuropsychiatric toxicities, including medication-induced anxiety, psychotic and depressive disorders, agitation, delirium, somnolence, paresthesias, hypertonia, and seizures; here again, however, concurrent administration of corticosteroids and cyclosporine clouds the issue (DeMartini et al. 2005). The panoply of steroid-induced neuropsychiatric syndromes will be familiar to the practicing consultation psychiatrist.

Calcineurin inhibitor agents like tacrolimus and cyclosporine require therapeutic blood levels to prevent rejection and are more prone to cause neurotoxicity when supratherapeutic (DeMartini et al. 2005). For this reason, particular attention needs to be paid to pharmacokinetic interactions of immunosuppressants with psychotropics, particularly those blocking or inducing the cytochrome P450 IIIA4 subsystem. As described by Manitpisitkul and colleagues (2009), CYPIIIA4 inhibitors such as nefazodone and fluvoxamine can elevate both cyclosporine and tacrolimus levels and nefazodone has been shown to increase these drugs' levels by a factor of 10. In vitro data would indicate that sertraline would be least liable to IIIA4 inhibition among the selective serotonin reuptake inhibitor (SSRI) antidepressants, though there is conflicting data on its effects on cyclosporine levels. Fluoxetine, citalopram, and paroxetine do not alter cyclosporine levels and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine also has little IIIA4 effect. Nefazodone should certainly be avoided. Solid information on the SNRIs desvenlafaxine and duloxetine is lacking (Manitpisitkul et al. 2009). Carbamazepine can induce hepatic metabolism and precipitate a decrease in cyclosporine levels, resulting in organ rejection. In this respect, valproate may be a less problematic choice. Use of the common herbal psychotropic St. John's Wort can also induce CYP450 IIIA4 and decrease both cyclosporine and tacrolimus levels (Cohen et al. 2006). Immunosuppressant medications may affect psychotropic blood levels; an example of this would be the potential for cyclosporine to raise levels of quetiapine or for tacrolimus to precipitate hypotension with mirtazapine (Fraile et al. 2009).

Pharmacodynamic interactions of psychotropics with immunosuppressants may also occur.

An example of this would be serotonin syndrome precipitated by synergism between cyclosporine and sertraline (Wong et al. 2002). Other examples would be the potentiating of lithium nephrotoxicity by calcineurin inhibitors, combined effects of antipsychotics, and calcineurin inhibitors on QTc and mycophenolate-clozaril agranlocytosis (Manitpisitkul et al. 2009).

Finally, the consultant should be aware that there have been cases of intentional overdose of immunosuppressants by suicidal patients, along with cases of unintentional toxic ingestion. Acute overdoses of tacrolimus have been remarkably well-tolerated (Curran et al. 1996; Mrvos et al. 1997; Sein et al. 2005), although there is at least one report of inadvertent toxicity leading to self-injurious and aggressive behavior (Hardoy et al. 2012). Cyclosporine overdoses have been more injurious, with neurotoxicity the most salient acute effect (Zylber-Katz et al. 1994; Sketris et al. 1993; Nghiem 2002) and with one recorded death due to intracerebral edema in an accidental intravenous overdose (De Perrot et al. 2000). In acute tacrolimus toxicity CYP450 IIIA4-inducers like phenytoin have been used to bring down levels more quickly (Jantz et al. 2013).

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Immune-Compromised Patients: HIV and Organ Transplantation

29

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29.1 Introduction

The consultation-liaison psychiatrist has no greater opportunity and obligation to contribute to patient care, practitioner training and research than in advancing the work with immune-compromised patients. This area of health care has grown enormously in the past quarter century with the global emergence of the AIDS epidemic. New case numbers continue to rise in the established geography of the disease and AIDS continues to enter areas heretofore untouched by the condition. Current projections suggest that by the year 2030, AIDS will take more lives than were lost in any of the other great plagues of humanity (Global AIDS Epidemic Report, UNAIDS 2006).

In contrast to the viral assault on the immune system associated with HIV disease, the compromise of immune regulation and response associated with transplantation medicine is induced by the interventions developed by the field. Success in expanding the organ types and their post-transplant longevity has increased the number of potential beneficiaries and the population of living organ transplant recipients.

The AIDS and organ recipient patient populations will grow and increasingly reflect the clinical

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challenges of caring for the chronically ill. As such, the consultation psychiatrist provides expertise regarding the psychosocial aspects of illness experience and coping, transplant candidacy and care, and health behaviors, including treatment adherence. The psychiatrist also plays a critical role in the assessment, referral and ongoing treatment of pre-existing or newly developing mental and substance use disorders. This is a special need in immune-compromised patients, given the nature of the high-risk groups for AIDS and organ failure. Psychiatric treatments are considered and provided in a behaviorally and medically complex context. In providing effective treatment of co-existing mental disorders and dysfunctional health behaviors, the consultation psychiatrist may alter quality of life, impact treatment decisions, and extend patient longevity.

As the scale and dimensions of mental health care for the immunocompromised patient have grown, the research field of psychoneuroimmunology has emerged. This rapidly growing area of investigation provides sound evidence that psychosocial and behavioral factors can modulate immune function (Glaser 2005). Observation and intervention studies are advancing our understanding and creating a framework for the optimal provision of clinical evaluation and treatment of the patient with immune dysregulation.

29.2 HIV Patients

29.2.1 Vignette

J.K. is a 33-year-old man referred by his internist for psychiatric assessment after an initial medical evaluation revealed that he was infected with HIV. The patient had brought himself for medical evaluation, knowing that his sexual and drug use habits had significantly increased his risk of infection. Recently, he'd met someone, hoped to begin a new romantic relationship and was encouraged by this individual to clarify his HIV status. With the disclosure of the positive HIV test result by the internist, the young man became intensely overwrought—he seemed both surprised and exquisitely apprehensive. Summoning all the advantages of his lengthy experience working with HIV-infected patients, the physician tried to calm, reassure, and support the patient in his first response to the test results. As the patient's distress remained largely refractory to the physician's approach, the internist decided to refer the patient for psychiatric consultation.

Days later, the patient met with the consulting psychiatrist and expressed fear of a decline in his health, rejection by others, especially by his new found friend, and a sense of terror, reflective of his having received a 'deadly' diagnosis. J.K. reported experiencing shortened, restless sleep, general nervousness admixed with waves of discouragement and behavioral withdrawal. He admitted special difficulty refraining from drug use since his meeting with the internist. He sketched out a history of occasional days-long episodes of mild depressive symptoms that cleared without special action or intervention, but otherwise denied a significant personal or family history of psychiatric disorder.

The consultant understood the episode as subsyndromal depression or, perhaps adjustment disorder with mixed emotional features. The primary care provider was advised to continue to emphasize in subsequent appointments with the patient, the elements of the medical monitoring and treatment plan and their potential positive impact on J.K.'s quality of life and longevity. It was suggested that monitoring includes checks on the patient's mood and affect, attitude about his illness and prognosis, and screening for elements of suicidal ideation or impulse. The psychiatrist underlined the need for psychosocial screening in the event of missed medical appointments or deteriorating adherence to treatment.

The patient met twice more with the psychiatrist—sessions in which added sources of apprehension were identified and addressed. Special emphasis was placed on effectively managing the disturbing effects of disclosure of HIV status on key relationships. Recognizing the increased risk of major depression in those with subsyndromal depression, the psychiatrist and the patient considered beginning an antidepressant medication trial. However, J.K.'s dysphoria subsided and the antidepressant trial was not undertaken.

Over the next 9 months, the patient saw his internist three times, apparently content with the care he was receiving. At the third of the visits, his

internist revealed that the patient's CD4 cell count had fallen below 350, raising the need to begin antiretroviral treatment. The patient became obviously apprehensive and very dispirited with this news. The need for specific HIV treatment represented a fearful downturn and confirmation of the relentless progression of his condition. Both the patient and the practitioner agreed that further consultation with the psychiatrist was indicated.

The psychiatrist met with the patient 10 days later. By then, J.K. was despondent and apprehensive on a daily basis. He was experiencing sleep-onset difficulties, compromised energy to carry out daily activities and considerable withdrawal from contacts with others. The patient's presentation suggested the leading edge of a probable major depressive episode. Despite some reluctance, the patient agreed to a trial of fluoxetine.

Over the next 3 months and three visits to the psychiatrist, the patient experienced a gradual improvement in mood, energy, behavior, and sleep quality. The visits provided a setting for J.K. to identify sources of pathological fear and despair and reduce their influences. During the same period, the patient and his internist were able to review and prepare for the challenges and complexities of initiating three-drug antiretroviral treatment. Over the following 6 months, J.K. managed to effectively integrate the antiretroviral protocol, the antidepressant regimen and his response to a new phase of his illness and its treatment into his ongoing perspective and activities.

29.2.2 Introduction

The HIV illness experience is unique for each infected individual, yet there are common issues and themes across the various illness phases. In the first subsection, we explore aspects of illness experience and response, illness narratives, and psychosocial treatment considerations relevant to the CL psychiatrist. As meaning of illness, social support and adaptive coping have been associated with improved psychological and physical outcomes in HIV-illness (Farber et al. 2003), we look at specific interventions that address these areas.

Patients with psychiatric disorders, including personality disorder (especially borderline and antisocial personality disorders), are at higher risk of HIV infection (Perkins et al. 1993). For infected individuals, psychiatric disorder can impact the subjective experience of infection, as well as the treatment of HIV and related illness. Therefore, appropriate assessment and effective treatment of psychiatric conditions is of paramount importance. The diagnosis and treatment of certain psychiatric disorders can be similar to that in non-infected individuals—there are also unique diagnostic and treatment considerations in the setting of HIV-infection. Finally, there are unique neuropsychiatric manifestations of HIV/AIDS and related medical sequelae. We will address these issues related to psychiatric and neuropsychiatric illness in the second subsection.

29.2.3 Psychosocial Issues and Treatment Considerations

There are common intrapsychic and interpersonal conflicts and issues that are illness-phase specific. Some familiarity with these themes affords us a better understanding of our HIV-infected patients and allows for more appropriate psychosocial treatment. Sensitivity to these dynamics can guide therapeutic contacts, which can provide support and be powerful facilitators of growth and healing. In addition, during longer hospitalizations there can be a role for more structured, brief psychotherapy. Themes that are identified during this work can be further explored and addressed in subsequent outpatient psychotherapy.

29.2.3.1 New Diagnosis

A patient's response to HIV diagnosis can depend on their awareness of pre-testing risk behaviors. For those unaware of their high risk, there may be disbelief or concerns that the results are inaccurate. Once a patient tests positive, there may be periods of denial and also significant anxiety related to issues of mortality, impact on life dreams, uncertain disease course and treatment, and uncertain response from family and loved ones (including feared rejection). There may be guilt related to high-risk behaviors and feelings

of shame in relation to social stigma. Patients and their loved ones can also exhibit other symptoms associated with loss, including guilt, sadness, anger, bargaining, and acceptance (Cohen 1990).

Once diagnosed, patients must also deal with the issue of whether or not to inform friends and family. Sometimes this involves acknowledging sexual or drug-related lifestyles that were previously undisclosed. Sexual partners current and past need to be informed by the patient—the patient should be encouraged to do this, once they have processed the diagnosis adequately themselves. Some states require this disclosure to intimate relations. At the appropriate time, patients must also be counseled on safe-sex practice to decrease their likelihood of transmitting the virus and contributing to the epidemic.

Suicidality should be evaluated—the suicide rate in patients with AIDS has been reported as 36 times that of the general population (Cohen 1990). This rate has decreased with the introduction of highly active antiretroviral therapy (HAART), but continues to be higher in patients with HIV infection and AIDS (Jia et al. 2012). Patients without prior history of suicidal ideations may talk of suicide when they are overwhelmed and trying to manage feelings of despair, loss of control, helplessness, and fear of the future—the major intervention here is to help the individual manage and work through the overwhelming anxiety. As well, lowered self-esteem, impact on sense of identity, alienation from friends and family can also contribute to suicidal ideations—crisis intervention, communication, and support are important here (Cohen 1990). Patients with pre-infection history of depression, anxiety, personality disorder, and suicide attempts can be at much higher risk for suicide and need to be managed appropriately (Sheridan and Sheridan 1988).

29.2.3.2 Early Illness

After being diagnosed, the patient struggles to integrate the diagnosis and its treatment into their life. Here it becomes important to explore the meaning of illness, including illness-related fears. Fears of unknown illness and treatment, lack of cure, and the possibility of premature death can lead to significant anxiety (Cohen 1990). Complexes related to earlier interpersonal loss can become constellated, especially when these losses have not been adequately worked through. There can be significant anxiety and anticipatory mourning regarding the potential impact of HIV-infection on previously held dreams and ambitions. It is important to create a safe space for these painful feelings to be expressed—both allowing for mourning, while also providing hope.

Patients also often struggle with larger existential questions such as, "Why did this happen to me?" Even in the time-limited setting of consultation psychiatry, it can be invaluable to create a safe space to begin gentle exploration and engagement with these questions. If the consultant is not comfortable with transpersonal and existential themes, and if it seems appropriate, pastoral, spiritual, or religious support can be recruited.

Patients often have misconceptions regarding HIV infection and treatment—many are unaware that modern antiretroviral treatment has transformed HIV-infection from a death sentence to a chronic illness. It can be important to provide education regarding this, or to facilitate the exchange of this information via the primary team and hospital educational resources.

The psychiatric consultant can also facilitate linkage with community resources and support groups. It is important to be aware of medical clinics or providers in the community who are comfortable with or specialize in work with HIV-positive individuals. Social work can often assist with educating the patient and making referrals to resources that can help with insurance issues, legal aid, and other HIV-related services.

29.2.3.3 Chronic Illness

There are other themes that are common and may need to be explored and addressed when relevant. These can include dealing with social stigma and the interpersonal response to their infection, the need for chronic medical care and medical morbidities, the worsening of medical condition when it occurs, AIDS-related cognitive changes, and processing the impact of HIV/AIDS on

educational and vocational pursuits. For some of these issues it becomes important to draw from grief work and both mourn the loss as well as facilitate and co-construct new meanings and life goals with the patient. Again, the psychological and physical interpenetrate—recent research shows that patients who experience maladaptive grief show more rapid loss of CD4 T-cells over time, even when controlling for age, health status, use of antiretrovirals, and illicit drug abuse (Goforth et al. 2009). In addition to these themes, HIV-related symptom onset and an increase in symptoms can be key triggers for hopelessness and demoralization, which need to be addressed.

29.2.3.4 Terminal Illness

There is significant existential anxiety around death in American culture, which often leads to avoidance in caregivers who are uncomfortable with emotional engagement with the dying patient. At the time the patient needs human contact the most, the opposite often happens. This can be especially true in busy public hospital settings, with indigent and often homeless populations who have limited, if any, social network. When these networks exist, even if in the form of case managers, they should be recruited and attended to. When these networks don't exist, the psychiatric consultant is often the primary source of human contact (in teaching hospitals, medical students can be valuable allies). It is critical to engage with the dying patient in a sincere and compassionate way. The consultant can work with the primary team in addressing treatable issues, such as poorly managed pain. The consultant can help facilitate communication with relationships that have been strained or broken. Often times, the patient needs help in thinking through those people he or she wishes to contact, with what needs to be expressed, and with problem-solving in making these connections. In this modern age, the Internet can be invaluable for locating phone numbers and other information.

It can be crucial to explore the patient's spiritual beliefs, especially perspectives on the afterlife, and engage with this in appropriate ways. For patients with significant guilt, forgiveness and self-compassion work can be crucial for a less tormented and anxious passing. For spiritually inclined patients, culturally syntonic rituals can be co-constructed and engaged in. Appropriate spiritual bibliotherapy can be carefully integrated in some instances. For those patients who identify with specific religious belief systems, texts from those belief systems can be requested or spiritual figures from respective churches, mosques, synagogues, or temples can be incorporated into the care. Finally, when a patient dies, the consultant must tend to his/her own emotional responses. Ideally, the consultant has engaged with this inevitable existential reality beforehand. It is important to take time, even in the busy workday to mourn the loss of a person, to find ways to take care of one's own grief response and find ways to restore one's own energy, and then move forward (Sheridan and Sheridan 1988).

29.2.3.5 Special Issues: Adherence to Antiretroviral Treatment

Compliance with Highly Active Antiretroviral Therapy (HAART) can be challenging even independent of any psychiatric diagnoses or significant psychological distress. Often there are many pills to take at once. The medications often have multiple dosing times each day. Therefore, the complicated dosing regimens often impact other life involvements. HAART often has significant side effects that can be distressing and also have other psychosocial impact. For some, the medications are a reminder of having a disease they would rather forget. There can also be anxiety that people will find out and discriminate against them if the medications are seen, which can also negatively impact medication compliance. Thus, compliance with HAART requires a serious commitment from even the most well compensated patient.

Major depression can further reduce adherence (Singh et al. 1996). Depressed patients often have decreased interest in self-care and may ignore medical symptoms and problems. They may be too withdrawn to present for care and medical follow-up. Depression can interfere with problem solving which is important to negotiate complex medication regimens and approach issues such as medication side effects.

With a sense of hopelessness and negative thinking, some patients may doubt the potential benefits of treatment. In HIV-positive patients with depressed mood, one group found that a single-session that targeted the rehearsal of adherence-related behaviors led to enhanced HAART adherence (Safren et al. 2001). In addition to interventions that specifically address medication non-adherence it becomes crucial to treat major depression, as there are studies that show antidepressant treatment increases viral suppression, likely due to improved adherence (Tsai et al. 2010).

29.2.3.6 Special Issues: The Role of Spirituality

Spirituality is a potentially important component and dimension at every level and phase of care. There is some literature that looks at spirituality and religiosity in the setting of HIV-infection. Nelson et al. (2002) studied 162 patients with terminal illness, 78 patients of whom had terminal AIDS—spirituality, religiosity, and depression were assessed in these patients. There was a strong negative association between spiritual well-being and depression (i.e., higher spirituality was associated with lower depression)—especially the (existential) subscale that looked at meaning and depression. The authors recommended existential or spirituality-based interventions for terminally ill individuals with HIV. A more recent study (Ironson and Kremer 2009), spoke of spiritual transformation as occurring in up to 39 % of individuals with HIV, and in looking at 147 people with HIV, found that spiritual transformation was associated with better treatment success (undetectable viral loads, higher CD4 counts), better medication adherence, fewer symptoms, less distress, more positive coping, different life attitudes (i.e., existential transcendence, meaning in life, optimism, death acceptance), and substance abuse recovery. Notably, survival up to 5 years was 5.35 times more likely in these individuals.

29.2.3.7 Illness Narratives

"Narrative is a fundamental human way of giving meaning to experience. In both telling and interpreting experiences, narrative mediates between an inner world of thought-feeling and an outer world of observable actions and states of affairs…" (Garro and Mattingly 2000, p. 1). Telling stories allows the patient/author to represent and understand their experience, and to expand and reshape concepts and values—creating a personal narrative that is more cohesive, enriching, and more meaningful. These revised stories create new understandings of self and other that can reshape one's experience of the past, present, and anticipated future.

In telling stories, certain parts are left out because of attentional biases. As a person's story is explored, neglected, and forgotten aspects, as well as new perspectives and lines of inquiry can allow for new stories to be created. "Patient and doctor together reconstruct the meaning of events in a shared mythopoesis … Once things fall into place; once experience and interpretation appear to coincide, once the patient has a coherent "explanation" which leaves him no longer feeling the victim of the inexplicable and the uncontrollable, the symptoms are, usually, exorcised" (Eisenberg 1981).

Farber et al. (2000) looked at resilience factors associated with adaptation to HIV disease, focusing on the construct of hardiness. They describe hardiness as having three dimensions: (1) commitment, which relates to one's sense of meaningful and purposeful engagement with life, (2) challenge, which relates to ones sense that change is fundamental and can allow for growth, and (3) control, the sense that one can influence the life course as it unfolds. In their study of 200 patients with symptomatic HIV, they demonstrated that high hardiness was associated with lower psychological distress, higher perceived quality of life in physical health, mental health and overall functioning domains, and more positive personal beliefs.

In a subsequent study, Farber et al. (2003) looked at 203 symptomatic patients with HIV and AIDS, measuring meaning of illness, problem-focused coping, social support, psychological well-being, and depressed mood. Positive meaning was associated with a higher level of psychological well-being and a lower level

of depressed mood. This contribution of positive meaning of illness was over and above the contributions of problem-focused coping and social support. The authors suggest the use of psychotherapy that supports problem-focused coping when appropriate, but also pays attention to HIV-related meaning can help decrease distress and increase psychological well-being. Therapy interventions that focus on meaning and purpose and focus on the articulation of meaning and purpose may reduce distress, facilitate coping, and increase positive adaptation.

29.2.3.8 Psychosocial Treatments Relevant for CL Psychiatry

Narrative Therapy

Much of psychotherapy can be considered as a form of narrative work—whether this is schema-focused work in cognitive behavioral traditions or an implicit orientation guiding Jungian psychoanalysis. "… Narrative therapy is characterized by telling one's story; examining the roots of that story; seeking aspects of that story previously overlooked; exploring how incorporating new aspects of the story changes the meaning attributed to different events; anticipating how self-image, priorities and relationships change as a result of the new meanings; and finding an appreciative audience for the new growth" (Petersen et al. 2005).

Words can contain and transform difficult affects and self-states, yet both the verbal and non-verbal aspects of the relational experience between clinician and patient are important. This includes the tonal and rhythmic dimensions that carry the dialogue—this is the intuitive music, or art of our work (Singh 2013). Within this dynamic relational field, "telling the story desensitizes patients to threatening cues that trigger anxiety, decreasing fear and avoidant behavior" (Petersen et al. 2005). Yet, "while retelling provides some comfort and momentary relief, the story must change in order to add therapeutic advantage" (Petersen et al. 2005). Appraisals are labeling of experience that shape emotional and behavioral response. Positive reappraisal results in assigning new meaning to the event, integrating confusing aspects into a coherent conceptualization, which can then lead to emotional and cognitive resolution (Petersen et al. 2005). Again, positive meaning of illness is associated with decreased depression and improved psychological well-being in individuals with HIV and AIDS (Farber et al. 2003).

This co-creation of a more adaptive and meaningful narrative can be engaged via questioning in a way that promotes contemplation of potential growth or lessons learned through the illness process. The idea of transformative suffering can be brought up, including the Jungian concept of the "wounded healer." Sometimes amplification can be attempted with fairy-tales and myth, for example, using the mythological tale of Chiron, who drew his strength from a poisoned arrow inflicted upon him by Zeus. Patients can find it interesting and useful to hear that in shamanic cultures, the healer often gained their power through an encounter with severe suffering. These can provide cognitive models that can shape the appraisal of illness experience in more adaptive ways. Not only can one find new areas of strength through the illness experience, but one also has an opportunity to offer something back to other individuals in the community. The important skill or art is to not disavow the pain or suffering as well, as this can be an important part of the grieving and mourning process. If these feelings are prematurely, or superficially dealt with, they often return in a variety of ways including delayed grief reactions, projections and projective identifications, or psychosomatic responses. As Edwards (1993) reminds us: "Countertransference from our own fear or pain may prompt us to get ahead of the patient by focusing on empowerment or hardiness. Anger and sorrow must be expressed and relieved before natural restitutive urges appear. There is a natural rhythm to grieving …" He goes on to say, "After patients have expressed and worked through their intense diagnosis-related feelings, they are often intrigued and mobilized by the suggestion that, although they cannot change the fact that they are HIV-positive, they do have control over their response to the disease."

29.2.3.9 Addressing Relational Deficits and Conflicts

The lack of perceived social support is associated with low self-esteem, depression, and poor quality of life (Safren et al. 2002). It is therefore important to explore and address this when possible. The consulting psychiatric team can provide an important relationship. Supportive visits can be very powerful—even when there are constraints on provider time, as long as one conveys to the patient that he/she is cared for and being listened to. It is also important to assess for community relationships that can be integrated—friends, family members, and case managers. Sometimes problem-solving or work targeting suspended or damaged relationships can be helpful (and followed through in subsequent outpatient psychotherapy). The consulting psychiatrist can attempt to arrange family meetings—sometimes it is possible to involve families even after many years of separation. "The support from family and loved ones can make the difference between dying with despair and dying with dignity and love. The fact that this does not always work is never a reason not to try" (Cohen 1990). Depending on the patient's unique needs, referrals can be made to outpatient mental health programs, to individual psychotherapy or counseling, to religious or spiritual groups, to 12-step groups or to HIV-specific resources—all of which can provide therapeutic relationships.

29.2.3.10 Adaptive Coping Techniques

Coping refers to mechanisms that regulate distress and there are three categories described (Clarke and Kissane 2002): problem-focused (e.g., information-seeking, problem-solving, direct action), emotion-focused (e.g., escape and avoidance, seeking social support, cognitive reframing, behavioral interventions including mindfulness and affect regulation techniques), and meaning-focused. Active and adaptive coping styles are associated with improved outcomes, including decreased depression (Safren et al. 2002). Maladaptive coping is associated with worsened physical health in HIV-positive individuals (Armon and Lichtenstein 2012). Thus, it is important for the psychiatric consultant to evaluate the patient's coping repertoire, expanding it when needed. Important work that addresses coping skills can be initiated even in time-limited consultations. The patient can further develop this after discharge, sometimes with the support of community resources (meditation centers, stress management groups) or in individual psychotherapy.

It is first helpful to question patients about what has helped them cope with difficulty in the past, including prior experience with mindfulness and relaxation exercises. Often, exploration of approaches appraised as "not helpful" reveal that they weren't tried for long enough or that normal responses (e.g., the mind wandering repeatedly during meditation) were labeled as signs of ineffectiveness or failure. Here it can be useful to provide corrective information, since that particular technique may be valuable to revisit.

Some specific approaches that can be powerful include mindfulness and acceptance-based work. Mindfulness is a form of practice that cultivates a gentle attention in the present and looks at arising thoughts and sensations as fleeting events in the mind to be neither attached to nor averse to, but to simply "be with" as they rise and fall. There is a substantial literature on the use of mindfulness in a spectrum of conditions, including anxiety, depression, chronic pain, substance use disorders, borderline personality disorder, and psychosis. Acceptance-based work has various shades, including cultivating self-acceptance, as well as acceptance of one's experience in the moment. Basic exercises utilizing these approaches are not difficult to learn, but to be most effectively utilized, do require additional training and personal practice by the provider.

There are other relaxation techniques, different from mindfulness, which can be taught in single sessions and assigned as "homework" between sessions. This often shifts the locus of control into the patient and strengthens their sense of agency, which can be crucial for patients who are struggling with bodies and medical courses that may seem out of control. Some relaxation techniques include deep, diaphragmatic breathing; visualization and guided imagery exercises; the use of relaxing music or

ambient sounds; and yoga or other physical movement.

Having people list their concerns and needs can help break things down, making them more manageable in times that otherwise seem overwhelming. Utilizing written cognitive behavioral therapy handouts on problem-solving can be a concrete intervention that allows goals to be broken down into a series of steps, sometimes with pros and cons for branch points. This allows patients more active involvement and can break through the frozen paralysis of overwhelming states. The tactful use of these active approaches can counter the emotional weight of ambiguity inherent in medical care. Sometimes patients need the gentle and active coaching style encouraged in cognitive behavioral approaches, even when one is also simultaneously attending to deeper psychodynamic conflicts and themes, to transference-countertransference process and to dreams and other symbolic material. As always, one needs to be mindful of giving room for the expression of feeling and to one's own potential resistance to the raw human experience of the suffering other.

Finally, music and expressive arts modalities can be effective. Non-verbal communication and expression can allow access and processing of material that is otherwise threatening and defended against. It is also a way to give shape to and digest as of yet unformulated emotion and psychic material. As Aldridge (1993) states, "By painting, singing, dancing, acting or making music together we can bring the emotion of suffering into the world in concrete form. Suffering made external as expression and brought into form as art gives the individual the chance to grapple with the meaning of that suffering and thereby to bring about change." Artistic involvement can also provide refuge, and a place where creativity and play are nourished.

29.2.3.11 Brief Psychotherapy and Additional Considerations

We often have a limited number of sessions available with our patients—especially in this age of managed care, which pushes for short hospital stays. Despite this, patients are sometimes hospitalized for longer time periods. In this case more formal brief psychotherapies can be attempted. The narrative approaches we've discussed can be expanded into these longer courses. There are also brief psychodynamic, interpersonal, and cognitive behavioral approaches that can be helpful and which often explore and address previously mentioned themes. If there are specific psychiatric disorders, one can utilize evidence-based psychotherapeutic approaches. Sometimes grief work can be engaged. Some patients with HIV have significant punishment beliefs for which techniques such as positive affirmations or cognitive restructuring can be attempted—as well, we slowly shift these and other internalized, relational models and self-understandings through new relational experiences with the clinician. If there are particular skill deficits, skill-building work can be attempted (for example, the skills utilized in dialectical behavior therapy for borderline personality disorder, including distress tolerance, interpersonal effectiveness, and mindfulness skills). Antiretroviral medication adherence issues can be targeted in brief therapy.

29.2.4 Specific Psychiatric Syndromes in HIV Patients

29.2.4.1 Mood Disorders

Depression is the most common psychiatric disorder for which HIV-positive individuals seek treatment and there is evidence that mood disorders are more prevalent in HIV-positive individuals. In part this reflects higher rates of mood disorder in the main risk groups—intravenous drug users and homosexual men.

Depression: Diagnostic Considerations

Diagnosis and treatment of Depression in HIV infection can be complicated by somatic symptoms shared by both disorders—these include attention and concentration difficulties, sleep disturbance, appetite disturbance, and fatigue. Co-morbid substance abuse can also complicate the diagnosis. It is also imperative to differentiate demoralization and adjustment disorder from

other forms of depression, as the treatment approach can be quite different, with more focus on psychotherapeutic intervention. Especially with demoralization, it becomes important to not pathologize what can be considered a normal response to intense circumstance. In addition, once must also consider unresolved grief issues, dysthymic disorder, major depression, and bipolar depression.

Demoralization and Adjustment Disorder

In demoralization, patients have sadness that is often specifically related to a particular event or circumstance. Sometimes, this can be difficult to differentiate from major depression. Unlike in major depression, the patients often report feeling fairly normal when they are distracted from thinking about the event or circumstance causing their distress (Angelino and Treisman 2001) and this sadness ameliorates if the event or circumstance achieves some resolution or improvement. In one HIV Clinic, the distinction between depression and demoralization was explored and approximately half of the patients with depressive complaints were felt to have major depression, whereas the other half experienced demoralization (Lyketsos et al. 1994).

At the heart of demoralization is a breakdown in coping—when these mechanisms are insufficient, distress and helplessness ensue (Clarke and Kissane 2002). Breakdowns in hope and meaning are also important contributors to demoralization—a breakdown in one's assumptive world, with loss of meaning, can happen in response to events such as major illness or bereavement (Clarke and Kissane 2002). When demoralization is due to illness, it will abate as the patient's health improves—even when there is a terminal illness, demoralization will improve if the physician understands their concerns and addresses them (Slavney 1999). Demoralization may also be common in the context of addiction, when during periods of sobriety the person struggling with addiction faces losses and also from a sense of powerlessness over the drug craving (Angelino and Treisman 2001).

An important distinction between major depression and demoralization is that the former is characterized particularly by anhedonia, whereas the latter is characterized by a subjective feeling of incompetence. "A depressed person has lost the ability to experience pleasure generally, whereas a demoralized person, while being unable to look forward with pleasant anticipation, may laugh and enjoy the present moment. The demoralized feel inhibited in action by not knowing what to do, feeling helpless and incompetent; the depressed have lost motivation and drive even when an appropriate course of action is known" (Clarke and Kissane 2002).

It has been argued that demoralization is a normal response under certain circumstances; though people differ in their vulnerability to it, even the most resilient have their breaking point (Slavney 1999); others argue that this minimizes the importance of demoralization and that though it can at times be understandable, it is always abnormal (Clarke and Kissane 2002). Patients who are estranged from family and friends, and patients with physicians who are distant or condescending may be more vulnerable to demoralization (Slavney 1999).

Demoralization, when diagnosed, needs to be explained and validated to both the patient and their physician as a normal response to a difficult situation. Sometimes physicians are uncomfortable with emotional distress and want the psychiatrist to recommend an antidepressant—there is a great opportunity for psychoeducation here and it should be made clear that they are not suffering from a psychiatric disorder (Slavney 1999). Adjustment disorder, on the other hand, is diagnosed when marked distress that is in excess of what would be expected given the nature of the stressor, or by significant impairment in social or occupational (academic) functioning is present. For billing purposes for Demoralization Syndrome, the ICD-9 code V71.09 ("Other suspected mental condition") can be used (Slavney 1999).

Clarke and Kissane (2002) describe some important therapeutic tasks in demoralization: (1) symptomatic relief of physical and mental symptoms; (2) cognitive work that includes information and reassurance, reality-testing, problem-solving, exploring appraisals and meanings, identifying and challenging cognitive distortions, looking at meaning and purpose; (3) a behavioral component that links the exploration of meaning and purpose

with goal setting and scheduling of positive activities, which can assist in redeveloping a sense of mastery and control, re-engagement in relationships, enjoyment of pleasurable activities; and (4) providing an empathic understanding of the patient, which reduces alienation and reinforces their value as a person.

Secondary Depression

This includes depression secondary to medical conditions, medication-induced depressive symptoms, and substance-induced depression. Careful history taking, physical exam, and appropriate medical work-up are important to investigate these etiologies of depressive symptoms. In addition to the usual organic workup, testosterone deficiency should be considered and antiretroviral medications with potential mood effects should be assessed for (e.g., efavirenz (Sustiva)). When there is significant substance abuse, clear diagnosis can be challenging. It can be helpful to inquire about periods of sobriety and assess the presence of mood symptoms during these periods. It can also be helpful to inquire about the temporal sequence—i.e., did the depressive symptoms predate the substance abuse or vice-versa.

Testosterone deficiency, present in up to 50 % of men with HIV, is a specific medical condition that is associated with HIV-infection, which can lead to depressive symptomology. Symptoms of hypogonadism can include depressed mood, fatigue, diminished libido, decreased appetite, and loss of body mass. Evaluation includes testing for serum testosterone (below 300–400 ng/day is abnormal) and treatment is testosterone. Depot testosterone (400 mg IM biweekly) has been shown to improve mood in HIV-positive men with major depression in a double-blind placebo-controlled study. Transdermal testosterone replacement can also be considered and may offer a more physiologic pharmacokinetic profile (Colibazzi et al. 2006).

Mania: Diagnostic Considerations and Differential

As with manic-like states in non-HIV patients, substance-induced (e.g., psychostimulants) etiologies need to be considered, as well as medication-induced etiologies (e.g., corticosteroids, androgens, zidovudine, didanosine, efavirenz) (Colibazzi et al. 2006). In primary mania, there is often a preexisting bipolar disorder or at least family history of a mood disorder. In secondary mania, there is less association with family history, but more association with progression of underlying HIV disease and CNS involvement. The symptomology of secondary mania is different and may include more irritability, less pressured speech, more psychomotor slowing, and more cognitive impairment (Ferrando and Wapenyi 2002).

Mood Disorders: Treatment Considerations

Depression

In addition to improving the general quality of life, in HIV-positive individuals, treatment of clinical depression has been shown to increase health-related quality of life and increase antiretroviral adherence (Elliot and Roy-Byrne 2002). There is now growing data to support the pharmacologic and psychotherapeutic treatment of major depression in the setting of HIV-infection.

TCAs (imipramine) have been shown to be effective in HIV-depression, but significant side effects lead to frequent discontinuation. Coupled with potential lethality in overdose, TCAs have become second-line agents (Ferrando and Wapenyi 2002). SSRIs (fluoxetine, paroxetine, sertraline, citalopram, escitalopram) have been shown to be effective in HIV, across HIV illness stages, in both open label and double-blind, placebo-controlled trials—they have been shown to be as effective as TCAs, but with more tolerable side effect profiles. The response rates and adverse effects do not vary as a function of CD4 count (Ferrando and Wapenyi 2002). There is some evidence that HIV-positive patients receiving antiretroviral treatment and SSRI treatment may be at increased risk for developing serotonin syndrome (DeSilva et al. 2001). Mirtazapine, venlafaxine, bupropion have been studied in small, open label trials with major depression and HIV with favorable response rates (>70 %) and few adverse effects (Ferrando and Wapenyi 2002).

For augmentation in partial response, one can consider lithium, thyroid hormone, buproprion, antipsychotic medications, or methylphenidate (Angelino and Treisman 2001). There are open

label and placebo-controlled studies that support the use of psychostimulants in advanced HIV, demonstrating quick response and good tolerability. Caution should be used with substance abusers, given abuse potential though there are no published reports of abuse of prescription psychostimulants in HIV patients under medical supervision (Ferrando and Wapenyi 2002). Recent RCTs have demonstrated the benefit of modafinil (Rabkin et al. 2010) and armodafinil (Rabkin et al. 2011) for HIV-related fatigue, and may provide benefit for patients with depression in which anergia predominates.

Regarding Complementary and Alternative Medicine (CAM), St. John's Wort is not recommended as it may decrease levels of protease inhibitors. Overall, research into CAM interventions for clinical depression in HIV-positive individuals is lacking and an area for further research.

Aerobic exercise has been shown to be safe and potentially beneficial for those living with HIV/AIDS (O'Brien et al. 2010) and as beneficial in depression. There are intriguing, emerging perspectives that look at neuroimmunomodulatory effects of physical activity on the brain in depression, with evidence suggesting that exercise can enhance the beneficial and reduce the detrimental effects of the neuroimmune system (Eyre et al. 2013). Extending this research to reflect on the relation of exercise to the immune system in the HIV/AIDS context may provide a more compelling basis for this intervention with the depressed HIV patient. One study of psychotherapy and HIV compared interpersonal psychotherapy, cognitive behavioral therapy, supportive therapy plus imipramine, and supportive therapy alone—interpersonal therapy and supportive therapy plus imipramine were superior to the other treatments (Markowitz et al. 1998). Interpersonal therapy works with four themes: role transition, interpersonal deficit, interpersonal conflict, and grief/loss. When the major depression is treated, there are often other issues that can still benefit from psychotherapy.

Mania

Practice guidelines recommend lithium, valproic acid, or carbamazepine. Lithium has been shown to be effective in HIV-positive individuals, but it has a low therapeutic index and can be neurotoxic and poorly tolerated in HIV-positive individuals. Valproic acid has been the best studied with one study using doses up to 1,750 mg/day and serum levels >50 μg/L and another study finding efficacy at levels between 90 and 100 μg/L (Ferrando and Wapenyi 2002). There is some in vitro evidence of increased HIV replication, but this has not been shown in vivo, including an in vivo trial that showed valproic acid does not affect viral load in patients on antiretroviral therapy (Maggi and Halman 2001). Newer data have shown that valproic acid may ameliorate neurotoxicity associated with AIDS Dementia Complex (ADC) (Schifitto et al. 2006). In addition to anticonvulsants, atypical antipsychotics, including risperidone, olanzapine, and quetiapine, can be effective mood stabilizers. One needs to be mindful of potential metabolic side effects, especially with olanzapine and clozapine. Finally, benzodiazepines can be a useful short term adjunct—there is a case report using clonazepam 2 mg PO TID with success in controlling HIV-related manic symptoms (Ferrando and Wapenyi 2002).

29.2.4.2 Anxiety Disorders

Patients at various illness phases can have significant anxiety relating to HIV-infection and sequelae. Current anxiety symptoms are present in up to 11 % of HIV patients (Sewell et al. 2000). Somatic etiologies need to be considered—e.g., substance intoxication and withdrawal states, medication side effects (e.g., interferon, petamidine, AZT, 3TC), opportunistic illness-related anxiety symptoms, and other medical conditions such as anemia, hypoxia, and various metabolic disturbances. Anxiety and agitation can frequently be seen in the setting of delirium and ADC. In addition to anxiety secondary to somatic etiologies, the differential includes adjustment disorder with anxious features and other anxiety disorders, including social phobia, generalized anxiety disorder, post-traumatic stress disorder, panic disorder, and obsessive-compulsive disorder. There has been recent interest in PTSD resulting from illness and also in caregivers for

the ill and dying, with PTSD quite common in these contexts. In addition to subjective distress, PTSD has been shown to negatively affect medical outcome. Special attention should be paid to evaluating for illness-related PTSD symptoms.

Anxiety Disorders: Treatment Considerations

SSRIs are first line agents for generalized anxiety disorder, social phobia, panic disorder, obsessive-compulsive disorder, and post-traumatic stress disorder. Mirtazapine (Remeron) and venlafaxine (Effexor) are also good options. Other options include gabapentin (Neurontin) and buspirone (Buspar). Atypical antipsychotics such as quetiapine can be considered (Buoli et al. 2013), but potential metabolic side effects and drug interactions need to be considered (Pollack et al. 2009).

Patients often seek benzodiazepines because of immediate relief—yet safety concerns, cognitive side effects, and abuse potential need to be addressed. For patients who request benzodiazepines, but who are at high risk of negative consequence (e.g., patients with substance abuse or dependence), it is important to express an intention to treat their anxiety, but to also set gentle but firm limits. For non-high risk patients, benzodiazepines can be considered for short-term use, or as a time-limited agent to bridge the gap before antidepressant effect has taken place. Lorazepam, oxazepam, and temazepam are the agents of choice for patients taking protease inhibitors.

Relaxation and meditation techniques can be effectively taught to patients in the hospital setting and can be powerful, non-pharmacological anxiety-management tools. For patients with longer anticipated hospital stays, cognitive behavioral material specific to their anxiety disorder can be incorporated. The advantage of these non-pharmacological approaches is that they can allow the patient a sense of internal control, helpful in countering demoralization, and there are usually no side effects to deal with. Music can be a useful relaxation tool as well and other expressive arts modalities should also be considered.

29.2.4.3 Psychotic Disorders

Psychotic Disorders: Diagnostic Considerations

Psychosis in HIV can have multiple etiologies, including substance intoxication or withdrawal states, medication-induced, opportunistic infection-related, or secondary to other organic etiologies. HIV-patients with delirium or dementia can have psychotic symptoms. Given the higher prevalence of antisocial personality disorder in HIV-positive populations, malingering also needs to be considered.

It is important to rule out substance-induced and organic etiologies before making a primary psychiatric diagnosis. Primary psychiatric disorders that can involve psychotic symptoms include mood disorder with psychotic features, schizoaffective disorder, schizophrenia, as well as certain personality disorders—mainly borderline-personality disorder.

Psychotic Disorders: Treatment Considerations

HIV-positive patients can be more susceptible to extrapyramidal side effects (EPS) as a consequence of HIV-induced neuronal damage to the basal ganglia (Work Group on HIV/AIDS 2000). Also, movement disorders such as acute dystonias and Parkinsonism can be seen in advanced HIV in the absence of neuroleptic treatment (Ferrando and Wapenyi 2002). With regard to typical antipsychotics, haloperidol has been shown to be effective in HIV-positive patients with schizophrenia, but with high EPS incidence. With regard to atypical antipsychotics, both clozapine and risperidone have been shown to be safe and effective in HIV-positive patients (Lera and Zirulnik 1999; Singh et al. 1997). Overall, atypical antipsychotics are preferable given the lower rate of EPS. However, there are limited data for antipsychotics and larger, controlled studies are needed to expand our knowledge on the appropriate use of second-generation antipsychotics in HIV-infected patients (Hill and Lee 2013). Finally, there is evidence to support the use of cognitive behavioral therapy in psychotic disorders such as schizophrenia (Rector et al. 2012),

and limited data examining CBT in the HIV treatment setting (Goldberg et al. 2011).

29.2.4.4 Substance Abuse/ Dependence Disorders

In substance use disorders, substance use often impairs judgment and leads to impulsivity and high-risk sexual behaviors. Certain substances such as cocaine and methamphetamine can increase sexual desire and lead to high-risk situations. In the context of intravenous drug use, the sharing of contaminated needles is a major risk factor for HIV infection. Substance abuse and dependence can increase the risk of infection and also decreases compliance with HIV treatment. Substance intoxication and withdrawal states can also complicate the diagnosis of psychiatric disorders.

Substance Disorders: Treatment Considerations

This can be similar to treatment in non HIV-positive substance abusers. Motivational enhancement techniques can be especially valuable for ambivalent patients. Patients should be educated that longevity is now possible with properly treated HIV, and that this also involves treating chemical dependency. For patients who previously viewed HIV-diagnosis as a death sentence, this corrective information can partially address feelings of illness-related hopelessness and thus affect their motivation towards treatment.

The overall treatment can be seen as consisting of four steps: detoxification, rehabilitation, treatment of co-morbid conditions, and relapse prevention. Referral to 12-step groups can be helpful, especially trying to link the patient with a sponsor. Education on safe-sex behavior (condom use) and high-risk drug behaviors (needle-sharing) to decrease the risk of spread is important. Finally, vocational rehabilitation, social rehabilitation, and the creation of a drug-free environment are essential to preventing relapse (Angelino and Treisman 2001).

29.2.4.5 Personality Disorders

Patients with personality disorder, especially borderline and antisocial personality disorder, are more likely to contract HIV due to impulsivity and increased high-risk behavior. Once infected, personality disorder affects all aspects of HIV-infection and its treatment. Intrapsychic issues such as meaning of illness, behavioral response including coping, and interpersonal dynamics including those between patients and care providers are all affected. A thorough examination of this topic is beyond the scope of this section and can be found elsewhere.

In the hospital, the "difficult patient" is a common cause for psychiatric consultation. There are interventions that can be implemented with both patient and providers. For providers, including ward staff, it is often important to create a space for angry and hostile feelings arising in providers to be voiced, minimizing the chance that they will be disowned and projected completely onto the patient. As well, it becomes important to frame the patient as a wounded individual deserving of compassion, as well as needing limits. Gentle, strict, but non-punitive limits need to be set on inappropriate patient behavior and sometimes formal contracts need to be constructed. There is often room for direct skills-building work with the patient. If some relationship can be established with the patient, distress tolerance and interpersonal communication skills can be worked on. Mindfulness and stress-management techniques can be introduced to deal with distress and affective dysregulation, and thus decrease acting out behaviors. Through chain analysis and therapeutic conversation, patient behaviors that detract from receiving deserved care can be addressed and new avenues of getting needs met can be explored.

Sometimes, patients who are otherwise higher functioning can regress in hospital settings and appear personality disordered. Other times, history-taking, including dialogue with collateral sources, clarifies a longer-standing pattern of frank personality disorder. In this case, it is critical to make referral to psychotherapy and to consider referral to HIV-specialty clinics where there is psychiatry and psychology presence—this is critical since the personality disorder will undoubtedly surface in areas of medication and treatment compliance, provider interactions, and also in high-risk behaviors which are risks for further spread of HIV in the community.

29.2.4.6 Cognitive Disorders: Delirium and Dementia

Delirium

When the HIV-positive patient presents with altered mental status, special attention should be paid to ruling out organic processes associated with HIV-infection—these include direct HIV-infection of the CNS, opportunistic infections associated with HIV, other disorders related to HIV, as well as neuropsychiatric side effects of HIV treatment. As well, when a patient with unknown status (but high risk) has altered mental status of unclear etiology, HIV-testing should be done, as positive status necessitates additional evaluation.

Delirium is one of the most common diagnoses in HIV-positive patients evaluated by consultation psychiatry. HIV-positive patients have less cognitive reserve and are more likely to develop delirium. Delirium is characterized by rapid onset of fluctuating level of consciousness, markedly poor attention, disorientation, as well as perceptual disturbances. This diagnosis needs to be suspected even in patients with pre-existing psychiatric diagnoses. Practitioners often focus on more obvious phenomenon such as delusional content or hallucinations, deeming the etiology as psychiatric—disorientation and waxing/waning consciousness are not typical of a primary psychiatric illness and should be a tip-off to delirium. There is often a significant role for the consultant to provide education regarding delirium and its medical nature, despite neuropsychiatric and behavioral phenomenon.

As with non HIV-positive patients, the etiology is often multifactorial and the differential can include withdrawal/intoxication states, medication effects (especially anticholinergic medications, benzodiazepines, and narcotic analgesics), metabolic disturbances (e.g., hypoxia), electrolyte imbalances (hyponatremia, hypercalcemia), liver and renal failure, infection and sepsis (in HIV, one needs to consider HSV, VZV, CMV, and HIV encephalitis; as well as cerebral cryptococcus and toxoplasmosis), cerebral hypoperfusion (e.g., from shock and severe hypotension), postictal states and other CNS events (e.g., ischemic and hemorrhagic stroke).

The workup should include careful gathering of history from friends, family, case managers, and care providers in the community, to establish a better baseline and course of cognitive decline. A careful physical examination should be performed, including detailed neurological exam. Lab testing should be done and include evaluation of electrolytes, renal and hepatic function, syphilis serology, vitamin B12 level, and toxicology screen. Head imaging and unless contraindicated, lumbar puncture should also be performed. Review of current medications and evaluation of recreational drugs and alcohol consumption are also important. Electroencephalogram can be helpful if epileptiform activity is suspected, and diffuse slowing is consistent with delirium.

Lumbar puncture in HIV-positive individuals is complicated by frequent non-specific findings (e.g., mild elevations in white blood cell count, mild elevations in protein, mild decrease in glucose). Regardless, lumbar puncture can be critical for detecting treatable CNS diseases, including cryptococcal, syphilitic, tuberculous, or lymphomatous meningitis. CSF PCR for TB, varicella zoster virus (VZV), herpes simplex virus (HSV), cytomegalovirus (CMV), and JC virus (in progressive multifocal leukoencephalopathy, PML) can be useful tools when available.

Regarding imaging, MRI is more sensitive than CT, but CT with double-dose contrast can be a good alternative. Diffuse white-matter abnormalities can be suggestive of PML or HIV encephalitis. Periventricular contrast enhancement is sometimes seen with CMV or varicella zoster virus. Focal cerebral lesions are often abscesses (e.g., toxoplasmosis) or primary CNS lymphoma.

Treatment Considerations

Of course, attempts need to be made to treat the underlying disease(s) and other potentially exacerbating factors. Pharmacologic approaches can be useful for managing the delirium, especially the use of atypical antipsychotics, which have a lower risk of EPS. Haloperidol and chlorpromazine in small doses have also been shown to be effective in HIV/AIDS delirium without much EPS (Breitbart et al. 1996). Non-pharmacologic

approaches are also useful, including providing frequent reorientation, avoiding sensory overstimulation or deprivation, providing soothing music, and having friends, family members or community providers providing contact and presence. Once the delirium has cleared, it is important to process the experience of delirium with the patient, who can often experience it as intensely frightening and sometimes as indication of "going crazy."

HIV-Associated Neurocognitive Disorders (HAND) and HIV-Associated Dementia (HAD)/AIDS Dementia Complex (ADC)

The term HAND encompasses a spectrum of progressively severe CNS involvement, ranging from asymptomatic neurocognitive impairment to HAD/ADC. With the introduction of HAART, the incidence of AIDS Dementia Complex (ADC) has dramatically reduced. There is encouraging recent data which looked at a small sample (74) of older (mean age 51) HIV-infected individuals with a mean duration of infection of 17 years, and found successful cognitive aging (defined as an absence of neurocognitive deficits) in 32 %. This, in turn, was associated with better everyday functioning outcomes, including lower rates of decline in activities of everyday living, superior outcomes in dealing with medication management, and a lower rate of major depression and other forms of depression and anxiety (Malaspina et al. 2011). Despite this, HAND and ADC persist and recent estimates of less severe forms of the latter still hover around 20 % (Manji et al. 2013).

Some investigators maintain that HIV-1 proliferation in the brain is needed for development of ADC, while others argue that neurotoxicity can be an indirect result from pro-inflammatory cytokines and chronic, sustained immune activation in the CNS (Tan and McArthur 2012). For patients with ADC on effective antiretroviral regimens, it has been shown that macrophage secretions cause a dysregulation of proteins critical for regular function, but not outright neurotoxicity—thus for patients on antiretroviral therapy ADC is typically milder and a more slowly progressing deterioration in mental functioning.

Some HIV-infected individuals are manifesting a dementia more similar to Alzheimer disease than typical ADC—for example, demonstrating deficits in long-term memory. Some theories include: as patients with AIDS are living longer and aging, they may simply be developing Alzheimer's; some of the newer antiretroviral drugs might be increasing the risk of Alzheimer disease by affecting lipid metabolism and the processing of amyloid; and chronic, low-grade brain inflammation, as occurring in HIV-associated brain disease, might be contributing to a vulnerability to Alzheimer disease. Patients now need to be evaluated for cortical dysfunction as well as the subcortical dysfunction of more "classical" ADC.

Early manifestations of ADC include: (1) cognitive dysfunction, including forgetfulness, slowing, impaired concentration and attention, sequencing problems, (2) behavioral issues, including withdrawal and disinhibition, and (3) motor dysfunction, including slowing, unsteady gait, weakness, and poor coordination. Later manifestations can include: (1) cognitive dysfunction, including memory loss, word-finding problems, poor attention/concentration, impaired judgment, (2) behavioral issues, including withdrawal, apathy, irritability, agitation, disinhibition, (3) psychiatric issues, including mania, depression, psychosis, and (4) motor dysfunction, including slowing, spasticity, paraplegia, and incontinence.

There are neuropsychological tests that can be helpful in the identification of HAND and ADC. The International HIV Dementia Scale (IHDS) is a brief, bedside method that requires no equipment and includes a memory-recall test, a psychomotor-speed test, and a motor-speed test. Using a cutoff of 11 points or lower, researchers report 72 % sensitivity and 44 % specificity for all forms of HAND, even though it was developed for detection of ADC (Spudich et al. 2012). Examination of CSF for HIV RNA can be helpful—"CNS escape" occurs when there is HIV RNA detectable in CSF, but not in plasma. Thus when there is significant HAND or ADC and CNS escape is detected, further cognitive improvement can occur when the antiretroviral

regimen is modified to be more CNS-penetrating (Valcour 2011).

ADC also needs to be differentiated from delirium, which can sometimes be hard in the acute setting. Collateral history can be helpful in this regard, as delirium has an acute or subacute onset, whereas ADC has a more gradual decline. Of course, the two conditions can often be comorbid. Thus, when a patient with ADC develops an acute worsening in mental status, delirium workup should proceed.

Treatment Considerations

HAART can lead to significant improvement in AIDS-related cognitive deficits and AIDS-dementia, provided the particular agent has good CNS penetration. Some are proposing that nanotechnology may one day allow further control in characteristics that allow better penetration of the blood–brain barrier, and are urging research into active drug targeting systems that include nanoparticles. Their hope is that this will one day provide relief for neurological impacts of HIV/AIDS—i.e., HAND and HAD/ADC (Saxena et al. 2012). Case reports have described the use of risperidone (up to 6 mg/day) and clozapine in psychosis associated with HIV-dementia with significant improvement in symptoms and low EPS (Dettling et al. 1998; Zilikis et al. 1998). Behavioral and non-pharmacologic approaches should also be integrated (see Chap. 7).

29.2.5 Drug Interaction Issues in the Psychopharmacological Treatment of Patients with HIV and AIDS

Drug interactions are an important consideration and one needs to have an index of suspicion and investigate potential interactions prior to initiating psychotropic treatment (Ferrando and Wapenyi 2002). An increase in plasma concentration does not always translate into clinical significance—this depends primarily on the therapeutic index of the drug involved (Ferrando and Wapenyi 2002). Most documented interactions involve ritonavir, a potent inhibitor of the CYP 450 3A enzyme (Ferrando and Wapenyi 2002). Ritonavir causes a 145 % increase in AUC (area under the plasma concentration curve) of desipramine, so dose reduction and plasma level monitoring is recommended. Buproprion was listed as contraindicated with ritonavir, but this has been removed since it is metabolized by the 2B6 isoform, not significantly affected by ritonavir. Clozapine, pimozide and several benzodiazepines (clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam), and zolpidem are listed as contraindicated since ritonavir presumptively raises their serum levels. One study did show non-significant effects with zolpidem, so this contraindication is questionable. Methadone levels may be decreased by rifampin (used for TB treatment) and also the antiretrovirals ritonavir, nevirapine, and possibly efravirenz. It is advisable to follow serum methadone levels before and after initiation of HAART (Ferrando and Wapenyi 2002). Sildenafil levels may be raised by concurrent administration of ritonavir, saquinavir, and indinavir resulting in potentially dangerous cardiac side effects. Despite the need to be cautious, there have been few serious drug interactions documented and it is important to provide treatment when needed (Ferrando and Wapenyi 2002).

29.3 Organ Transplantation Patients

29.3.1 Unique Psychosocial Issues and Treatment Considerations

While HIV is an unanticipated "acquired" condition, transplantation-related immunodeficiency is often a long contemplated, desired, and "required" condition for survival. The field of transplantation is based upon the ability to adequately suppress a transplant recipient's immune system to allow tolerance of the graft, ensuring function, while minimizing infectious risk.

Since first attempted in the 1950s, transplantation has become a more common and accepted treatment by the public. Discussion of transplant

candidacy and issues such as adherence to medication are beyond the scope of this chapter, but are well described in the literature (Olbrisch and Levenson 1995; Levenson and Olbrisch 1993; Chisholm 2002). The focus of this section is on general characteristics of transplant recipients of all organ systems. Balanced information is presented to allow practitioners who have not previously treated transplant recipients to approach them with a sense of confidence that they can evaluate and initiate appropriate treatment plans.

A tenuous state of pharmacologically controlled immune function is required for survival among solid organ transplant recipients. This delicate balance requires ongoing vigilance of the recipient and healthcare team for warning signs of rejection and infection, which are primary threats to survival. Strict adherence to medications, diet, and self-surveillance are a way of life among those who adjust well, while depression, anxiety, and other psychiatric issues may result in those who have more difficulty coping (Perez-San-Gregorio et al. 2005).

Improving the side effect and efficacy profile of immunosuppressive agents has been a focus of attention over the last 30 years. The number and type of agents available has grown as a result, but remains limited in scope. All immunosuppressive agents are associated with potentially serious toxicity and side effects that impact short- and long-term functional ability (Hathaway et al. 2003; Umeda et al. 2011; Corbett et al. 2013). Table 29.1 summarizes agents, mode of action, general, and neuropsychiatric side effects that may be observed.

Table 29.1 Immunosuppressive agents commonly used in transplantation with associated medical and psychiatric side effects (Trzepacz et al. 1991; Trzepacz et al. 1993a, 1993b)

Class	Agent	Mode of action	General side effect profile	Psychiatric side effect profile
Corticosteroids (Hathaway et al. 1996; Cerullo 2006; Prasad et al. 2003)	Prednisone methyl prednisolone	Anti-inflammatory	Diminished signs of infection, osteoporosis, impaired glycemic control, hypertension, hyperlipidemia	Depression (especially with late phase weaning) Insomnia cognitive decline Mania Confusion Agitation (prominent in pulse dosing for rejection)
Anti-metabolites (Crawford et al. 1996)	Azathioprine	Blocks DNA synthesis	Neutropenia, increased likelihood of infection, bone marrow suppression	None noted in existing literature
Calcineurin inhibitors (CNI) (De Groen et al. 1987; Ciancio et al. 2004; Chegounchi et al. 2006)	Cyclosporine tacrolimus	Inhibit calcineurin phosphatase and T cell activation	Nephrotoxicity, vulnerability to viral infection, hypertension, diabetes, hyperlipidemia	Depression Confusion Cortical blindness Quadriplegia Seizures Coma
Purine synthesis inhibitors (Prasad et al. 2003)	Mycophenolate mofetil	Prevent B and T cell proliferation	Gastrointestinal cramping diarrhea, neutropenia	Distress from GI side effects
Target of rapamycin inhibitors (TORI) (Kasner et al. 2005)	Sirolimus	Inhibit interleukin 2T cell Proliferation	Hyperlipidemia, thrombocytopenia	None noted in existing literature
Depleting antibodies	ATG (antithymocyte globulin) OKT3 (muromonab-CD3)	Deplete T and/or B cells that have been activated and are acutely injuring graft	Allergic reaction, fever, flushing, hypotension, aseptic meningitis, coma	Confusion Lethargy Coma

Table 29.2 Psychiatric symptoms and medical mimics

Psychiatric symptom	Symptom delineation	Medical mimic
Depression	Fatigue, low energy, difficulty concentrating	Anemia: hemoglobin of 6 Severe B12 deficiency Lymphoproliferative disorder
Anxiety	Apprehension Inability to relax Frequent dyspnea	Sepsis Rejection (pulmonary/cardiac) Pulmonary embolism
Psychosis	Hallucinations Delusions	Stroke CMV infection Cyclosporine toxicity
Mania	Impaired sleep, Motor agitation, racing thoughts, impulsive behavior	Thyrotoxicosis Steroids Central nervous system herpetic infection
Dementia	Forgetfulness, confusion, difficulty concentrating	Hypothyroidism Vascular insufficiency Stroke in evolution

29.3.2 Psychiatric Co-morbidities

29.3.2.1 Diagnostic Issues

Individuals who undergo transplantation are generally very ill and often exhausted by their chronic conditions; the stress and concomitant physiologic dysfunction associated with chronic organ dysfunction may be associated with adjustment, anxiety, cognitive, and mood disorders addressed in other areas of this text. Preexisting symptoms and syndromes may be exacerbated post-transplantation if treatment is not rendered. Willingness to accept mental health care is often challenging post transplantation due to a number of factors, such as limited resources and impaired ability to access treatment due to tenuous health as well as poor motivation on the part of the patient. Preoperative psychosocial assessment can have beneficial effect by educating potential recipients and providers of the likelihood of worsened symptoms post transplantation.

29.3.2.2 Specific Assessment Considerations

Each individual who has undergone solid organ transplantation is unique. Those referred for psychiatric assessment and treatment are manifesting symptoms that are generally significant enough to have raised the attention of their families and/or transplant providers. Attention to detail of pre-transplant, peri-operative, and post-transplant courses will provide the necessary information to accurately diagnose and treat individuals who present for care.

There are general caveats that should guide the approach to all transplant recipients with new onset psychiatric symptoms: (1) symptoms are of an organic etiology unless (and occasionally, even if) medical evaluation is negative; (2) a full review of somatic symptoms will often guide further necessary evaluation; and (3) attention to the timeline of all prescribed medications, supplements, and herbal remedies with respect to psychological symptoms will often provide a clue for iatrogenic symptoms. Table 29.2 presents acute medical mimics of psychiatric symptoms and syndromes.

Unlike more routine evaluations, exposure histories are essential in teasing out potential infectious etiologies for psychiatric symptoms. In addition, inquiry regarding adherence to medications and utilization of herbal remedies should be addressed to the recipient (and support persons if available), as the complexity of treatment regimens leaves little room for error. Moreover, data indicate that adherence can be strongly impacted by the presence of psychiatric disorders and psychosocial problems (Krahn and DiMartini 2005; Carrasco et al. 2009). Up to date medication lists are essential in determining if medications

have been added by outside physicians not associated with the transplant program. Immunosuppressive toxicity or organ rejection related to inadequate immune suppression can result from the addition of a medication(s) that interacts with transplant regimen.

29.3.2.3 Cognitive Disorders/Organic Brain Syndrome (OBS) and Delirium

OBS and delirium are common in early transplant recipients and in the pre-transplant period. The full range of symptoms from quiet withdrawn states to acutely agitated psychotic states may be seen in post-transplant recipients and often serves as an "early warning sign" of an undeclared infection or impending graft dysfunction. The effect of chronic immunosuppressive agents on cognitive decline noted post-transplantation remains unclear though there is evidence of at least short-term neurocognitive effects (Cupples and Stilley 2005; Aridon et al. 2009; Emirolglu et al. 2006; Umeda et al. 2011). Cognitive deficits secondary to prior addictions may be unmasked in the post-transplant period, while pre-transplant decline attributed to organ dysfunction may not remit, suggesting the presence of dementia (Sorrell et al. 2006).

Common underlying medical illnesses associated with organ failure requiring transplantation, including hypertension, diabetes, and hyperlipidemia, place the recipient at an increased risk for central nervous system small vessel ischemic disease, which may manifest as a stepwise progressive cognitive decline. An abrupt, profound change or a progressive decrement in cognitive functioning also requires evaluation for progressive leukoencephalopathy which has been associated with the utilization of calcineurin inhibitors (Munoz et al. 2006; Umeda et al. 2011). Additionally the potential for rare, but debilitating progressive multifocal leukoencephalopathy associated with polyomavirus is a concern in the absence of other definable causes for decline (Shitrit et al. 2005).

29.3.2.4 Mood Disorders

Post-transplantation depressive disorders have been reported in up to 60 % of solid organ recipients (Corbett et al. 2013). Presentation of mood disorders may range from a subtle return to smoking or other unhealthy behaviors, sudden non-adherence to medications or necessary follow up, to pronounced symptoms such as mania and suicidality. Depressive symptoms may be a continuation or exacerbations of those experienced in the pre-transplant period, or occur after transplantation. In the latter case, depression may be part of an adjustment reaction, or be secondary to an incipient medical condition or due to a medication effect. The recognition of depressive symptoms in the post-transplant period is crucial as studies have shown that depression and its related effects predict poorer outcomes such as reduced quality of life, graft failure, and a higher rate of mortality (Favaro et al. 2011; Zelle et al. 2012; Rogal et al. 2013). A recent study of liver transplant recipients found that those with increasing or persistent depression had a two times higher risk of death when compared with patients with more minor symptoms (DiMartini et al. 2011a, b). Research to date indicates that depressive symptoms occurring after transplant may more strongly correlate with adverse outcomes than do pre-existing symptoms (Rosenberger et al. 2012). However, it has yet to be clearly established that treatment of depression results in a reduction in mortality, though some studies have shown that reducing depressive symptoms may promote graft function (Rogal et al. 2013).

Essential evaluation should include a careful review of symptoms, physical evaluation, and if indicated, a diagnostic work-up prior to ascribing a primary psychiatric etiology for the symptoms.

29.3.2.5 Anxiety Disorders

Anxiety symptoms are also prevalent in organ transplant recipients with rates ranging from 14 to 40 % (Dew et al. 2012; Limbos et al. 2000; Tanriverdi et al. 2004). Acute presentation of anxiety symptoms may herald an imminent life threatening illness, and the potential for acute physiologic decompensation needs to be considered. Despite the conviction of many physicians, it is unusual for panic disorder to develop late in life. Thus, new onset anxiety should be viewed as of primary organic etiology until proven otherwise. In addition, substance abuse and

withdrawal may also contribute to anxiety states. More recently, PTSD secondary to medical illness and treatment has been appreciated, particularly in the setting of critical illness, ICU stay and associated delirium (DiMartini et al, 2007). It has been estimated that the prevalence of PTSD in the transplant population is 11–17 % (Favaro et al. 2011) and a recent study found that the prevalence of PTSD in a cohort of lung transplant recipients was two times higher than in the general population (Gries et al. 2013). While the data on PTSD in transplant patients are somewhat limited, evidence to date indicates that post-traumatic symptoms can negatively impact quality of life, and may impair drug adherence and sleep quality. PTSD symptoms have also been correlated with higher rates of re-hospitalization, disease relapse, and increased morbidity and mortality (Favaro et al. 2011; Guimaro et al. 2011; Cavalcanti-Ribeiro et al. 2012; Jin et al. 2012; Gries et al. 2013), and should be considered in the setting of new-onset anxiety.

29.3.2.6 Psychotic Disorders

Transplant centers rarely accept individuals with a known history of schizophrenia or schizoaffective disorder. As such, the number of recipients with these illnesses is small though many have been treated successfully. New onset psychotic disorders post-transplant are usually of organic etiology (Chegounchi et al. 2006; Southworth and Dunlap 2000; Hotson and Enzmann 1988). Central nervous system infection, drug toxicity, systemic infections, and delirium may present with hallucinations, paranoid delusions, disorganized behavior, and thought disorder and must be carefully ruled out.

29.3.2.7 Substance Abuse/ Dependence Disorders

Resumption of prior addictions needs to be considered in evaluating new onset cognitive, mood, anxiety, or psychotic illnesses, especially when substances were utilized in the pre-transplant period, as there is evidence that recipients with a history of substance abuse have a higher incidence of mood and anxiety symptoms and poorer quality of life post-transplant (Stilley et al. 2010). The extent of substance use is also important and should be clarified. Approximately, 70–75 % of liver transplant recipients meet DSM-IV criteria for alcohol dependence, and 20–25 % for alcohol abuse (DiMartini et al. 2008). Return to alcohol consumption has been studied extensively in the liver transplant population (Kelly et al. 2006; Beresford et al. 2004; DiMartini et al. 2002; DiMartini et al. 2006) and it is estimated that 30–50 % of transplant recipients may relapse. However, the incidence of serious use of alcohol is somewhat less, at 10–15 % (Surman et al. 2009). Noted predictors of relapse are a diagnosis of mental illness, lack of insight into substance problem, lack of a stable partner, daily quantity consumed in years prior to transplant assessment, active substance use at time of evaluation, and prior alcohol rehabilitation (DiMartini et al. 2006; Kelly et al. 2006; Bellamy et al. 2001). Resumption of disordered alcohol consumption increases the risk for non-adherence to medications and inattention to self-surveillance, which may lead to increased morbidity, graft failure, and mortality.

Of equal import although less frequently addressed is return to nicotine dependence. Recidivism is common post-transplantation and can negatively affect graft function and place individuals at higher risk for infection (DiMartini et al. 2005; Mehra et al. 2005).

Relapse with other illicit substances is less common, as those who receive transplants are typically carefully selected. Currently, limited numbers of individuals are transplanted while participating in Methadone Maintenance Treatment (MMT) (Koch and Banys 2001, 2002) though a return to opiate abuse appears to be low, with variable reports of survival (Liu et al. 2003; Kanchana et al. 2002). Anecdotal evidence suggests that recipients should remain on methadone unless carefully monitored as the rate of opiate relapse is high when patient is taken off of methadone (DiMartini et al. 2011a, b).

Chronic pain and the neuropathic sequelae of illnesses such as diabetes and *Herpes zoster* require coordinated management to optimize quality of life and assure judicious administration of controlled substances. Overall, it is

recommended that pre-transplant pain regimens should be re-established after surgery (Surman et al. 2009) though dose adjustments in opiates and methadone may be required after transplant when hepatic metabolism normalizes (DiMartini et al. 2011a, b). This may also provide an opportune time to wean the patient from a chronic analgesic opioid dependency (see Chap. 22).

29.3.3 Approaches to Treatment

The adage "start low, go slow, and be aware of side effects" is also appropriately applied in transplant recipients. Symptom identification and treatment are the primary goals of evaluation and an inclusive biopsychosocial approach can facilitate appropriate diagnosis and treatment planning.

Thoughtful consideration of medication side effect profiles may enhance treatment tolerability. For example, the use of an activating agent is imprudent in an agitated depression, while a sedating agent would be ill advised in someone who is unable to get out of bed or attend to activities of daily living. Further, with the addition of many new medications post-transplant, there is a potential for drug–drug interactions, and monitoring for symptoms of toxicity or lack of therapeutic efficacy is important (Vella and Sayegh 1998; Surman et al. 2009). In general, newer psychotropics should be used with special caution in transplant recipients and collaborative planning with a transplant pharmacist can be helpful in establishing a treatment regimen.

The recovery and return to function in family, community, and employment environments simultaneously present the potential for added stressors. The recipient's support system can be severely challenged by the procedure and recuperative period and the role adjustment for patients and those around them can generate significant distress for all.

With an already complex medication regimen to follow, patients may be more open to psychosocial interventions for mood and anxiety symptoms. Psychotherapeutic interventions to treat post-transplant recipients such as cognitive behavioral and mindfulness based approaches have demonstrated promise (Baines et al. 2004; Kreitzer et al. 2005; Gross et al. 2009, 2010) as well as music therapy (Madson and Silverman 2010; Ghetti 2011). Therapies to promote adherence have also been shown to be effective (Lisson et al. 2005), and individual and group psychotherapies can provide an environment for recipients and their support persons to address the challenges inherent to the transplant process.

The solid organ transplantation field strongly requires assessment studies that accurately evaluate the impact of psychosocial factors present prior to transplant on a variety of outcomes as the evidence demonstrates that they are highly correlated with significant morbidity and mortality, primarily through their effect on adherence. The role of the psychiatrist thus is key in aiding the transplant team assesses for pre-transplant psychiatric and psychosocial issues as well evaluating for the presence of new-onset psychiatric disorders after transplantation which may result in poorer medical and psychological outcomes.

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The Liver-Impaired Patient

30

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Contents

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30.1 Introduction

Among all organs in the human body, the liver is the largest and carries out the greatest number of functions. The liver's important and multiple activities impact all body systems, including the nervous system. The relationship between the liver and the brain has been known for centuries (Frerichs 1860; Lewis and Howdle 2003; Tarter et al. 1989; Wilson 1912). Patients with hepatic dysfunction frequently experience neuropsychiatric syndromes, of which the most well known is hepatic encephalopathy (Ferenci et al 2002).

Chronic liver disease in the USA is a significant cause of morbidity and mortality for adults. In 2010, cirrhosis and chronic liver disease accounted for the 12th leading cause of all deaths in the USA (Murphy et al. 2013). With the increase in incidence of diagnosed nonalcoholic fatty liver disease and the epidemic of chronic hepatitis C (CHCV) infection, the number of chronic liver diseased adults in the USA is expected to escalate in the next decades. There are approximately 3.9 million cases (2 % of the US population) of HCV infection in the USA, of whom 85 % are expected to develop CHCV. Alcoholic liver disease (ALD) may occur independently, though ALD is often comorbid with CHCV, resulting in a more rapid progression to cirrhosis. Nonalcoholic fatty liver disease, which may be the most common liver disease in the USA (accounting for 5 % of the US population), has a high prevalence in the obese, type 2 diabetic population, and can lead to nonalcoholic steatohepatitis (NASH) (Farrell 2003). There are also a number of less common diseases which affect the liver including Wilson's disease, mitochondrial hepatopathies, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), porphyria, hemochromatosis, and chronic hepatitis B liver disease.

Individuals with psychiatric and substance-use disorders have a much greater risk of developing chronic liver disease, including CHCV and fatty liver disease, than the rest of the population. Hepatitis C has been termed the "psychiatric epidemic." It is estimated that 20 % of severely mentally ill patients have HCV, which is more than ten times the prevalence in the general US population. Substance-use disordered individuals are at even higher risk (40 % and higher) for CHCV from intravenous or intranasal drug abuse, and they often have comorbid alcoholic liver disease. Further, psychiatric patients, due to factors of lifestyle and medication exposure, often develop metabolic syndrome in adulthood, which can lead to nonalcoholic fatty liver disease. Because liver disease is prevalent among psychiatric patients, and since hepatic dysfunction itself creates neuropsychiatric symptoms, psychiatrists in the twenty-first century must be equipped to diagnose and treat the liver-impaired patient.

30.1.1 Neuropsychiatric Symptoms in Chronic (Mild, Noncirrhotic) Liver Disease

30.1.1.1 Neuropsychiatric Symptoms of Mild (Noncirrhotic) Chronic Liver Disease, All Etiologies

In patients with hepatic dysfunction which has progressed to cirrhosis and end-stage liver disease, neuropsychological impairment has been well studied (Lewis and Howdle 2003). However, in patients with mild chronic liver disease who may have two decades or more before developing complications of cirrhosis, neuropsychiatric symptoms including cognitive impairment have only recently been evaluated. Now neuropsychological abnormalities have been described from mild liver disease to end-stage liver disease and the spectrum of symptoms has expanded so that the full range is from subtle changes in concentration and attention to the severe impairment of coma and death due to cerebral edema. The level of neurocognitive impairment seems to correlate directly with the degree of liver pathology (Hilsabeck 2003). The neuropsychiatric abnormalities in chronic liver disease include (1) cognitive impairment, (2) fatigue, and (3) depression and anxiety.

30.2 Cognitive Impairment

Cognitive impairment in liver disease ranges from mild cognitive changes to overt hepatic encephalopathy (Collie 2005; Lewis and Howdle

2003). Although extensive serial studies of cognitive decline in liver dysfunction of all types have not been done, evidence to date suggests that concentration abilities and complex attention are affected earlier in the liver disease process, while problems with psychomotor speed, learning, and mental flexibility occur later, in more diseased patients, and verbal skills are less impaired (Hilsabeck 2003).

The varieties of liver disease in which cognitive dysfunction has been documented have expanded to include other liver diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, alcoholic liver disease, and Wilson's disease (Collie 2005). Impaired performances have been reported in up to 50 % of noncirrhotic patients (Hilsabeck 2003). Most of the studies to date have compared liver pathology with neuropsychiatric dysfunction without specifying the etiology of the liver disorder, and there are few comparative studies on neuropsychiatric differences among these distinct diseases (Collie 2005). Individuals who are affected cannot perform driving, household, and job duties as accurately as before their liver disease, and often make disability claims (Hilsabeck et al 2003).

There is growing evidence of neuroinvasion of the HCV virus which either directly or indirectly causes the cognitive deficits in this group of patients. In a recent study of 201 CHCV patients with advanced fibrosis, one-third showed evidence on neuropsychological testing of a mild, nonfocal processing deficit (Fontana et al. 2005). Using proton magnetic resonance spectroscopy (MRS), Forton et al. (2002) detected cerebral metabolite abnormalities in the white matter and basal ganglia of HCV patients with mild liver disease. These abnormalities were not evidenced in chronic hepatitis B patients or healthy controls. The same researchers later found that the HCV patients were more impaired on cognitive tasks than those who had cleared HCV and healthy controls, with the most notable differences being in measures of concentration and information processing speed. The most impaired patients had the greatest neuroimaging abnormalities, which supports a cerebral effect of the HCV virus associated with neurocognitive deficits. Depression, fatigue, and intravenous drug use history could not account for the differences in cognitive functioning (Forton et al 2005).

30.2.1 Assessment and Treatment

Cognitive dysfunction in noncirrhotic liver disease has been measured by neuropsychological tests which can assess attention, motor ability, learning, and memory, and assist in the evaluation of an individual's functional capacity. Objective testing is helpful for clinical assessments because the patient's self-assessment often does not correlate with the measured abilities or deficits. Such a battery might include the Repeatable Battery for the Assessment of Neuropsychological Status, the Rey Complex Figure Test, Digit Cancellation, Trail Making Test, Symbol Digit Modalities Test and the Number Connection Test. Providing education about neuropsychiatric test results to the patient and family is recommended. The natural history of cognitive dysfunction in liver disease is unknown and there are no well-controlled studies of specific treatments for this dysfunction, apart from treatment of the underlying liver disease, including hepatitis C.

30.3 Fatigue

Fatigue, which may or may not correlate with neurocognitive dysfunction, has also been well documented in chronic liver disease patients (Wessely and Pariante 2002). From a review of the literature, Wessely and Pariante (2002) concluded that there is no compelling epidemiological evidence that fatigue and depression are specific to HCV liver disease per se, but instead may be simply a correlation of chronic liver disease of any type. These reviewers argued that fatigue (and depression) are associated with HCV simply because the HCV patients have the same risk for metabolic and mood disorders, demographics, and lack of exercise, as for patients with other physical illnesses.

In two studies, fatigue was not related to neurocognitive dysfunction, as measured by cognitive tests or by electrophysiologic measurement of P300 event related potentials (Hilsabeck 2003; Kramer et al. 2002). In 2005, Kramer et al. emphasized that fatigue severity and age correlated with the measured health-related quality of life, whereas neurocognitive dysfunction or hepatic function did not, and reported the need for effective therapy to reduce the burden of fatigue in HCV patients.

30.3.1 Assessment and Treatment

Fatigue in chronic disease patients, including hepatitis C, has been measured by the Fatigue Severity Scale, the Fatigue Impact Scale and the Brief Fatigue Inventory. The serotonin antagonist, odansetron, at 4 mg twice a day for a month, significantly relieved fatigue symptoms in chronic hepatitis C patients in a randomized, placebo-controlled, double-blind trial. Another medication, modafinil, which has been approved for narcolepsy, has shown reduction in symptoms of fatigue and depression for HIV-positive patients in an open label study and has been used clinically for chronic liver disease patients. Finally, escitalopram, a serotonin reuptake inhibitor, was reported to improve measures of both fatigue and pain in hepatitis C patients.

30.4 Depression and Anxiety

Patients with chronic liver disease experience mild levels of depression and anxiety regardless of hepatic disease etiology, although hepatitis C patients are the most studied. In one study of affective disorders in chronic liver disease, the present of a history of intravenous drug abuse did not affect levels of anxiety or depression. However, depression and anxiety were more prevalent in those with a history of both psychiatric disorders and drug abuse (Hilsabeck and Malek-Ahmadi 2004).

30.4.1 Pathogenesis

The pathogenesis of affective symptoms in chronic liver disease is unclear. Apparently there is no association between the severity of liver disease and depression or anxiety levels (Forton et al 2005). Certainly many patients with hepatitis C have comorbid psychiatric disorders and substance use disorders which may be the sole etiology of the affective symptoms.

30.4.2 Assessment and Treatment

A variety of antidepressants have been used to treat depression in HCV patients. Based on a recent review, caution should be used in prescribing selective serotonin reuptake inhibitors for patients with severe liver disease (cirrhosis, portal hypertension, or liver failure), in combination with aspirin or nonsteroidal anti-inflammatory drugs because of the increased risk of hemorrhage.

30.5 Chronic Diseases of the Liver

30.5.1 Hepatitis C

Hepatitis C virus (HCV) is a single-stranded, positive-sense, enveloped ribonucleic (RNA) virus of the Flaviviridae family, which includes the West Nile virus and the Japanese encephalitis virus. HCV has six major genotypes; genotype 1 accounts for about 75 % of US cases. The hypervariable mutations in the viral envelope protein produce vast quasispecies rapidly, allowing the virus to avoid the host immune response (Crone 2006).

The virus is transmitted primarily by parenteral exposure to infected blood, such as blood transfusions, hemodialysis, or injections with infected needles. In the USA, the major risk of contracting the virus is through intravenous drug use; also intranasal cocaine users, tattoo recipients, individuals who received dental care in a third world, and health care workers who suffer

accidental needle sticks are at risk. In the past, hemodialysis and blood transfusion recipients prior to 1992 were at risk (Crone et al 2006; Bonkovsky and Mehta 2001).

About four million Americans are infected with hepatitis C virus. Although the incidence of acute cases has dropped, there are more chronic cases being detected each year. There are high rates of chronic HCV infection among individuals in the correctional system, as well as for those with psychiatric and substance use disorders (Hensley and Withers 2003). For example, 40 % of 360 male patients seeking substance abuse treatment were HCV antibody positive (Withers 2003). Of 134 patients referred for HCV therapy in an outpatient medical setting, 71 % had a psychiatric disorder and 96 % a substance-use disorder; 70 % were dually diagnosed. In this study, point prevalences for psychiatric disorders were affective, 42 %; anxiety, 37 %; and psychotic, 7 % (Hensley and Withers 2003).

Of infected patients, 85 % develop a chronic disease. This high rate of chronic viral persistence results from both weak host T cell responsiveness and specific viral mechanisms of immune escape. Spontaneous HCV viral clearance is negatively associated with human immunodeficiency virus (HIV) coinfection and alcohol use disorders, and positively associated with hepatitis B (HBV) coinfection and not associated with race. Both acute and chronic hepatitis C are asymptomatic in most patients. However, the disease is slowly, chronically progressive and in about 20 % of HCV patients cirrhosis evolves in 20 years; and of these 20 % develop hepatocellular carcinoma. The considerable variability of end organ damage (fibrosis to cirrhosis) in individuals may be due to host genetic polymorphisms in genes governing the immune response and fibrosis pathways in addition to viral pathogenicity factors. The virus is hepatotropic but can also replicate in leucocytes, including monocytes and macrophages. There are also a number of extrahepatic manifestations, including mixed cryoglobulinemia with leukoclastic vasculitis and porphyria cutanea tarda (Bonkovsky and Mehta 2001). Factors which worsen the progression of HCV liver disease include coinfection with HIV or HBV, alcohol abuse, fatty liver, and iron overload (Crone et al 2006).

Fatigue, depression, anxiety, and cognitive dysfunction are the most commonly reported symptom in CHCV patients (Hilsabeck and Malek-Ahmadi 2004). In fact, fatigue is considered a hallmark symptom in hepatitis C virus infection. Anxiety and mood symptoms are also prevalent. Of 134 male patients with CHCV being evaluated for interferon and ribavirin therapy, more than half the patients experienced significant anxiety (54 %), and almost half (45 %) had depression and aggression symptoms, and 41 % reported a low or very low quality of life. Anxiety was more commonly reported by African-Americans or Hispanics. Depression scores were significantly influenced by a diagnosis of PTSD or being without a partner; and aggression scores were higher in those diagnosed with either PTSD or an alcohol or substance use disorder (Hensley et al. 2003). The cognitive deficits noted on neuropsychological testing in HCV patients include impaired attention, psychomotor and working memory, with intact verbal skills and visuoconstructional abilities. They are commonly experienced by patients as “brain fog” or “mental clouding” (Forton et al 2005; Hilsabeck et al. 2002).

As discussed previously, since HCV patients often have substance use or psychiatric disorders, it is difficult to determine whether or not the virus itself contributes to the preexisting anxiety, aggression, depression, or “brain fog.” However, there is a growing body of recent literature which postulates HCV neuroinvasion.

30.5.2 Hepatitis B

30.5.2.1 The Hepatitis B virus (HBV) Deoxyribonucleic Acid (DNA) is a double-stranded Virus from the Family Hepadnaviridae

The HBV is transmitted through sexual contact and intravenous transmission, including intravenous drug use. For adult-acquired infection, less than 5 % develop a chronic infection. In contrast to HCV which regularly develops into a chronic

infection, hepatitis B infection in most adults (95 %) is an acute infection only. After the acute attacks, most adults recover completely and remain immune to future hepatitis B infection.

About 1.2 million persons in the USA have chronic hepatitis B infection. Among severe mentally ill patients, HBC (based on antibodies to core HBV) is estimated to be five times more prevalent than in the general US population, or 23.4 %.

Of the 5 % of adults who develop a chronic hepatitis infection, about 12–20 % develop cirrhosis. Symptoms vary from the inactive carrier state to the development of cirrhosis, end stage liver disease, hepatic carcinoma, and death. The course varies with the clinical setting. In one study of 296 HbSag-positive blood donors, in a 30-year follow-up period, the incidence of any clinically significant liver-related morbidity was not significantly different from the HBV-negative blood donors. It seems that in low-risk areas, the majority remain asymptomatic with very little risk of cirrhosis or hepatocellular carcinoma.

Many patients with chronic hepatitis B are asymptomatic, while others have nonspecific symptoms like fatigue. Depression and anxiety have also been reported. Chronic hepatitis B liver patients also have similar cognitive deficits, as CHCV patients, with poorer functioning in tasks requiring attention and psychomotor speed, though all these neuropsychiatric symptoms are not as prominent as in the CHCV patients (Hilsabeck, Perry, and Hassanein 2002).

30.5.3 Alcoholic Liver Disease (ALD)

ALD develops when humans chronically ingest too much alcohol. Some adverse liver changes can be seen with as little as 20 g per day in women (one drink = 14 g) and 40 g in men; however liver cirrhosis develops in less than 20 % of humans ingesting this amount of alcohol. Whether or not there is a dose–response relationship between alcohol and liver damage is arguable, but it is generally agreed that between 50 and 80 g, or 4–6 drinks daily or more for 10–20 years substantially increase the risk of cirrhosis, which is 2–3 times greater in women than men (Reuben 2006). Factors which accelerate alcoholic damage to liver tissue are certain drugs, high-fat diet, HCV infection, and genetic factors (female sex, enzymatic polymorphic forms of ADH and ALDH, hemochromatosis) (Lieber 2005).

The epidemiology of alcohol dependence is estimated to be 10–15 % of the adult population in the USA. The incidence of alcohol liver disease is less than this, but estimates vary widely depending upon the population surveyed. Often chronic liver disease is undetected until late stages (cirrhosis) when symptoms become apparent. Also, it is difficult to separate the impact of alcohol from other factors and diseases affecting the liver.

Chronic and excessive ethanol consumption is associated with cellular proliferation, fibrosis, cirrhosis and cancer of the liver. In the past half century it has become apparent that alcohol's toxicity to liver is not primarily due nutritional deficiency (Lieber 2005). Instead, alcoholic hepatoxicity is linked to the metabolic disturbances associated with the oxidation of ethanol by liver alcohol dehydrogenase (ALD) pathway and the redox changes produced by the generated NADH, which in turn affects the metabolism of carbohydrates, lipids, proteins, and purines. The clinical result is hyperuricemia, hypoglycemia, and hepatic steatosis by inhibiting lipid oxidation and promoting lipogenesis. There is also an alternative pathway of ethanol metabolism, the microsomal ethanol-oxidizing system. Alcohol increases both the activity of the main enzyme [ethanol-inducible cytochrome p450E1 (CYP2E1)] and its gene, resulting in ethanol metabolism and tolerance to alcohol. Activation of this enzyme, CYP2E1, explains the susceptibility of heavy drinkers to liver damage by solvents and other compounds. Induction of the microsomal pathway contributes to increased acetaldehyde generation which promotes glutathione depletion, free radical-mediated toxicity, and lipid peroxidation. Acetaldehyde increases hepatic collagen synthesis and thus development of fibrosis and cirrhosis (Lieber 2005).

Alcoholic hepatitis may complicate preexisting alcoholic fatty liver or cirrhosis. The exact pathogenesis of alcoholic hepatitis is uncertain,

but it is known to involve metabolism of alcohol to toxic products, oxidant stress, acetaldehyde adducts, the action of endotoxin on Kupffer cells, and impaired hepatic regeneration. Cytokines and immunity are actively involved in its pathogenesis. In alcoholic hepatitis, inflammation contributes to portal hypertension. Mild alcoholic hepatitis reverses with abstinence and the long-term prognosis is determined by the underlying alcohol-use disorder. Severe alcoholic hepatitis is associated with an almost 50 % mortality rate. Meta-analysis of well-designed clinical trials revealed that, contrary to popular opinion, milk thistle did not significantly improve the course of patients with alcoholic and/or hepatitis B or C liver disease (Rambaldi et al 2005).

Cognitive impairment in alcoholics without liver disease is reported to include impairment in executive functioning, as well as visuospatial, verbal, and nonverbal working memory. Neuroimaging shows alcohol-related damage to the frontal lobes and cerebellum. It is well established that individuals with alcohol dependence are at risk of developing Wernick–Korsakoff's syndrome, which is related to a depletion of thiamine in alcoholism. The neurocognitive deficits are typically impairments in the formation and retrieval of new memory (Collie 2005).

Few studies have investigated the contribution of liver disease to cognitive dysfunction in alcoholics. Although it would be expected that alcoholic liver patients would have greater cognitive dysfunction than alcoholics without liver disease, studies to date on the two groups showed equal level of dysfunction in tests of learning, memory, simple and complex attention, psychomotor function and general intellectual ability (Collie 2005). Walton and Bowden (1997) correlated liver disease status (measured by serum GGT and albumin) with mental ability, and did not find an influence. They concluded that in alcoholics without cirrhosis, liver disease does not appear to be involved in chronic alcohol-related cognitive impairment. However, in cirrhotic patients with Wernicke's encephalopathy, quantitative morphology suggests that alcoholic liver patients lose a disproportionate amount of subcortical white matter compared with cortical gray matter. Further studies are needed to assess the contribution of liver disease to cognitive deficits and morphological changes in the brains of alcoholics.

30.5.4 Nonalcoholic Steatohepatitis (NASH)

NASH is the hepatic manifestation of the metabolic (or insulin resistance) syndrome. It is a result of necroinflammatory changes in the liver. A certain proportion of individuals with nonalcoholic fatty liver disease (NAFLD) can develop NASH (Farrell 2003).

The pathophysiology for NASH involves insulin resistance, which causes steatosis. The second factor is oxidative stress, which produces lipid peroxidation and activates inflammatory cytokines resulting in NASH. Risk factors include type 2 diabetes and obesity. Cases occur most commonly in obese, middle-aged women with diabetes (McCullough 2002).

About 2–4 % of all adults have NASH. The NAFLD affects 5 % of the US population or about 20 % of all adults; about one-fifth of these develop NASH. Cirrhosis from NASH is now the second most common age-related cause of death in type 2 diabetes. It is estimated that by the year 2025 more than 25 million Americans may have NASH-related liver disease (McCullough 2002). Psychiatric patients who develop metabolic syndrome are at risk of developing NASH.

In this disorder, the diagnosis is often delayed. The syndrome of NAFLD and NASH may be clinically silent and undetected by aminotransferase levels or diagnostic imaging. Diagnosis is based on biopsy. The course of the disease is affected by the comorbidities: obesity, diabetes, and hyperlipidemia. Weight reduction and increased exercise, and avoidance of hepatotoxins such as alcohol, can slow the liver damage. Ursodeoxycholic acid has shown benefit and is being investigated as a treatment option. About 25 % of those with NASH develop cirrhosis. Fatigue and cognitive dysfunction, including reduced attention and psychomotor speed, have been reported in patients with NASH (Hilsabeck et al 2002).

30.5.5 Porphyria

The porphyrias are genetic or acquired deficiencies of enzymes in the heme biosynthetic pathway. It is thought that the periodic madness of King George III was a manifestation of hepatic porphyria.

The hepatic porphyrias result from specific enzymatic defects in the synthesis of heme. Interruption of the biosynthetic pathways results in an accumulation of heme precursors in the tissues, serum, urine, and feces. The classification is based on the specific enzyme deficiencies and tissues involved. The symptoms have been divided into "neurovisceral" and "photocutaneous." The neurovisceral symptoms include abdominal pain, psychiatric and neurological symptoms. The porphyrias associated with increased production of delta aminolevulinic acid and/or porphobilinogen are associated with central and nervous system damage and symptoms. The etiology of these symptoms is not clear, but hypotheses include neurotoxicity caused by the precursors, decreased gamma amino butyric acid (GABA) concentration, loss of heme in the CNS, increased levels of brain tryptophan, and decreased plasma melatonin. Photocutaneous symptoms develop because porphyrins cause photosensitization and skin damage through exposure to ultraviolet light, with production of tissue-damaging free radicals.

There is considerable interaction between environmental factors and genetics, so that not all gene carriers develop clinical symptoms. Underlying hepatic disease may be a factor in attacks of porphyria cutanea tarda. These liver diseases may be from HCV, HIV, alcoholic liver disease, hepatocellular carcinoma, and drugs which induce cytochrome 450 activity iron overload states. In many patients, porphyria cutanea tarda was found to be associated with a hemochromatosis gene.

Porphyrias are uncommon. The prevalence of acute intermittent porphyria, the most common form, is estimated to be about 1–8 per million in the USA. Among hospitalized psychiatric patients, acute intermittent porphyria may occur as often as 1 per 500.

The illness consists of a serious of "attacks" which are brought on by a number of triggers including drugs, fasting, surgery, infection, and psychological stress. Symptoms begin after puberty. Variegated porphyria and coproporphyria may cause a photosensitive rash. The symptoms may include acute onset of abdominal pain accompanied by vomiting and constipation. Delirium occurs perhaps with visual hallucinations. A psychosis may appear instead of the delirium. A peripheral sensorimotor polyneuropathy may develop, and the dominant manifestation is a motor neuropathy which may progress to quadriplegia and respiratory failure. The recovery from this may occur within weeks to a year, and symptoms may not remit completely. There is an association between cigarette smoking and repeated attacks of porphyria. Treatment involves avoiding precipitating factors and UV light (for photocutaneous porphyria), oral carotenoids, stress reduction, prompt treatment of infections, and smoking cessation. Individuals can suffer greatly and may die during an attack if not diagnosed and treated appropriately. Liver transplantation for severe hepatic porphyria has had favorable outcomes.

Neuropsychiatric symptoms are associated with the "neurovisceral" presentation of porphyria, and may include episodic presentation of psychoses and/or delirium. Psychiatric medications which are unsafe in porphyria include barbiturates, carbamazepine, clonazepam, and valproic acid; gabapentin is considered safe.

30.5.6 Hemochromatosis

Hereditary hemochromatosis is an autosomal recessive disorder in which mutations cause increased intestinal iron absorption, perhaps through an interaction with the transferrin receptor. The result is iron overload with excessive deposition in tissues, including liver, heart, pancreas and pituitary. The prevalence is 0.5 % in the USA for homozygotes; heterozygotes have a frequency of about 10 % in the Caucasian population.

Many patients are asymptomatic when diagnosed on a routine screening panel showing elevated serum iron levels. Symptoms include liver disease, skin pigmentation, diabetes mellitus, arthropathy, impotence in males, and cardiac enlargement. Liver disease is caused by progressive iron deposition, which leads to hepatomegaly and eventual cirrhosis. The changes are initially reversible with iron removal. Iron overload in hemochromatosis potentiates the development of alcoholic liver disease as well as the deleterious effects of the hepatitis C virus infection on the liver (McDonnell et al. 1999).

One large study, which surveyed 2,851 hemochromatosis patients who reported symptoms for an average of 10 years before diagnosis, determined that the most common symptom was extreme fatigue (46 %), followed by arthralgia (44 %) and loss of libido (26 %) (McDonnell et al. 1999).

30.6 Psychiatric Issues in Treatment of Hepatitis C

30.6.1 Psychiatric Pretreatment Assessment for Hepatitis C Therapy with Interferon Alpha and Ribavirin

Treatment options for chronic hepatitis C infection include subcutaneous interferon alfa-based therapies. Since 1995, interferon alfa has been combined with oral ribavirin for enhanced treatment. Recently, protease inhibitors have been added, promising to improve greatly treatment efficacy (Bakulin et al. 2014). Ribavirin does not affect HCV directly but may enhance immunomodulation. Interferon alfa has been primarily administered in the pegylated form which allows weekly dosing and has yielded, with oral ribavirin, an improvement in viral eradication, with reduction in liver tests and HCV-RNA level and decrease in hepatic inflammation. The treatment course depends on genotype, and may last for 6 or 12 months. The sustained virological response (SVR) has been reported as 63 % for patients who received more than 80 % of their interferon and ribavirin for 80 % of the treatment course, and the SVR is durable for years (Desmond et al. 2006). Factors which influence the SVR include these viral factors: HCV genotype and viral load, and host factors: age, sex, race, body weight, amount of liver fibrosis, alcohol use, and compliance. The dose of interferon/ribavirin can also influence the outcome. The treatment is lengthy and has significant side effects. The major side effects are neuropsychiatric (Crone and Gabriel 2003). Current guidelines consider the natural history of the virus, the cost of treatment, and lack of uniform benefit, and have recommended that therapy should be provided to those at the greatest risk of progressive liver disease and to those in whom quality of life is reduced from chronic HCV infection. Addiction psychiatrists have an important role in assisting the hepatitis C clinic with the selection of patients who are considered capable of withstanding the difficult course of treatment. An important objective is to determine which patients, especially among the psychiatric and substance-use disordered, can be safely treated and to determine how to optimize their treatment outcomes. Positive treatment outcomes include not only viral eradication but also acceptance and completion of antiviral therapy as well as a delay in the progression of hepatic fibrosis to cirrhosis, complications of cirrhosis, and hepatocellular carcinoma.

Appropriate guidelines have been recommended to assist the psychiatrist in the selection process. In general, a 6-month period of abstinence and/or sobriety is recommended, urine toxicology and the AUDIT C can be used to screen for individuals who may require more intensive addiction treatment before and during CHCV therapy. Similarly, screening for psychiatric symptoms using the Beck Depression Inventory II, the Beck Anxiety Disorder Index, and the Aggression Questionnaire are simple methods to define which individuals require more psychiatric stabilization before initiation of therapy. In one study of 134 pretreatment HCV individuals, 12 % had severe symptoms of aggression, depression, or anxiety, and would require further stabilization and reevaluation before initiation of therapy (Hensley and Withers 2003).

30.6.2 Psychiatric Side Effects Induced by Interferon Alfa and Ribavirin

The major neuropsychiatric side effects of interferon and ribavirin therapy which have been reported include cognitive dysfunction, fatigue, depression, anxiety, and irritability (Crone et al. 2006; Kraus et al. 2003). A clinical observation was made that some patients undergoing interferon therapy have experienced anger, reported as episodes of domestic violence, "road rage," and other interpersonal conflicts (Withers 2003). In two separate studies, 16–25 % of patients reported interferon-induced aggression during long-term therapy for CHCV (Withers 2003; Kraus et al. 2003). In patients treated for melanoma, interferon alfa (at higher doses than is used for hepatitis C) led to mood instability with manic symptoms. Studies have shown that the depressive side effects from interferon alfa are dose related. Reported rates of depressive symptoms range from 0 to 80 % across studies; serious episodes have resulted in interrupted treatment, suicidal behavior and completed suicides (Crone and Gabriel 2003; Kraus et al 2003). Symptomatic autoimmune thyroid disorders occurred in 4 % of 439 patients during HCV treatment (Doi et al 2005). Fatigue and cognitive deficits are also exacerbated during interferon and ribavirin therapy for CHCV (Kraus et al 2005). Agranulocytosis has been induced by concomitant use of clozapine with ribavirin and interferon for CHCV in a case report. In a retrospective study, more than half of CHCV patients on interferon described moderate to severe physical, mental and social difficulties and a third quit work or reduced their work hours.

The pathophysiology of psychiatric symptoms from interferon alfa and ribavirin is hypothesized to be multifactorial, involving neurotransmitters, including serotonin and dopamine; proinflammatory cytokine production, nitric oxide, and endocrine regulation including the hypothalamic-pituitary-adrenocortical axis (Crone et al 2006; Crone and Gabriel 2003). Ribavirin can also cause psychiatric symptoms, though there have been no studies on ribavirin (only) induced side effects in HCV treatment, only in conjunction with interferon. Patients who develop severe psychiatric side effects may require dosage reduction or discontinuation of interferon and ribavirin therapy. Substance use disordered patients who are in recovery from alcohol or drug dependence are at risk for relapse on substances during HCV therapy (Hensley and Withers 2003).

In several large clinical studies involving treatment with interferon alfa and ribavirin, depression was the most common severe adverse side effect and the most common reason for dose modification or discontinuation (Raison et al. 2005). Despite the significance of the interferon and ribavirin induced psychiatric side effects in treatment of chronic HCV, only a few studies have investigated the predictors of psychiatric side effects, and the role of pharmacologic options in managing them (Reichenberg et al. 2005). Depression and mood disorders before initiation of interferon and ribavirin are associated with higher levels of treatment-induced depressive symptoms (Reichenberg et al 2005).

30.6.3 Treatment of Neuropsychiatric Side Effects Induced by Interferon Alfa and Ribavirin During Long-Term Therapy for Chronic HCV

While antidepressant treatment may have an important role in supporting interferon therapy, its indication and timing is uncertain (Reimer et al. 2005). Clinical reports suggest that the depressive and anxiety symptoms can be reduced with serotonergic agents, whereas the nausea, anorexia, pain, and psychomotor slowing may respond to more activating medications such as bupropion, modafinil, psychostimulants, or mirtazapine (Crone et al. 2006). Treatment of mania may be managed safely with gabapentin.

30.7 Cirrhosis and End-Stage Liver Disease, Without Hepatic Encephalopathy

Subclinical hepatic encephalopathy (SHE) is a syndrome of cirrhotic individuals who have normal mental status examination but show

abnormalities on formal neuropsychiatric testing. Over two decades ago, quantifiable neuropsychological abnormalities were found to be present in the majority of the ambulant, non-encephalopathic cirrhotic patients. Because of the noted impaired short-term visual memory and delayed reaction times to stimuli, it was cautioned that those patients would be at risk when driving or operating heavy machinery. More recently, 300 patients presenting for liver transplantation were neuropsychiatrically evaluated. The cognitive impairment was highest among those with alcoholic liver disease, and those patients with a history of alcohol abuse or dependence performed more poorly on neuropsychological testing. The patients with cholestatic liver disease, after correcting for liver pathology, had the least cognitive impairment when compared to other groups (Sorrell et al. 2006). In contrast, Pantiaga et al. (2003) found no significant differences in neuropsychological testing between patients with cirrhosis of alcoholic origin and those with cirrhosis from all other etiologies. The patients with cirrhosis had cognitive impairment which was greater with increasing liver damage. The Child C cirrhosis group showed moderate dementia with auditory attention deficit and reduced short-term retention. The liver transplant recipients showed some degree of dysfunction in comparison with the control group, but overall had better results than the cirrhotic patients. These authors confirmed prior findings that neuropsychological testing is valid in liver disease and found the Trails Making Tests A and B to be more sensitive for determining cognitive deficits, but commented that magnetic resonance imaging can detect a large proportion of patients with SHE than neuropsychological testing. A study correlating structural brain abnormalities with cognitive deficits in ten cirrhotic patients showed that the degree of cognitive impairment was directly correlated with functional abnormalities in the basal ganglia and limbic cortex. Another group, (Klos et al. 2005), found evidence of brain manganese accumulation in the basal ganglia associated with neurological syndromes, one of which was cognitive impairment with psychiatric features. The authors found that brain manganese toxicity may result in symptoms other than parkinsonism (Klos et al. 2005). Recent studies showed that reduced blood flow in the anterior cingulate gyrus measured by SPECT or impairment of P3000 may be a good indicator of cerebral functional changes in patients with cirrhosis (Kramer et al. 2002).

In summary, patients with cirrhosis without hepatic encephalopathy suffer neuropsychiatric symptoms with cognitive deficits which seem to be similar but slightly more severe than those noted in chronic liver disease with fibrosis and no cirrhosis and distinct from hepatic encephalopathy. Although cognitive deficits clearly increase with worsening of liver pathology, there are no consistent findings to date to indicate that one etiology (e.g., alcoholic liver disease or hepatitis C pathology) leads to greater worsening of cognitive impairment.

30.8 Hepatic Encephalopathy in Cirrhosis

Hepatic encephalopathy, which occurs in the setting of cirrhosis, end-stage liver disease, or acute liver failure, is a reversible decline in neuropsychiatric function associated with a worsening of hepatic function. It is estimated that 60–80 % of cirrhotics suffer hepatic encephalopathy. Hepatic encephalopathy is characterized by disturbances of consciousness, mood, behavior, and cognition, and can include symptoms of gross disorientation, confusion, agitation and coma (Crone et al 2006; Ferenci et al. 2002; Lewis and Howdle 2003). The stages of hepatic encephalopathy are rated as follows:

Stage 0: sleep disturbances, mild attention deficits

Stage 1: psychomotor slowing, lack of attention, asterixis

Stage 2: personality changes, disorientation, bizarre behavior, lethargy

Stage 3: rigor, pyramidal signs, major speech disturbances, severe ataxia, somnolence, stupor

Stage 4: coma

The earliest signs of hepatic encephalopathy, stage 0, are often sleep disturbances and subtle behavioral changes, which may be reported by

the patient's family. As hepatic encephalopathy progresses to stage 1, problems with attention, mild confusion, asterixis and psychomotor slowing are noted. In stage II there is lethargy and disorientation, which progresses to stage III of somnolence or stupor. In stage IV the patient is in a coma with or without response to painful stimuli (Crone et al. 2006).

The pathophysiology of hepatic encephalopathy is not fully understood. It has been known for decades that elevated ammonia from hepatic dysfunction is implicated and there may be a role for inhibitory neurotransmission through gamma-aminobutyric acid (GABA) receptors in the central nervous system and changes in central neurotransmitters and circulating amino acids. The precipitating cause may often include factors such as gastrointestinal bleeding, increased protein intake, hypokalemic alkalosis, infection, constipation, and use of sedatives and tranquilizers. Treatment involves correction of the underlying disorder. Benzodiazepines should be avoided in hepatic encephalopathy. One new therapy being evaluated involves the hypothesis that the GABA receptor complex, which includes a benzodiazepine receptor site, is a contributor to neuronal inhibition in hepatic encephalopathy. Several studies which have investigated a new drug, flumazenil, a benzodiazepine receptor agonist, reported only some short-term improvement in the symptoms of hepatic encephalopathy.

30.9 Liver Transplantation

To determine priority for deceased liver allocation in the USA, the model for end stage liver disease (MELD) was adopted in February 2002. This new policy gives priority to donate the deceased livers within designated geographic regions to chronic liver disease patients with the highest MELD score, and therefore the greatest waiting list mortality. The MELD score can be calculated based on a formula incorporating the serum bilirubin and serum creatinine levels and an international normalized ratio.

Psychiatrists are consulted to assist with addiction psychiatric assessment before the transplant. Contraindications to liver transplantation are evolving; for example, HIV patients are now considered for transplantation because of improvements in antiretroviral therapy. The current contraindications involving addiction psychiatry are active substance abuse and noncompliance with medical care. There are concerns about the risk of recidivism as well as noncompliance after transplantation. Psychiatrists are asked to review history of suicide attempts and dangerousness, as well as current psychiatric and psychosocial stability. An addiction history, including participation in alcohol and drug treatment programs, and random urine toxicology is important for assessment. Typically a minimum of 6-month sobriety and abstinence is required before liver transplantation can be considered.

Once the transplant evaluations are completed, the patient is placed on the United Network for Organ Sharing (UNOS) waiting list with a MELD score. Typically a median MELD score at transplantation might be 27. Another option for liver transplant is living donor liver transplantation (LDLT). The advantages for living donor transplantation include avoidance of the waiting time for the UNOS listing based on MELD score; transplantation can take place earlier. The disadvantages include the risk to the donor.

Transplantation for patients with either alcoholic liver disease or with heroin dependence on methadone maintenance therapy has been controversial. The reluctance to transplant such individuals is the poor prognosis for treatment of addictions in general, with high rates of relapse and poorer medical compliance, the presence of comorbid medical and psychiatric conditions, and moral evaluations about drug and alcohol use. More recently, a consensus has evolved that patients with alcoholic cirrhosis should be considered for liver transplantation, though the length of the period of abstinence remains uncertain. The relapse rate to return to alcohol use post-transplantation in alcoholic liver disease has been reported as an average of 20 %. There are no nationally accepted selection criteria for

predicting long-term sobriety and compliance. A recent study found that previous alcohol consumption, including length of abstinence before transplant, dependence, number of withdrawals, and family history of alcohol dependence predicted severe relapse to alcohol after transplantation. Another concern is nicotine dependence and impact on development of cancer due to relapse to smoking post-transplant. In one study, more than 40 % of patients who had quit smoking relapsed. Despite the lack of reliable predictors, 6 months of abstinence and sobriety from drugs, including nicotine and alcohol, is required in most programs.

Extension of life after liver transplantation is well documented; research has shown significant improvements in physical health, sexual functioning, ability to perform daily activities, social functioning, and general health-related quality of life. However, improvements in neuropsychiatric functioning post-transplant have been less well established. Pre-transplant candidates typically demonstrated impaired neurocognition, including problems with complex attention, and visuomotor, visuospatial, and memory deficits as well as affective symptoms of depression and anxiety, whereas post-liver transplant patients showed improvements in all areas of neurocognitive abilities, but not to the premorbid level of functioning. The affective psychiatric symptoms of anxiety and depression do not necessarily improve upon transplantation and may increase due to post-transplant stressors, including managing multiple antirejection medications and concerns about returning to the workplace (Hilsabeck et al. 2003).

A prospective study of 164 patients who were assessed for liver transplantation revealed that they had memory impairment, psychomotor slowing, anxiety, and depression, which are consistent with other studies on patients with cirrhosis and end stage liver disease. One year post-liver transplantation, these patients showed significant improvement in most domains compared with a control group and patients who did not undergo transplantation. Immunosuppressive medications did not affect quality of life, fatigue, or affective status. Higher levels of anxiety at pretransplant assessment predicted worse psychosocial outcome at 1 year post-transplantation. The individuals with good psychological outcome at 1 year maintained this at the 3-year follow-up (O'Carroll et al 2003).

30.9.1 Safety of Psychiatric and Pain Medications in Liver Disease

30.9.1.1 Psychiatric Medications

The impact of liver disease on medication pharmacokinetics is complex. Generally, in the setting of mild liver disease, the same dosage and type of medications as would be used in healthy individuals can be administered safely. Susceptibility to adverse effects increases with worsening liver function, due to altered pharmacokinetics and hemodynamic changes. Usually changes in drug dosing begin at the development of cirrhosis and/or renal insufficiency. In cirrhosis, portal hypertension develops which delays drug absorption through the small intestine vasculature. Further, fluid retention (ascites, edema) and the reduced hepatic production of albumin alter the distribution of drugs. Most psychiatric drugs are protein bound in the serum, and the albumin reduction results in higher levels of free active drug. In addition, the slowed hepatic metabolism which is typical in liver disease can lead to even higher serum drug levels for certain psychotropics (Crone et al 2006).

Some useful, general clinical guidelines to assist with psychiatric medication dosing in the setting of liver disease have been provided recently (Crone et al 2006). The clinician is cautioned to review the therapeutic and toxic plasma concentrations of each drug as well as make an assessment of the patient's liver disease, based on the Child-Pugh Score calculations (Childs A, B and C). Three-quarters to full amount of the standard initial dose is recommended for psychiatric patients with Childs A liver disease. More caution should be applied for patients with Childs B liver disease; the initial dose should be half of the normal dose with more gradual dose increases to accommodate the prolonged elimination half-life. The CPS Class C liver disease patients

commonly have hepatic encephalopathy. If hepatic encephalopathy is present, any psychiatric medications must be monitored very closely to avoid worsening of the encephalopathy (Crone et al 2006).

In general, drugs which are lipid soluble are primarily metabolized in the liver, whereas those which are more polar (hydrophilic or water soluble) are excreted largely through renal clearance. Most of the psychiatric medications belong to the hepatically metabolized, hydrophobic group. These are oral medications which are absorbed from the gastrointestinal tract and then are modified by hepatic metabolism which changes by hydroxylation, oxidation, reduction, or conjugation of the lipophilic forms to water-soluble compounds ready for renal excretion. Hepatic metabolism has two phases: I and II. Phase I hepatic metabolism (CYP; CP 1-10) involves oxidation, hydrolysis, or reduction, and utilizes the cytochrome 450 enzymes which are found on endoplasmic reticulum. Of the cytochrome 450 enzymes, most drugs and toxins are metabolized by the CYP3a subfamily. In phase II hepatic metabolism, drugs are conjugated (acetylation, glucuronidation, or sulfation) in the hepatocyte cytoplasm. Phase II glucuronidation is largely preserved in cirrhosis. Chlorpromazine and valproate can reduce phase II reactions.

Diet and alcohol intake can affect drug metabolism. For example, cruciferous vegetables induce CYP enzymes whereas grapefruit juice inhibits CYP3a activity; low-protein diets and malnutrition also reduce CYP activity. Alcohol reduces the availability of glutathione and thus leads to greater hepatotoxicity from acetaminophen or cocaine. Low-protein diets and malnutrition reduce CYP activity.

It is safer in liver disease to avoid drugs which require phase I metabolism, as they may have higher serum levels and reduced metabolism, and to use instead medications which pass through phase II glucuronidation. Drugs which use phase II glucuronidation include olanzapine, lorazepam, and oxazepam and would not require dose reduction in liver disease. For phase I metabolized drugs, including alprazolam, midazolam, diazepam, fluoxetine, paroxetine, nefazodone, bupropion, sertraline, and risperidone, a dose reduction by half is recommended for patients with hepatic impairment. Phenothiazines should be avoided because they can cause cholestasis. The renally excreted psychiatric drugs, including lithium, gabapentin, and topiramate, should only be used with caution and careful monitoring (Crone et al 2006).

Acute liver failure has been reported in case studies, particularly in children, with valproic acid. Recently, in India, there were two cases of children with valproate-induced hyperammonemic encephalopathy enhanced by topiramate. Mitochondrial disease represents a risk factor for valproate-induced liver failure. However, valproic acid may be used safely in most hepatitis C patients, with enzyme monitoring. The transaminase, alanine transferase (ALT), was not elevated during use of valproic acid in hepatitis C patients; the ALT increases were instead correlated with hepatitis C status. In a recent case report, the mood stabilizer, lamotrigine, caused acute hepatitis which led to liver failure, and the patient was managed with the Molecular Adsorbents Recirculating Systems (MARS).

Nefazodone has been associated with liver failure (1 %) and should be discontinued for any signs or symptoms of hepatic failure. In 2005, the Food and Drug Administration (FDA) removed pemoline from the market after receiving 13 reports since 1975, of liver failure from this medication resulting in transplantation or death. An antidepressant, duloxetine, which is a selective serotonin and norepinephrine reuptake inhibitor, has had a revision in its FDA labeling in 2005 to include new precautions that duloxetine has caused liver injury and can aggravate liver damage. In a recent case report, duloxetine caused fulminant hepatic failure and death in an individual with no prior liver disease. Most episodes of drug-induced liver injury are idiosyncratic. Typically the drug-induced heptotoxicity presents as acute hepatitis and/or cholestasis, but may take any pattern of liver disease. Monitoring serum ALT is of unproven effectiveness but should be considered if there is a risk of delayed serious hepatitis reaction. Drug-induced hepatotoxicity has also been reported for

chlorpromazine (cholestatic injury), trazodone and venlafaxine. Hepatic injury has been reported from ingestion of kava root. This traditional herb, kavakava, is used in New Caledonia, for anxiety and insomnia. Apparently kava inhibits all CYP 450 enzymes which leads to significant drug interactions. Patients should be advised to avoid kava due to risk of hepatotoxicity and drug interactions. Psychiatrists should routinely screen for the use of herbs and provide education about the risk of liver damage and/or drug interactions with herbal supplements.

30.10 Pain Medications

The recommendations for safe use of acetaminophen in cirrhosis is to use the limit of 2 g per day if there is a risk of any alcohol abuse, and possibly 4 g per day with alcohol abstinence. All patients should be warned of the risk of severe hepatotoxicity from active alcohol intake and concomitant use of acetaminophen, which can occur regardless of the severity of liver disease. Nonsteroidal anti-inflammatory drugs (including aspirin) should be avoided in patients with cirrhosis, because of the increased risk of variceal hemorrhage, impaired renal function, and diuretic resistant ascites. Opioids should be used with caution; morphine, oxycodone, and hydromorphine should be used at reduced doses and prolonged intervals.

30.11 Addiction and Liver Disease

In patients with cirrhosis, alcohol withdrawal is best managed with a fixed dose of benzodiazepines, with reassessment for daily tapering. The Clinical Institute Withdrawal Assessment for Alcohol (CIWA-AR) is a protocol commonly used, but its use may be impractical and not useful for a population of alcoholics who are at risk of alcohol withdrawal delirium. One reason is that if the protocol is ordered, the patient may not get necessary benzodiazepines, because of the complicated nursing ratings necessary to determine each dose. If medical detoxification is necessary, a simpler technique for cirrhotics is to use a fixed ratio of oxazepam (15–45 mg) every 4 h for the first 24 h, and to hold a dose if patient is asleep. Lorazepam is not recommended because of risk of possible exacerbation of symptoms due to the short half-life leading to repeated withdrawal. Doses can be decreased on a daily basis as symptoms resolve (see also Chaps. 12 and 20 for detoxification techniques).

The diagnosis of liver disease, including HCV, can become a strong motivating factor for a patient to engage in comprehensive alcohol and drug treatment. The use of brief intervention together with motivational interviewing can reinforce and enhance the patient's commitment to abstinence and sobriety. Brief intervention has consistently been measured to be the most effective in terms of evidence-based treatment methods for alcohol-use disorders. In the HCV clinic setting, the AUDIT C is a useful screening test. The identification of lab markers for HCV or HIV in a psychiatric patient is a trigger to inquire about past intravenous drug-use and current drug- or alcohol-abuse disorders (Withers 2001).

The cornerstone for therapy for alcoholic liver disease is drinking cessation; even reduction in alcohol intake improves the rate of liver tissue degeneration from fibrosis to cirrhosis and finally hepatocellular carcinoma. In fact, the ability to maintain sobriety has a major impact on the outcome of patients with alcoholic cirrhosis because maintaining abstinence can lead to significant regression of fibrosis and possibly early cirrhosis. In studies, alcohol intake is often measured as drinks; 1 drink is approximately equal to 14 g of ethanol. In a large prospective clinical trial, veterans who had been drinking 16 drinks per day were assessed by repeated liver biopsy at baseline and 24 months. It was found that with even 2.5 drinks a day, the liver pathology still progressed one stage. The hepatitis C virus patients showed accelerated progression of liver disease. In total, one of five patients showed progressive liver damage even at moderate levels of drinking.

30.12 Summary

It is critical for psychiatrists to appreciate that hepatic dysfunction, even in mild forms, can cause neuropsychiatric symptoms. Some liver diseases, including acute intermittent porphyria, have been misdiagnosed as psychiatric syndromes such as schizoaffective disorder or major depression with psychotic features.

The mechanisms by which hepatic dysfunction can cause cognitive deficits, fatigue, affective symptoms and psychoses are not well understood, although there is growing information from various neuropsychological, neurophysiological, biochemical, and imaging studies which compare liver diseased patients with each other or controls. There appear to be some symptoms and mechanisms common to all liver disease, and others which differ based on type of liver pathology or severity of liver disease. It has been postulated that the neuropsychiatric symptoms of hepatitis C may be the result of direct or indirect neuroinvasion of the virus. Fatigue and cognitive deficits compatible with subcortical dysfunction have been reported in almost all forms of chronic liver disease, and hepatic encephalopathy can evolve regardless of the etiology of the underlying liver disease. Medications which are hepatically metabolized can exacerbate or precipitate liver disease, and should be used with caution in patients with cirrhosis or hepatic encephalopathy. The treatment of chronic hepatitis C, which involves administration of interferon alpha and ribavirin for months, induces neuropsychiatric side effects and requires addiction psychiatric management before and during treatment. Similarly, addiction mental health clinicians provide pretreatment evaluation and management for pre- and post-liver transplant patients. Finally, psychiatric patients have a higher prevalence of liver disease (including hepatitis C, alcoholic liver disease, porphyria, nonalcoholic steatohepatitis) than the general population, and these comorbidities significantly impact the course of psychiatric illness and its treatment.

Case Vignettes

(a) A 59-year-old married white male is referred to psychiatry for mental health evaluation before initiation of interferon and ribavirin for chronic hepatitis C. He has been diagnosed with post-traumatic stress disorder, chronic, major depression, recurrent, amphetamine dependence in sustained full remission, and alcohol dependence in early full remission. Although he has entertained thoughts of suicide in the past, he has never acted on them. He reports chronic insomnia with only about 4 h of sleep at night, and intermittent nightmares, with chronic guilt feelings and social isolation. His employers retired him from work as a truck driver at age 54 when his driver's license was revoked for reasons which are not apparent to the patient. He quit smoking 20 years ago. His medical problems include lumbosacral degenerative joint disease which causes chronic back pain, for which he takes four tablets a day of hydrocodone (5 mg) with acetaminophen (500 mg). Source of HCV is thought to be intravenous drug abuse (which he stopped at age 30); HCV is genotype 1 with a viral load of 700,000. Liver biopsy shows grade 3 with moderately active hepatitis C, with stage 2, periportal fibrosis. He is HCV treatment naïve; he declined treatment in the past.

On pretreatment assessment, his psychiatric medications included bupropion 75 mg twice a day; gabapentin 300 mg HS, trazodone 100 mg HS. His last drink was 6 months ago. His AUDIT C score was 8 (high), pain reported as 4 of 10, BDI II 28 (moderate depression), BAI 21 (moderate anxiety), quality of life measured as very low, and overall aggression measured as average. He was started on pegylated interferon alfa 2a weekly injections with ribavirin

at 600 mg twice a day. By week 2, his depressive symptoms worsened to severe (31 on BDI II). He saw the same psychiatrist at monthly intervals for support, assessment and medication management. Medications which were tried and discontinued due to side effects or inefficacy included mirtazapine, hydroxyzine, doxepin, clonidine, quetiapine, and citalopram. Although his mood remained severely depressed throughout, he had some slight improvement with an increase in bupropion to 150 mg bid, and in gabapentin to 1,200 mg HS, which helped with his sleep disturbance. He reported a headache for 1 day following interferon injection; loss of appetite with weight loss up to 20 lb during treatment. His sleep did not improve beyond 4 h/night. He experienced low motivation and fatigue. At week 4 he complained of worsening back pain, by week 8 he was distraught and "on edge," he reported to his psychiatrist thoughts about grabbing a knife and stabbing himself, though he did not act on this. Citalopram was initiated but discontinued by patient due to sensation of "an electric shock" in his body. Mirtazapine was initiated but discontinued because he felt it was ineffective and did not help him fall asleep, and just made him more sedated. By week 12, his depression was better, but he reported feeling so fatigued that it was an effort just to get out and cut the grass. At this point he was given filgrastim by the HCV clinic for neutropenia. His HCV viral load was undetectable at week 12. By week 18, he reported feeling better; he thought that the increased bupropion was helping with depression and fatigue. He did report "mind fog," or mild difficulty remembering tasks or staying on task. By week 32 he reported worsening nightmares; gabapentin was increased to 1,200 mg HS, which improved his sleep pattern and by week 36, he said the nightmares were less frequent and occurred about three times a month. By week 44, he reported increased irritability and feeling "like a bomb ready to explode." The slightest incident annoys him and he felt like yelling and lashing out; however, he did not act on these feelings. By week 48, he was pleased and surprised that he was able to complete interferon and ribavirin treatment. His HCV viral load was undetectable at week 48. One week after the end of treatment he already reported feeling less irritable.

Discussion: This vignette demonstrates that even very depressed patients, such as this patient with chronic PTSD and depression, can tolerate interferon and ribavirin therapy for CHCV with close mental health treatment and support. The symptoms he reported during his 48 weeks of therapy which include headache, fatigue, irritability, exacerbation of depression, pain and insomnia, and anergia are typical for HCV therapy. In this case, the most effective psychotropic medications were bupropion and gabapentin.

(b) Mr. J. is a 50-year-old married white male referred for mental health evaluation for liver transplantation. His comorbid medical diagnoses include end stage liver disease with hepatosplenomegaly and pancytopenia, rheumatoid arthritis with chronic pain, and hepatitis C. His psychiatric diagnoses include heroin, marijuana, and alcohol dependence in sustained full remission; he admits to a history of intravenous drug abuse which is most likely the source of hepatitis C. He completed four treatment programs for drug and alcohol treatment; three of these were court ordered. He attends regular alcoholics anonymous and narcotic anonymous meetings and has a sponsor. His current medications include levofloxacin, amiloride, potassium, furosemide

and hydrocodone (5 mg) with acetaminophen (500 mg) TID. Spironolactone was discontinued due to gynecomastia. He agrees to discontinue opioids in preparation for transplant. He quit smoking at age 38. He worked as a plumber but became disabled this year due to inability to concentrate.

He reports chronic pain, especially in his legs and knees, insomnia, and low energy but reports "I still show up." His concentration is poor and he cites daily problems with forgetfulness. For example, he would forget where he parked the car, which items he was supposed to buy at the store, or even to turn off the shower when he was interrupted by the telephone. These symptoms were unimproved by a trial of psychotropic medications including fluoxetine, modafinil, and bupropion.

On pretreatment assessment, his urine toxicology was negative, Quality of Life was measured as average, and he had symptoms of mild depression (BDI II—10), moderate anxiety (BAI—29), and average aggression. The Repeatable Battery for Assessment of Neuropsychological Function (RBANS) was well below normal, with a total score at the 0.3 percentile. None of the scores were normal; he was most impaired on attention and delayed memory (0.4 percentile), severely impaired also on immediate memory and visuospatial constructional abilities (both at 1st percentile), and language was measured at the 19th percentile.

Mr. J's adult son agreed to be the donor for living donor liver transplantation (LDLT), and the right lobe of his son's liver was successfully transplanted into Mr. J. His son recovered rapidly; Mr. J's recovery was complicated by postoperative infections and he still complained of significant chronic pain. Two months post-transplant, he was retested. This time he again reported average aggression, but depression had increased to moderate and his anxiety was rated as severe. However, he showed marked improvement on the RBANS with total score improved to a normal range (44 %). Attention improved the most; to 35 %; visuospatial to 30 %, delayed memory to 8 %; immediate memory to 16 %; and language to 35 %. Mr. J. was pleased to learn of his improved performance on neurocognitive testing.

Discussion: This case history demonstrates that end stage liver disease patients suffer from impaired neurocognition, including attention, visuospatial, and memory deficits which improve post-transplant. Most patients, like Mr. J, show significant improvements in all areas of neurocognitive functioning, albeit not to premorbid levels of functioning. Mr. J. was not tested before the onset of his liver disease, so premorbid test results are not available. In contrast, psychiatric symptoms do not necessarily improve and may become increased by post transplant stressors, such as managing and paying for multiple antirejection medications, pressure to return to work, loss of social support, and concern about the health of the donor, who is often a family member. In Mr. J's case, both his depression and anxiety worsened. It is important to educate liver transplant patients about potential neuropsychiatric symptoms pre- and post-transplant, and to provide mental health support throughout the process.

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Obstetrics and Gynecology Patients: Menstrual Cycle, Pregnancy, and Postpartum-Related Psychiatric Disorders

31

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Contents

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31.1 Introduction

Women have a significantly higher risk for developing mood disorders with a lifetime prevalence that is approximately twice that of men. Sex difference in the rates of depression begins to appear in adolescence. Although reasons for this gender difference are not fully understood, the changing level in reproductive hormones throughout a woman's life may be playing a direct or indirect effect on her mood. Studies on bipolar disorder suggest that women are more likely than men to be rapid cyclers (Arnold 2003), which is attributed to the increased occurrence of hypothyroidism and menstrual cycle irregularities in women. Pregnancy and the postpartum period are considered to be vulnerable times in a woman's life with significant increase and drop in reproductive hormones and increased risk of psychiatric symptoms. Oral contraceptives, hormone replacement therapy, and menopause dampen the cyclicity of ovarian function and can cause mood symptoms. Reproductive hormones modulate neuroendocrine, neurotransmitter, and circadian rhythms, all of which have been implicated in the pathophysiology of mood disorder. Changes or variability in

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reproductive hormones rather than absolute level increases the risk for symptoms in vulnerable individuals. Depression occurring in association with the reproductive cycle may sensitize a woman to future depression.

31.2 Menstrual Cycle–Related Affective Illness

31.2.1 Premenstrual Dysphoric Disorder

Premenstrual Dysphoric Disorder (PMDD) is a constellation of affective, behavioral, cognitive and somatic symptoms with a regular cyclical relationship to the luteal phase of the menstrual cycle. 90 % of women report at least mild premenstrual symptoms, 20–30 % of women may have moderate-to-severe symptoms that meet the criteria for premenstrual syndrome (PMS), but about 3–8 % of menstruating women can develop more severe and disabling symptoms that meet criteria for PMDD, causing impairment in their social and occupational functioning (Rapkin and Lewis 2013).

According to DSM-5 (2013), diagnosis of PMDD requires the presence of five of the following 11 symptoms, with one severe mood symptom causing functional impairment: (1) depressed mood, feelings of hopelessness, or self-deprecating thoughts; (2) marked anxiety, tension, feelings of being "keyed up" or "on edge"; (3) marked affective lability, such as feeling suddenly sad or tearful, or increased sensitivity to rejection; (4) persistent marked anger or irritability or increased interpersonal conflicts; (5) decreased interest in usual activities (work, school, friends, hobbies); (6) subjective sense of difficulty in concentration; (7) lethargy, easy fatigability, or marked lack of energy; (8) marked change in appetite, overeating, or specific food cravings; (9) hypersomnia or insomnia; (10) subjective sense of being overwhelmed or out of control; (11) other physical symptoms such as breast tenderness, swelling, headache, joint or muscle pain, sensation of "bloating" or weight gain. Impairment in home, social, and occupational functioning related to the symptoms must be present for most menstrual cycles over the past year, and symptoms must be documented prospectively for at least two menstrual cycles to confirm the premenstrual timing of the symptoms and the postmenstrual symptom-free-interval.

The cause of these symptoms is not fully understood. Absence of symptoms in premenarchy, postmenopause and ovariectomized women indicates the role of gonadal sex steroids, particularly progesterone in causing the symptoms. Symptoms could be the result of exaggerated or abnormal response to normal hormonal fluctuations in susceptible women. Etiology of this "differential sensitivity" may be multifactorial and partially genetically determined. A recent study (Huo et al. 2007) demonstrated an allelic variation on the estrogen receptor α gene in women with PMDD when compared with control women. In addition, the allelic variation was only significant in women who had a valine/valine genotype for the catechol-*O*-methyltransferase enzyme. This significant study may identify a source of abnormal estrogen signaling during the luteal phase that leads to premenstrual affective, cognitive, and somatic symptoms.

The role of specific neurotransmitter, neuroendocrine, and neurosteroidal peptides in causing PMDD is not fully known. Metabolites of progesterone (allopregnanolone or ALLO and pregnanolone) have a positive modulating effect on the GABA neurotransmitter system in the brain and have been implicated in the pathophysiology of PMDD. Decreased peripheral levels of ALLO have been found in the luteal phase of affected women in some studies (Klatzkin et al 2006). Serotonergic dysregulation has been hypothesized as another etiological factor in causing PMDD. Studies have found lower density of brain serotonin receptors (Jovanovic et al 2006), and lower peripheral platelet uptake of serotonin (Ashby et al. 1988) in affected women. Tryptophan depletion in women with PMDD has been shown to exacerbate the symptoms of PMS (Menkes et al. 1994). Also, SSRIs and SNRIs have proven to be effective in the treatment of PMDD.

A recent study using fMRI and PET showed greater dorsolateral prefrontal cortex activation in patients with PMDD, and this correlated with PMDD severity, symptoms, age at onset and disease burden (Baller et al. 2013).

31.2.1.1 Clinical Course and Burden of illness

Premenstrual symptoms are described in women from menarche to menopause, but it is unclear whether symptoms remain stable or increase in severity with age. Symptoms should be assessed prospectively over two consecutive cycles to ensure that symptoms are premenstrual. It is important to rule out other medical or gynecological causes for the symptoms. Patients' dietary habits, amount of physical activity, and drug/alcohol use should be determined as part of the initial evaluation. Women who experience PMDD have a greater risk for future depression during pregnancy, postpartum, and perimenopausal period. Premenstrual symptoms can significantly affect health related quality of life and may result in increased health care utilization and decreased occupational productivity (Borenstein et al. 2003).

31.2.1.2 Treatment

Treatment involves education, lifestyle changes, support, and pharmacologic management of symptoms (Pearlstein and Steiner 2008).

31.2.1.2.1 Lifestyle Modifications, Nutritional Supplements, and Psychosocial Treatments

Education, support groups, biofeedback, massage, exercise both aerobic and anaerobic, reflexology, acupuncture have all been found to have some effect in reducing the symptoms.

Common dietary recommendations include increased consumption of complex carbohydrates, frequent snacks, reduced consumption of refined sugar and artificial sweeteners and caffeine (Sayegh et al. 1995).

Among dietary and herbal supplementations, the strongest evidence exists for the benefit of chasteberry or *V. agnus castus* (Dante and Facchinetti 2011). Other vitamins and minerals shown to be somewhat effective include B_6 (50–100 mg/day), calcium carbonate 1,200 mg/day in divided doses, magnesium, vitamin E 400 units/day, L-Tryptophan 6 g per day, fish oil and soy isoflavones.

Cognitive behavioral therapy (CBT) is consistently reported to be an effective treatment for women with PMDD (Hunter et al. 2002).

31.2.1.2.2 Pharmacological Treatment

Pharmacological treatment focuses on elimination of hormonal fluctuations with ovulation suppression treatments or correcting the neurotransmitter dysregulation with antidepressant or anxiolytic medications.

YAZ, an oral contraceptive containing ethinyl estradiol 20 μg and drospirenone 3 mg, administered as 24 days of active pills followed by a 4-day hormone-free interval (24/4), has reported superiority in reducing premenstrual emotional and physical symptoms when compared with placebo (Rapkin 2008). In 2006, YAZ received United States Food and Drug Administration (FDA) approval for the treatment of PMDD in women desiring oral contraception.

Gonadotropin-releasing hormone (GnRH) agonists suppress ovulation by downregulating GnRH receptors in the hypothalamus. GnRH agonists are administered parenterally (e.g., subcutaneous monthly injections of goserelin, intramuscular monthly injections of leuprolide, daily intranasal buserelin). GnRH agonists have been reported to be superior to placebo in 8 of 10 published randomized controlled trials in women with PMS or PMDD (Backstrom et al. 2003). They should be used only in patients who are resistant to other forms of treatment as they induce menopause and the side effects related to it, including hot flashes, vaginal dryness, depression, headache, osteoporosis, and increased risk for cardiovascular disease.

Oophorectomy and prolonged anovulation from danazol, a gonadotropin inhibitor, are not common treatments for PMDD, largely because of the medical risk associated with prolonged hypoestrogenic state, which leads to the same long-term health issues as those arising from use of GnRH agonists.

For physical symptoms, nonsteroidal anti-inflammatory drugs (NSAIDs) and diuretics, especially spironolactone, have been found to be helpful. For mood symptoms, selective serotonin reuptake inhibitors (SSRIs) have been found to be effective in multiple controlled trials (Marjoribanks et al. 2013). The SSRI dosages that are effective for PMDD are similar to or slightly lower than the dosages recommended for the treatment of major depressive disorder (MDD). Continuous dosing and intermittent late luteal phase dosing have both been shown to be effective. With intermittent dosing the antidepressant is started approximately 14 days before the onset of menses and continued until the onset of menses or shortly thereafter. Benzodiazepines can be effective for severe anxiety symptoms.

31.2.2 Perimenopause-Related Affective Illness

The menopausal transition is often marked by somatic symptoms (aches and pains, myalgia, fatigue), physiologic symptoms (hot flashes and nighttime awakenings, sleep disturbances, urogenital complaints), and psychological symptoms. The most prevalent mood symptoms during this period include irritability, tearfulness, anxiety, depressed/labile mood, lack of motivation and energy, poor concentration, and interrupted sleep.

The perimenopausal period is associated with a higher vulnerability for depression with risk rising from early to late perimenopause and decreasing during postmenopause. Women with past history of depressive disorder, premenstrual syndrome, oral contraceptive-induced dysphoria and depression associated with pregnancy and postpartum have a higher risk of developing depression during menopausal transition (Avis et al. 1994; Stewart and Boydell 1993). The perimenopausal period is associated with a two- to fourfold increased risk for the development of new onset depression in women with no previous history of depression (Cohen et al. 2006; Freeman et al. 2006; (Schmidt et al. 2004). Depressive symptoms can recur in women with bipolar disorder during this time (Khan et al. 2007). Also, risk of suicide in women increases from age 45 to 64 (Usall et al. 2009).

Untreated depression during perimenopause is associated with increased risk for medical illness including heart disease and stroke in women (Wassertheil-Smoller et al. 2004). Also, studies have shown decreased bone density in these women (Jacka et al. 2005, Eskandari et al. 2007). Increased risk for fall combined with osteoporosis results in higher rates of fracture and disability (Silverman et al. 2007).

Hormonal transition to menopause coexists with major stressors and social role changes in midlife. This complex interplay of biological and psychological factors increases vulnerability to develop psychiatric syndromes in susceptible women. Risk factors for developing depression during perimenopause include demographic factors (Caucasian race and lower educational level), psychiatric factors (history of depression), psychosocial factors (empty nest syndrome, changing roles, loss of parents and partner, other stressful life events, unhealthy lifestyle, negative attitudes regarding aging/menopause), and menopausal factors (vasomotor symptoms and other physical symptoms, premenstrual syndrome, early natural menopause, menopausal transition ≥ 27 months, abrupt/surgical menopause).

During the years leading to menopause, the estrogen level changes rapidly with decreasing levels of estradiol production by the ovaries, declining levels of androgens and increasing levels of pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Ovarian hormones modulate serotonin and noradrenaline neurotransmission. It has been postulated that changes in these hormonally mediated neuromodulatory effects may heighten the risk for mood disorders in women with sensitivity to normal hormonal fluctuations (for example during the premenstrual period, puerperium, and perimenopause).

31.2.2.1 Treatment

Routine screening of at-risk population followed by careful assessment for depressive symptoms can help identify the presence of MDD during menopausal transition. Recognition of menopausal

symptoms, with or without depression, is important given their potential impact on quality of life.

Intervention for depressive symptoms during perimenopause depends on the severity of symptoms. Mild depressive symptoms usually respond to psycho-education/counseling, life style changes including diet and exercise, minimizing physical discomfort, optimizing general health and improving social support. Cognitive behavior therapy, supportive psychotherapy and referral to support groups can help women deal with the associated psychosocial stressors.

Moderate to severe symptoms of depression may require pharmacotherapy, and or hormone replacement (Parry 2010).

31.2.2.1.1 Pharmacologic Treatment

Antidepressants: The serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) have been found to be effective to treat depressive symptoms as well as the some of the physical symptoms like hot flashes and are considered the first line treatment for perimenopausal depression.

Hormone Replacement: Although antidepressant medication is the mainstay of treatment, adjunctive therapy, especially with estrogen replacement, may be indicated in refractory cases, and may speed the onset of antidepressant action (Schneider et al. 1997; Rasgon et al. 2002). Although some antidepressants improve vasomotor symptoms, in general they are not as effective as estrogen alone for relieving these symptoms. Estrogen therapy has been shown to be effective in improving mood and in alleviating hot flashes in symptomatic peri- and postmenopausal women but its use may be accompanied by increased risk of stroke, cardiovascular events, breast cancer, and pulmonary embolism. Certain subpopulations of women might preferentially benefit from hormonal interventions such as women with other clinical indications for the use of estrogen replacement therapy (ERT), or women with pre-existing clinical conditions such as sexual dysfunction, which could get worse with the isolated use of antidepressants. The active form of estrogen, 17-beta estradiol, crosses the blood–brain barrier and exerts potential beneficial effects on mood, sleep, cognitive function, and vasomotor symptoms.

31.3 Psychiatric Disorders during Pregnancy

31.3.1 Vignette

A 32-year-old woman who was 22 weeks pregnant was admitted for fetal monitoring for twin pregnancy complications. The patient had a history of bipolar disorder and borderline personality disorder and had been prescribed valproic acid, quetiapine, clonazepam, and sertraline in the past but discontinued all her medications after she found out that she was 7 weeks pregnant. This was her seventh pregnancy and was unplanned. She had a history of repeated suicide attempts. During the psychiatric interview she reported feeling overwhelmed, depressed, anxious, crying easily, having insomnia, loss of appetite, and occasional suicidal thoughts, but no psychotic symptoms. When restarting her medications was discussed, the patient adamantly refused to take any psychotropic medications. She stated that she had been on psychotropic drugs during her last pregnancy, and her now 2-year-old son from that pregnancy was recently diagnosed with autism.

31.3.2 Introduction

The prevalence of mood disorder in women is similar in pregnant and non-childbearing women. The prevalence of major depression in pregnant women ranges from 3.1 % to 4.9 % and that of major or minor depressive episodes from 8.5 % to 11 % (Gaynes et al. 2005). The incidence of major or minor depression during pregnancy is about 14.5 %, major depression being about 7.5 %. Many women are advised to stop taking psychotropic medications during pregnancy or before conception because of our limited knowledge of their safety during pregnancy. Acute affective or psychotic disorders during pregnancy

can adversely affect the pregnancy, fetus, and the family as a whole.

31.3.2.1 Negative Consequences of Untreated Psychiatric Illness

Maternal negative consequences: Maternal negative consequences of untreated psychiatric illness during pregnancy include lack of self-care, poor compliance with prenatal care (Zuckerman et al. 1989), lower than expected weight gain, use of tobacco, alcohol, and illicit substances, increased risk of being a victim of violence, deciding to abort due to depression, and increased risk for self-injurious behavior and suicide (although suicide risk may be lower than in non-pregnant women (Marzuk et al. 1997)).

Negative consequences on the family unit: Psychiatric illness in the pregnant mother can affect the family as a whole causing interpersonal problems, marital discord, disruption in the mother–child interaction, and attachment problems.

Obstetric and neonatal complications: Untreated psychiatric illness during pregnancy has been reported to cause placental abruption, preeclampsia, higher need for epidural anesthesia, higher incidence of operative deliveries, preterm birth, low birth weight, smaller head circumference, lower Apgar score at birth, higher incidence of neonatal intensive care unit (NICU) admissions, and impairment in neonatal neurobehavioral functioning such as irritability in newborn, unconsolability, and excessive crying (Zuckerman et al. 1990). The exact etiology for these complications is unclear. It is hypothesized that increased stress, depression, and anxiety during pregnancy can result in increased maternal levels of cortisol and catecholamines which pass through the placenta and may adversely affect the placental function. This may explain the increased incidence of uterine irritability, preterm labor, and low birth weight. Maternal anxiety in pregnancy has shown to increase the uterine artery resistance index (Teixeira et al. 1999).

Long-term effects: Childhood behavioral problems have been reported in infants of mothers with untreated psychiatric illness. Children whose mothers experienced high levels of anxiety in late pregnancy exhibited higher rates of behavioral and emotional problems during early childhood, which persisted through middle childhood, after controlling for obstetric risks, psychosocial disadvantage, and postnatal anxiety and depression (O'Connor et al. 2003). Poor growth and increased risk for infection has been reported in children exposed to maternal depression (Rahman et al. 2004). Elevated cortisol levels, increased stress responsiveness, difficult temperament, language and cognitive impairment, impulsivity, aggressive behaviors, dysphoria, sleep problems, attention-deficit disorder have all been reported in children exposed to maternal depression during pregnancy (Huot et al. 2004).

Placental transmission of stress hormones to the fetus from maternal depression could affect fetal brain development which could explain the increased behavioral/emotional problem in children exposed to maternal depression and anxiety during pregnancy.

31.3.3 Risk Factors for the Emergence or Exacerbation of Psychiatric Disorders during Pregnancy

Personal and family history of affective illness, discontinuation of maintenance psychotropic medications during pregnancy, having anxiety, younger age, living alone, multiple children, marital discord, being exposed to domestic violence, recent adverse life events, inadequate psychosocial support, lower socioeconomic status, and unwanted pregnancy have been reported to increase the emergence or exacerbation of psychiatric illness during pregnancy.

31.3.4 Clinical Features of Psychiatric Disorders during Pregnancy

There is a significant overlap between prepartum and postpartum depression. Women with depression during pregnancy have an elevated risk of

postpartum depression (Gotlib et al. 1989; Koutra et al. 2014). Diagnostic criteria for depressive disorders during pregnancy are similar to depression during other times in a woman's life. Anxiety is common during pregnancy especially when comorbid with depression. Diagnosis of depression during pregnancy can be complicated by the significant overlap of the neurovegetative symptoms of depression with pregnancy, such as sleep disturbance, low energy, appetite change, and decreased libido. The clinical features that would help to make the diagnosis of depression include anhedonia, feelings of guilt, hopelessness, and suicidal thoughts. Suicidal behavior or a suicide attempt in women with clinical depression during pregnancy is found to be relatively lower compared to that in non-pregnant women (Appleby 1991; Marzuk et al. 1997). Women with a history of recurrent major depression who are on maintenance antidepressant medication and who discontinue their medication either before conception or during pregnancy are at significantly high risk for relapse (Cohen et al. 2004).

Pregnancy is now considered a time for an increased risk for relapse of bipolar depressive and manic episodes, especially following discontinuation of mood stabilizing maintenance treatment. The risk also increases sharply during the postpartum period (2.9 times). Recurrence risk is greater after rapid than after gradual discontinuation of lithium and for patients with more prior affective episodes (Viguera and Nonacs 2000).

Mild to moderate anxiety symptoms are common during pregnancy, but severe anxiety symptoms need prompt diagnosis and treatment, as anxiety can have a deleterious effect on pregnancy and the fetus and increase the risk for postpartum anxiety and depression (Heron et al. 2004). Similarly, women who discontinued treatment for panic disorder and obsessive compulsive disorder are three times more likely to relapse compared to those who maintained treatment during pregnancy (Roy-Byrne et al. 1989).

Posttraumatic stress disorder (PTSD) has been reported in women with traumatic birth experience including prolonged labor, severe pain during childbirth, and loss of control during delivery. It can affect a woman's decision on future pregnancy and her ability to breast-feed, and impair parent–child bonding (Beck 2004)

Psychotic disorders during pregnancy are associated with significant maternal and fetal morbidity and mortality. A new onset of psychosis during pregnancy requires systematic diagnostic evaluation to rule out secondary causes of the symptoms. It also increases the risk for postpartum psychosis. Acute psychosis during pregnancy is both an obstetric and a psychiatric emergency and needs prompt evaluation and treatment to reduce the morbidity and mortality associated with it.

31.3.5 Diagnosis and Treatment of Psychiatric Disorders during Pregnancy

Appropriate management of psychiatric disorder during pregnancy should involve prompt diagnosis, treatment and collaboration between the patient, family, obstetrician, and psychiatrist. Discussion with the patient and family should involve morbidity and mortality associated with untreated psychiatric illness, the risks and benefits of psychotropic medications including the risk of discontinuation of psychotropic medication, and alternative treatments available. These discussions should be initiated prior to conception in patients with a history of psychiatric illness and who are already on psychotropic medications.

Clinicians face specific challenges in treating pregnant women with psychiatric illness. All medications readily cross the placenta. Physiologic changes in a woman's body during pregnancy can alter the pharmacokinetics and pharmacodynamics of drug treatment. It is common for women to avoid or discontinue psychotropic agents either before conception or during pregnancy. The threshold for treating a psychiatric condition during pregnancy with medication tends to be higher compared to a non-psychiatric medical illness. Treatment with psychotropic medications is usually reserved for psychiatric conditions that cause severe impairment in maternal functioning. Treatment should be individualized after a collaborative and ongoing discussion with the patient

and her partner. Even if the decision is made to discontinue treatment, patients should be followed closely during pregnancy and in the postpartum period for early detection of relapse and rapid intervention, which may significantly reduce the morbidity.

31.3.5.1 General Guidelines for Treatment during Pregnancy

The choice of treatment with psychotropic medication during pregnancy is based on the severity of symptoms, patient's level of functioning, period of clinical stability with and without treatment, past history of treatment discontinuation and time to relapse, time to recovery with reintroduction of treatment, previous medication trials and responses, risk and benefits of treatment, and wishes of the patient.

Non-pharmacologic interventions such as CBT and interpersonal therapy (IPT) have proven efficacy for mild to moderate depression and anxiety and should be considered as a first-line treatment for these conditions whenever possible (Spinelli 1997). Both IPT and CBT can also be used to taper the dose of antidepressant or anti-anxiety medications prior to conception to decrease the risk of relapse.

None of the psychotropic medications are Food and Drug Administration (FDA) approved for use during pregnancy. General guidelines for use of psychotropic medications during pregnancy include: (1) select the safest medication with documented safety; (2) use the minimum effective dosage; (3) avoid abrupt discontinuation of medication; (4) simplify the medication regimen and avoid polypharmacy; (5) if medications were discontinued during pregnancy, consider restarting them postpartum, as this is the period of high risk for relapse.

Risks associated with the use of psychotropic medication during different stages of pregnancy include:

1. pregnancy loss
2. teratogenicity with exposure in the first 12 weeks
3. adverse pregnancy and delivery outcomes
4. perinatal syndrome or neonatal toxicity
5. long-term neurobehavioral sequelae in the exposed infant including cognitive, emotional, and behavioral problems

Antidepressants

Reported adverse outcomes with the use of antidepressants during pregnancy (Chaudron 2013) are associated with:

1. Increased risk for pregnancy-induced hypertension with or without preeclampsia with the use of SSRI during late pregnancy (Toh et al. 2009; DeVera and Berard 2012).
2. Slight increase in the risk for spontaneous abortion with the early pregnancy exposure to antidepressants: 12.4 % (exposed) versus 8.7 % (unexposed) (Gentile 2008). In a more recent meta-analysis (Ross et al. 2013), no significant association between antidepressant medication exposure during early pregnancy and spontaneous abortion was found.
3. Structural malformation: In a recent meta-analysis (Grigoriadis et al. 2013a), no associated risk of congenital malformation was found with exposure to antidepressants during early pregnancy. Conflicting association was reported with first trimester exposure to paroxetine (FDA Category D) and increased risks of cardiac malformations. Combination of an SSRI and a benzodiazepine may increase the risk for congenital heart defects.
4. Lower birth weight, small size for gestational age, slower rates of head growth, preterm birth, lower Apgar scores have been reported with antidepressant exposure during pregnancy (Ross et al. 2013).
5. There is a significant association between exposure to antidepressants during late pregnancy and overall occurrence of poor neonatal adaptation syndrome (PNAS) which manifest as irritability, jitteriness, poor muscle tone, weak cry, respiratory distress, hypoglycemia, temperature instability, low Apgar scores, and seizures. Studies of third trimester exposure to SSRIs and SNRIs have demonstrated such effects (Zeskind and Stephens 2004). These symptoms start within hours of delivery, but generally require only supportive care and fully abate within 1–2 weeks. Poor neonatal adaptation may occur in 30 % of infants with

exposure to SSRIs, with higher rates evidenced in premature infants (Grigoriadis et al. 2013b).

6. Persistent pulmonary hypertension (PPH) of the newborn with exposure to SSRI after 20 weeks: Persistent pulmonary hypertension in the newborn occurs when the pulmonary vascular resistance fails to decrease after birth and the ductus arteriosus remains open to ensure circulation. Mortality ranges from 5 % to 10 %. Perinatal risk factors for persistent pulmonary hypertension of the newborn include meconium aspiration, maternal overweight, smoking, diabetes, or use of nonsteroid anti-inflammatory drugs during pregnancy. PPH with exposure to SSRI was first reported in 2006 (Chambers et al. 2006). Since then studies have shown conflicting results on the increased risk of PPH with later gestational exposure to SSRI. A recent population based cohort study from the health registers from five Nordic countries involving 1.6 million births found an absolute risk increase from 1.2/1,000 base rate to 3/1,000 in SSRI exposed newborns. It was a class effect with no difference between the SSRIs (Kieler et al. 2012).
7. Long-term growth, IQ, and behavioral problems: Most studies show no association with use of SSRIs or TCAs during pregnancy and long-term neurobehavioral problems and IQ in exposed children (Pederson et al. 2013; Nulman and Rovet 2002; Nulman et al. 1997; Nulman et al. 2012). There is a recent report of twofold increased risk of autism spectrum disorder associated with SSRI treatment (Croen et al 2011) and subtle impairment in motor development with fetal exposure to antidepressants (Casper 2003).

31.3.5.2 APA and ACOG Guidelines for Treating Depression during Pregnancy (Yonkers et al. 2009)

Women thinking about getting pregnant: For women on medication with mild or no symptoms for 6 months or longer, it may be appropriate to taper and discontinue medication before becoming pregnant.

Medication discontinuation may not be appropriate in women with a history of severe, recurrent depression or who have psychosis, bipolar disorder, other psychiatric illness requiring medication, or a history of suicide attempts. Women with suicidal or acute psychotic symptoms should be referred to a psychiatrist for aggressive treatment.

Pregnant women currently on medication for depression: Psychiatrically stable women who prefer to stay on medication may be able to do so after consultation between their psychiatrist and ob-gyn to discuss risks and benefits. Women who would like to discontinue medication may attempt medication tapering and discontinuation if they are not experiencing symptoms, depending on their psychiatric history. Women with a history of recurrent depression are at a high risk of relapse if medication is discontinued. Women with recurrent depression or who have symptoms despite their medication may benefit from psychotherapy to replace or augment medication. Women with severe depression (with suicide attempts, functional incapacitation, or weight loss) should remain on medication. If a patient refuses medication, alternative treatment and monitoring should be in place, preferably before discontinuation.

Pregnant and not currently on medication for depression: Psychotherapy may be beneficial in women who prefer to avoid antidepressant medication. For women who prefer taking medication, risks and benefits of treatment choices should be evaluated and discussed, including factors such as stage of gestation, symptoms, history of depression, and other conditions and circumstances (e.g., smoking, difficulty gaining weight).

All pregnant women: Regardless of circumstances, a woman with suicidal or psychotic symptoms should immediately be hospitalized and see a psychiatrist for treatment.

Benzodiazepines

Abrupt discontinuation of benzodiazepines during pregnancy can result in rebound anxiety symptoms and potentially serious withdrawal symptoms. If the patient and clinician decide to

stop *a* benzodiazepine during pregnancy, it has to be gradually tapered over 2 weeks or more. Adjunctive CBT could be helpful to prevent relapse of symptoms. SSRIs and SNRIs should be tried as first-line agents for treatment of anxiety disorders, but patients may need augmentation with *a* benzodiazepine especially during the first few weeks of treatment till the antidepressant starts working.

Reported adverse outcomes with the use of benzodiazepines during pregnancy include:

1. *Teratogenic Effects:* Initial reports suggested that there may be an increased risk of cleft lip and palate with the use of benzodiazepines during first trimester. More recent studies and meta-analysis suggest a very modest increase in risk of oral cleft, 0.7 %, which represents a tenfold increased risk in relation to general population (Altshuler et al. 1996). All benzodiazepines are FDA Class D medications and should be used only if the maternal benefit outweighs the fetal risk. Currently, no systematic data are available on the reproductive safety of non-benzodiazepine anxiolytic agents, such as buspirone and hypnotic agents like zolpidem and zaleplon. Therefore, these medications are not recommended for use in pregnancy.
2. *Perinatal Toxicity:* Maternal use of BZD and/or benzodiazepine receptor agonists may increase the risk for preterm birth and low birth weight (Wikner et al. 2007). Late-trimester use and exposure to benzodiazepine during labor is associated with increased risk for floppy baby syndrome or marked neonatal withdrawal symptoms. Symptoms of floppy baby syndrome can include mild sedation, hypotonia, neonatal apnea, reluctance to suck, low Apgar score, cyanosis, and temperature dysregulation. Symptoms of neonatal withdrawal include hypertonia, hyperreflexia, restlessness, irritability, abnormal sleep patterns, inconsolable crying, tremors or jerking of the extremities, bradycardia, cyanosis, suckling difficulties, apnea, risk of aspiration when fed, diarrhea and vomiting, and growth retardation. This neonatal withdrawal can appear within a few days to 3 weeks after birth and can last up to several months because of slow neonatal metabolism. Infrequent use of benzodiazepines does not seem to cause this problem.
3. *Long-term neurobehavioral effects:* Data on long-term neurobehavioral sequelae following exposure to benzodiazepines in utero are scant and reports are mixed. In one study involving 550 children exposed to benzodiazepines and followed up to 4 years of age, there was no adverse effects on neurobehavioral development and IQ (McElhatton 1994).

31.3.5.3 Management of Bipolar Disorder during Pregnancy

It is challenging for clinicians to treat patients with a history of bipolar disorder who plan to conceive or who are pregnant. Because most mood stabilizers and atypical antipsychotic drugs have been categorized as FDA category C (human fetal teratogenicity cannot be ruled out) or category D (positive risk of human fetal teratogenicity has been demonstrated). Relative risk associated with the use these medications should be weighed against potential benefits and the likely morbidity and mortality associated with untreated bipolar illness. Treatment should be individualized with collaborative discussion with the patient and her partner and making an informed decision.

31.3.5.3.1 Mood Stabilizers

Lithium

Teratogenic Effect (Class D): (Gentile 2012) The risk of major congenital anomalies in lithium-exposed babies is about 4–12 % compared to 2–4 % in the general population. The use of lithium during the first trimester is associated with the risk of Ebstein anomaly, which is characterized by right ventricular hypoplasia and congenital downward displacement of the tricuspid valve into the right ventricle. Initially, this risk was thought to be approximately 400 times higher than in the general population, but recent epidemiologic data point to a risk of 4.45–7.6/1,000 live births. Report from the registry on 225 lithium babies identified 25 cases of congenital

anomalies (11.1 %) of which 18 babies (8 %) had cardiovascular defects and six (2.7 %) had Ebstein anomaly. Prenatal screening with high-resolution ultrasound and fetal echocardiography is recommended at around 16–18 weeks of gestation to screen for cardiac anomalies in the fetus exposed to lithium.

Pregnancy and delivery outcome: Lithium use during the second and third trimesters of pregnancy has been reported to cause polyhydramnios, premature delivery, thyroid abnormalities including nontoxic goiter and hypothyroidism and nephrogenic diabetes insipidus in the fetus.

Neonatal outcome: The lithium exposed newborn can develop floppy baby syndrome, with lethargy, muscular hypotonia, impaired breathing, and cyanosis. The higher the maternal lithium level, the greater the fetal complications detected.

Long-term neurobehavioral effects: Limited data are available on the neurobehavioral sequelae from lithium exposure during pregnancy. Two small studies (Van der Lugt et al. 2012; Schou 1976) showed normal growth, behavior and development in lithium exposed children indicating that continuing lithium therapy during pregnancy does not pose significant risk to the neurological, cognitive and behavioral development of exposed children.

General guidelines for using lithium: To minimize lithium-induced fetal complications, prescribe the minimum effective dose, use sustained-release lithium in divided doses to avoid peak concentrations, avoid diuretics with lithium, discontinue use of lithium 24 h before delivery and resume use after delivery to prevent postpartum decompensation, and maintain intravenous hydration during labor and delivery. Recent guidelines on the use of lithium during pregnancy suggest gradual tapering of lithium over a period of 2 weeks pre-pregnancy in patients with mild and stable forms of bipolar disorder. In patients with a moderate risk for relapse, tapering, and discontinuing lithium during embryogenesis can be tried. In patients with severe form of illness with multiple episodes of affective instability or who relapse on medication discontinuation, maintaining lithium throughout pregnancy is recommended, as the risk associated with lithium teratogenicity is outweighed by the risk associated with lithium discontinuation and relapse (Cohen et al. 1994; Cohen 2007; Armstrong 2008). Relapse of bipolar disorder during pregnancy is potentially dangerous to both mother and fetus, as it would require aggressive treatment including hospitalization and exposure to multiple psychotropic agents at higher dosages.

Valproic Acid

Teratogenic risk (Class D): The incidence of major congenital malformation is about 11 %. The rates of neural tube defect range from 3 % to 5 %, which is more than 50 times above the base rate of 0.05 % in the general population. This is of particular concern because the formation of the neural tube occurs during the first month of pregnancy, even before the diagnosis of pregnancy is made. Thus, women in their reproductive years who are on valproate should have reproductive counseling before deciding to get pregnant. Other congenital anomalies associated with exposure to valproate include craniofacial abnormalities, cardiovascular malformation, skeletal abnormalities, limb defects, genital anomalies, and CNS structural abnormalities including hydrocephalus. There is also an increased risk for minor malformations with exposure to valproate including rotated ears, flat nasal bridge, fingernail hypoplasia, which tend to disappear over time (Jager-Roman et al. 1986). Specific risk factors for teratogenesis include high maternal daily doses or serum concentrations, low folate level, and exposure to multiple anticonvulsants.

Perinatal toxicity: Perinatal toxicity reported with valproate exposure include intrauterine growth retardation, neonatal hypoglycemia, coagulopathies, neonatal hepatotoxicity, and hyperbilirubinemia and neonatal withdrawal syndrome, with irritability, jitteriness, hypertonia, feeding difficulties, seizures, and vomiting (Ebbesen et al. 2000; Thisted and Ebbesen 1993).

Long-term neurobehavioral effects: Data collected from the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study have shown lower IQs and increased risk of marked intellectual impairment among valproate-exposed children evaluated at 6 years of age (Bromley et al. 2013).

The use of valproate in pregnancy is relatively *contraindicated,* and pregnant women with first trimester exposure to valproate should have a high-resolution fetal sonogram and echocardiogram performed at 16–18 weeks of gestation along with a serum α-fetoprotein level to detect neural tube defects followed by amniocentesis if necessary to detect spina bifida. Supplementation with folic acid 4 mg daily is recommended. Prophylactic vitamin K supplementation 10–20 mg/day in the last month before delivery as well as 1 mg IM vitamin K administered to neonates is recommended because of the potential for valproate-induced coagulopathies. Lower doses of valproate (<1,000 mg/day) with serum levels <70 μg/ml and divided doses may reduce the risk of teratogenicity.

Carbamazepine (Class D)

Carbamazepine has been associated with about 0.5–1.0 % risk of spina bifida. The overall incidence of congenital malformation is about 5.7 %. Common teratogenic effects include microcephaly and other craniofacial defects, fingernail hypoplasia, cardiac abnormalities, coagulopathies, growth retardation, and possible developmental delays (Jones et al. 1989). A higher frequency of congenital anomalies is reported when carbamazepine is administered with valproate. Carbamazepine is relatively contraindicated during the first trimester of pregnancy.

Lamotrigine (Class C)

The risk of malformation with lamotrigine monotherapy during the first trimester, based on data from the lamotrigine pregnancy registry established by the manufacturer, is about 2.5 %. There have been recent reports of increased prevalence of cleft lip and/or cleft palate in infants exposed to lamotrigine during the first trimester of pregnancy.

Topiramate (Class D)

Data from the North American Antiepileptic Drug Pregnancy registry and UK Epilepsy and pregnancy registry show 4–5 % increased risk of major malformation in women exposed to topiramate, with a predominance of oral cleft (11times higher).

31.3.5.3.2 Antipsychotics

First Generation Antipsychotics (FGA) and Second Generation Antipsychotics (SGA)

Teratogenic risk: Antipsychotic medications are classified as FDA class C medications and have been associated with a small possible increase in the risk for birth defects as a whole, with no significant differences in malformation risk between classes and/or single medications. There are reports of increased risk of therapeutic abortions (Mckenna et al. 2005).

Perinatal effects: The use of both SGAs and FGAs during late pregnancy has been associated with increased rates of perinatal complications including low birth weight babies and extrapyramidal symptoms in the newborn. There are several reports of transient extrapyramidal side effects (EPSs), including motor restlessness, tremors, difficulty with oral feeding, hypertonicity, dystonic movements, and parkinsonism in neonates exposed to FGA in utero. But these symptoms are short lived, and infants were noted to have normal motor development. SGAs increase the risk for metabolic syndrome and the complications associated with it. Quetiapine showed the lowest amount of placental passage in a comparative study with both FGAs (haloperidol) and SGAs (risperidone and olanzapine) (Newport et al. 2007).

Reports on long-term neurobehavioral consequences of exposure to antipsychotics are limited and inconclusive.

Clozapine: Clozapine is FDA class B medication. Reproductive studies in animals at doses approximately two to four times the human dose revealed no harm to the fetus. In humans, information on the safety of clozapine in human pregnancies has been available since the early 1990s. Single cases of major malformations, gestational metabolic complications, poor pregnancy outcome, and perinatal adverse reactions associated with exposure to clozapine during various stages of pregnancy have been reported, though solely from case reports

and/or small case series studies (Nguyen and Lalonde 2003; Gentile 2010). The potential for clozapine-induced agranulocytosis warrants monitoring of the white blood count (WBC) in exposed newborns, although there have been no reports of leukopenia or agranulocytosis in such infants.

31.3.5.4 Treatment of Psychosis during Pregnancy

Independent of any safety considerations, treatment of psychosis during pregnancy becomes a psychiatric emergency because of the increased risk for harm to mother and baby. Antipsychotics are frequently administered to control the symptoms. Safety data on the use of FGAs are available for last 40 years and should be preferably used to treat new onset psychotic symptoms during pregnancy. If patients had been on certain antipsychotics before pregnancy, it is preferable to continue the same medication during pregnancy because trying new medication during pregnancy can result in exacerbation of symptoms.

31.3.5.5 Electroconvulsive Therapy During Pregnancy

Electroconvulsive therapy (ECT) is a relatively safe and effective treatment during pregnancy when done in collaboration with a multidisciplinary team and taking steps to minimize potential risks. It is indicated for severe psychotic depression and agitated mania with risk of impulsivity and self-harm.

A study that reviewed 300 case reports from 1942 to 1991 reported complications in 28 of the 300 cases that underwent ECT during pregnancy. These complications included transient benign fetal arrhythmias, mild vaginal bleeding, abdominal pain, self-limited uterine contractions, premature labor, miscarriage, stillbirth and neonatal death, neonatal respiratory distress, and teratogenicity (Miller 1994). Transient hypertension during seizures may increase the risk of abruption (Sherer 1991). Without proper preparation there is an increased likelihood of pulmonary aspiration from delayed gastric emptying during pregnancy, aortocaval compression during later stages of pregnancy, and fetal hypoxia from respiratory alkalosis. Pregnancy may alter the seizure threshold in unpredictable ways. Progesterone-driven hyperventilation with compensatory alkalosis, electrolyte disturbances, sleep disturbance, fatigue, and stress can lower the seizure threshold.

31.3.5.5.1 Effects of Medications Used in ECT

Muscle Relaxants: Succinylcholine, which is used most commonly as a muscle relaxant during ECT, in ordinary doses does not cross placenta in detectable amounts.

Anticholinergic Agents: Atropine or glycopyrrolate is administered before ECT to prevent excessive vagal bradycardia and to decrease oropharyngeal and tracheal secretions. Atropine and to a lesser extent glycopyrrolate quickly cross the placenta and can cause fetal tachycardia and decreased heart rate variability. Glycopyrrolate, because of its minimal effect on fetal heart rate, is preferred during pregnancy. Also these drugs can reduce lower esophageal sphincter tone, thus increasing the risk of regurgitation and aspiration.

Barbiturates: Short-acting barbiturates in doses administered during ECT have no known adverse effect unique to pregnancy.

Preparation for ECT during pregnancy should include a pelvic exam, discontinuation of nonessential anticholinergic medication, monitoring for uterine contractions, intravenous hydration, and administration of nonparticulate antacid. During ECT, elevation of the pregnant woman's right hip, external fetal cardiac monitoring, intubation (if beyond first trimester), and avoidance of excessive hyperventilation are recommended. Recheck for uterine contraction and vaginal bleeding after ECT is administered. Informed consent for ECT should include the patient's capacity to understand and rationally evaluate risks and benefits to herself and the fetus.

31.4 Postpartum Psychiatric Disorders

The postpartum period is a time of increased vulnerability to psychiatric illness in the life cycle of women. About 85 % of women experience some

kind of mood symptoms during this period, but in most cases symptoms are transient and mild. 10–15 % of women experience more severe and disabling symptoms, which, if unrecognized and untreated, can place both the mother and the newborn at risk, have a negative impact on the family as a whole, and have been associated with long-term effects on child development and well-being (Murray 1992).

Postpartum affective illness is clinically indistinguishable from affective illness occurring at other times during a woman's life. The risk for postpartum psychiatric illness is highest during the first 3 months after delivery, but the risk remains high during the first year after delivery.

Postpartum psychiatric disorders include:
Postpartum blues: incidence 50–85 %
Postpartum depression: incidence 10–15 %
Postpartum psychosis: incidence 0.1–0.2 %

31.4.1 Postpartum Blues (PPB), also called "Baby Blues"

This is a common benign, transitory, and self-limited condition occurring during the first 10 days postpartum. It peaks between days 3 and 5. Postpartum blues appear to be a specific affective syndrome associated with childbirth. Symptoms include rapidly fluctuating mood, tearfulness, irritability, anxiety, somatic symptoms, and sleeplessness. The central feature of postpartum blues is the marked lability of mood with increased emotional reactivity to stimuli, such as crying or becoming irritable, profoundly joyful, or sad, in response to stimuli that would normally not provoke such intense reactions.

Relationship to Other Affective Illness: History of depressive episodes, depression during pregnancy, premenstrual depression, family history of depression can increase the risk for PPBs. Women who experience severe postpartum blues have three times greater likelihood of developing postpartum depression (Henshaw et al. 2004).

31.4.1.1 Etiology

Psychosocial Factors: The role of demographic variables, current stressors, obstetric complications, and social support in causing PPBs appears to be minimal. It occurs across all social classes and cultures even though the incidence may vary. Psychosocial factors have been shown to influence the intensity of blues (M'Bailara et al. 2005)

Biologic Factors: The timing of symptoms coincides with a period of dramatic drop in the hormonal level, which points to a physiological cause for PPBs. The abrupt withdrawal of the hormones estrogen and progesterone in the immediate postpartum period may have a direct or indirect effect via neurotransmitters in causing the mood symptoms. It is the magnitude of drop rather than the absolute levels that cause the symptoms. One study found a greater drop in free estriol levels in women who developed postpartum blues compared to women who did not (O'Hara et al. 1991). Mood symptoms may be related to the large drop in the β-endorphin causing an endogenous opioid withdrawal state (Brinsmead et al. 1985). There is evidence of lower levels of free plasma tryptophan, a precursor of serotonin, in the early postpartum period that may trigger the blues in vulnerable women (Bailara et al. 2005).

31.4.1.2 Treatment

No specific treatment is indicated as symptoms are benign and resolve spontaneously. Support and reassurance could help. It usually does not affect the mother's functional ability to care for self and her newborn. If symptoms are severe or prolonged over 2 weeks, blues may indicate the onset of postpartum depression.

31.4.2 Postpartum Depression

The prevalence of postpartum depression (PPD) is 10–15 %. DSM-5 diagnostic criteria for PPD include symptoms of major depression lasting for more than 2 weeks with peripartum onset.

31.4.2.1 Risk Factors

Risk factors for PPD include low socioeconomic status, financial stress, marital discord, inadequate social and spousal support (both emotional and instrumental support), child care stress, stressful life events during pregnancy or early postpartum. Immigrant women who are culturally and physically separated from their support system are at risk for postpartum depression (Dennis et al. 2004). Other risk factors include very young or older age, having twins, a history of premenstrual dysphoric disorder, severe postpartum blues, depressive symptoms during pregnancy, anxiety symptoms during pregnancy, a personal history of mood disorder especially bipolar disorder (risk of recurrence is 30–50 %), a history of postpartum depression (rates of recurrence are as high as 40 %) (Cooper and Murray 1995), a family history of mood disorder, history of recurrent episodes of depression, and discontinuation of antidepressant medications during pregnancy (Robertson et al. 2004).

31.4.2.2 Clinical Features

Onset of symptoms of PPD is insidious within the first 3 months after delivery. Symptoms are more pervasive and interfere with the mother's ability to care for self and her newborn. Symptoms include depressed mood, irritability, tearfulness, emotional lability, sleep disturbance, fatigue, loss of appetite, poor concentration, feelings of inadequacy, guilt, lack of pleasure, lack of interest in the baby, and ambivalent or negative feelings toward the infant. Suicidal ideation is common but suicide attempts are relatively infrequent in women with nonpsychotic depression. Anxiety symptoms are prominent and may present with generalized anxiety disorder, panic disorder, or hypochondriasis. Woman may experience intrusive obsessive ruminations involving the child, often violent in nature, such as thoughts about smothering the baby or dropping the baby down the stairs. These thoughts are ego-dystonic and very distressing, and women appear to go out of their way to ensure their child's safety. Reality testing remains intact. Severity of depression may decrease over time, but in 30 % of women symptoms could persist for as long as 2 years with persistent psychosocial stress.

31.4.2.3 Etiologic Factors

Etiologic considerations of general depression hold in addition to the biology and psychology of the postpartum period.

31.4.2.3.1 Biologic Factors

During pregnancy, levels of estrogen, progesterone, β-endorphin, human chorionic gonadotropin (HCG), and cortisol rise steadily, peaking near term. There is a rapid decline in the levels of these hormones with the removal of the placenta. Estrogen and progesterone levels drop 200-fold, reaching pre-pregnancy levels by the fifth postpartum day. Estrogen and progesterone are known to influence neurotransmitter functions in the brain. The sudden drop in hormones may increase the risk of developing mood symptoms in a subpopulation of women who are vulnerable to changes in hormonal state.

7 % of women develop abnormal thyroid function in the postpartum period, compared to 3–4 % in the general population. Approximately, 12 % of postpartum women have thyroid antibodies, which may be due to a rebound immune phenomenon after the sharp drop in the cortisol levels after delivery. In one study 43 % of antibody-positive women developed depressive symptoms compared to 28 % of antibody-negative women (Harris et al. 1992). Antibody-positive women should be followed with thyroid function testing beyond the postpartum period, as many patients with anti-thyroid antibodies go on to develop overt hypothyroidism within 4 years. Diminished thyroid function may affect postpartum mood through its association with diminished central serotonin activity.

31.4.2.3.2 Psychosocial Factors

Psychosocial variables appear to play a major role in the etiology of postpartum depression. Inadequate social support, marital discord, and stressful life events during pregnancy and around the time of delivery increase the likelihood of postpartum depression (O'Hara 1986).

31.4.2.3.3 Cultural Influences

Culture influences individual's identity, expression of symptoms, the nature of social support and stressors, and the treatment relationship between the patient and the clinicians. Different cultures follow different rites of passage to parenthood, which may include ceremonies, rituals, seclusion, rest, solicitude, and return to the home of origin. A major function of these rituals is to provide support during times of emotional and physical vulnerability. This lessens the likelihood of developing depressive symptoms during the vulnerable period. Migration, individuation, and separation from the family of origin can reduce the social support and increase the emotional burden on both partners in the postpartum period. During assessment, clinicians should ask patients about cultural background, social support network, and traditional antepartum and postpartum practices.

31.4.2.4 Consequences of Untreated Postpartum Depression

Untreated postpartum depression can result in a disturbed mother–infant relationship, *future* psychiatric morbidity in the child (depression, conduct disorder, lower IQ), marital tension, vulnerability to future depression, and suicide/homicide.

A disturbed mother–infant relationship as a result of postpartum depression can result in both short- and long-term consequences. Maternal characteristics including emotional availability, accepting attitude, and responsiveness and sensitivity to the infant's signals and needs are critical during the first year of life. These characteristics result in a secure mother–infant bonding that is associated with a positive outcome in the child. If the mother has postpartum depression, she may have difficulty interacting with her infant, or she may manifest a lack of interest, neglect, negativity toward the infant, and less sensitivity and responsiveness to the infant's needs. Infants of mothers with PPD show decreased eye gaze during feeding, less reciprocity and playfulness with their mothers, limited engagement with the environment, and more muted affective expressions (Feldman et al. 2009).

Long-term effects on children of mothers with postpartum psychiatric illness include behavioral problems, sleep disturbances, feeding problems, and temper tantrums, which may persist over time. Several studies have documented less optimal cognitive development in offspring of mothers with postpartum mood disorder, including lag in developing the concept of object permanence and developmental delays in intellectual functioning. It can also cause social and interpersonal functional impairment, including reduced quality of interaction with their mothers, less sociability with strangers, and insecure attachment patterns (Edhborg et al. 2003; Cicchetti et al. 1998). Exposure to maternal stress, especially postpartum depression early in infancy, predisposes children to increased hypothalamic-pituitary-adrenal axis (HPA) function with an increase in cortisol level during a period of concurrent stress. These children were found to be at increased risk for emotional and behavioral difficulties at the end of the first grade in school (Essex et al. 2002).

31.4.2.5 Course and Prognosis

The duration of postpartum depression is variable. Episodes are often short lived and may last no more than 3 months. Women with a history of recurrent major depressive disorder (MDD) and with severe symptoms can have a more protracted course. Postpartum depression has a good prognosis with early diagnosis and treatment. There is a 40 % risk of recurrence with subsequent childbirth (Wisner et al. 2004a). There is also risk of recurrence of episodes unrelated to pregnancy and childbirth.

Exposure to maternal depression in the early postpartum months may have an enduring influence on the child's psychological development and can cause emotional, behavioral, cognitive, and interpersonal problems later in life.

31.4.2.6 Treatment of Postpartum Depression

Primary Prevention: Primary prevention involves identifying risk factors and taking measures to prevent these factors from causing or contributing to postpartum depression. It includes:

1. Screening for antenatal depression, history of postpartum depression, family history of depression.

2. Screening for other risk factors, such as age, social support, financial status, negative life events.
3. Screening for thyroid antibodies and thyroid function.

Providing continuity of care, education, support groups, continuous early and late antenatal care with additional focus on psychosocial issues, and timely postnatal counseling can help reduce the risk. Brief, group psychotherapy for pregnant, socially disadvantaged women who have one or more risk factors of depression, a single individual psychotherapy session shortly after birth for women who had elevated depressive symptoms, and extended home visits by nurses/midwifes to vulnerable families have all been found to be effective strategies for preventing postpartum depression. Interpersonal therapy has proven efficacious in the prevention of postpartum depression, with focus on role transition, conflict with other role interests, and maladaptive interpersonal patterns (Dennis and Dowswell 2013).

For women with history of recurrent major depression or postpartum depression or depression during pregnancy, prophylactic antidepressant treatment has been found to reduce the recurrence of postpartum major depression (Wisner and Wheeler 1994; Wisner et al. 2004b).

Secondary Prevention: Secondary prevention involves early diagnosis and treatment to minimize the consequences of postpartum depression. Most women do not report their symptoms to health care providers, and less than one third of women with PPD receive any type of intervention. Screening all women for depression during the postpartum period is advisable. The Edinburgh Postnatal Depression Scale is a 10-item self-rated questionnaire that has been used extensively for detection of PPD (Cox et al. 1987) (see Appendix at end of chapter). A score of 12 or more on this scale or an affirmative answer on question 10 (presence of suicidal thoughts) raises concern and indicates the need for more thorough evaluation. It can be integrated in the follow-up obstetric visit at 6 weeks and subsequent pediatric well-baby visits, which can significantly improve the detection of PPD (Chaudron et al. 2004).

Mild to moderate postpartum depression can be managed by psychological interventions like interpersonal therapy, cognitive behavioral therapy, self-help networks, peer and partner support, and nondirective counseling. Other interventions, such as relaxation/massage therapy, exercise, and mother–infant relationship therapy, have also been found to be helpful. Biologic interventions are usually indicated for moderate to severe depression including antidepressant medications, hormone therapy, and ECT.

Interpersonal Therapy: Evidence supports the effectiveness of interpersonal psychotherapy in treating mild to moderate postpartum depression (O'Hara et al. 2000). It also improves social adjustment in these patients and represents an alternative to pharmacotherapy, particularly for women who are breast-feeding. Interpersonal therapy has been found to be effective in both individual and group settings. It is time limited and focuses on role transition, integrating a new role with the established roles, exploring feelings and ambivalence about these roles, assessing satisfaction with relationships, defining patient's expectations of others, and renegotiating relationships.

Cognitive Behavioral Therapy: Cognitive behavioral therapy in individual or group settings has been shown to be effective in treating mild to moderate postpartum depression (Appleby et al. 1997; Prendergast and Austin 2001). It is time limited and focuses on negative thoughts, negative perceptions of self and infant, cognitive restructuring, and behavioral modification.

Other Psychosocial Interventions: Companionship and belonging to a support group have a protective effect on postpartum depression. Support groups, peer and partner support (Dennis 2003), telephone-based peer support, and nondirective or supportive counseling administered by public health nurses and social workers have all been found to be effective in reducing the depressive symptoms of PPD. Similarly, maternal/infant massage therapy, exercise, infant sleep interventions, and mother–infant therapy all hold promise

in reducing the symptoms of postpartum depression (Craig and Howard 2009).

Pharmacotherapy: Pharmacotherapy is indicated for moderate to severe depression. Antidepressant medication, especially SSRIs and some SNRIs, has been shown to be effective in treating postpartum depression in randomized controlled and open-label studies (Yonkers et al 2008; Misri et al. 2004). Women with postpartum depression may take longer to respond to treatment and may require more antidepressant agents at the time of response to treatment (Hendrick et al. 2000). The use of psychotropic medications during breastfeeding should be considered on an individual basis, weighing the risks and benefits of nursing, the risks associated with the exposure of the infant to psychotropic medications and understanding the risks associated with untreated maternal psychiatric illness on the mother, child and family as a whole. General principles and specific classes of drug use in lactating women are discussed at the end of this section.

31.4.3 Postpartum (Puerperal) Psychosis

Postpartum psychosis is a psychotic disorder occurring after childbirth. It is primarily a bipolar affective disorder or a variant of it. Evidence from studies of women with a history of bipolar disorder, longitudinal studies of women with puerperal episodes of psychosis, and family studies supports a link between postpartum psychosis and bipolar disorder (Chaudron and Pies 2003).

31.4.3.1 Epidemiology

One to two per 1,000 postpartum women are affected. A constant incidence rate is reported transculturally (Kumar 1994).

31.4.3.2 Risk Factors

Risk factors for postpartum psychosis include primiparity (70–80 % of index cases occur after first childbirth, 35 times more common in primipara), personal and family history of bipolar disorder, women with history of postpartum psychosis, and women with a history of schizophrenia. Perinatal mortality, obstetrical complications, and lack of partner or social support can also increase the risk for postpartum psychosis (Kendell et al. 1987; Nager et al. 2008; Spinelli 2009)

31.4.3.3 Etiology

Transcultural prevalence and occurrence in primipara suggest that biologic factors play a major role in the onset of postpartum psychosis. Family history of affective illness suggests a genetic predisposition for postpartum psychosis. Hormone withdrawal in the postpartum state can lead to dopamine receptor supersensitivity as estrogen increases dopamine receptor binding. Sleep deprivation in the postpartum period may trigger manic and hypomanic states in vulnerable women (Strouse et al. 1992; Sharma et al. 2004).

31.4.3.4 Clinical Presentation

Postpartum psychosis is the most severe form of postpartum psychiatric illness. The presentation of postpartum psychosis is often abrupt and dramatic, with onset of symptoms during the first 48–72 h after delivery. The majority of women with postpartum psychosis develop symptoms within the first 2 weeks postpartum. Symptoms resemble those of a rapidly evolving mania or mixed state. The earliest signs are restlessness, agitation, irritability, and insomnia. The symptoms are characterized by a mixture of delirium, psychosis with confusion and perplexity, emotional lability, delusions, and hallucinations.

Postpartum psychotic depression presents with depressed mood (worst in the morning), tearfulness, significant psychomotor retardation, sleep disturbances with early morning awakenings, appetite disturbances, preoccupation with feelings of guilt and worthless, delusions of the infant being dead or defective, and even hallucinations commanding the mother to harm the baby. In postpartum mania, the woman is excited, euphoric, grandiose, irritable, hyperactive requires little sleep and may have grandiose delusions about her baby, such as having special powers or that the child is either Satan or God.

Compared with episodes of nonpsychotic depression, women with postpartum psychosis who have thoughts of harming their infants are more likely to act on them, as their reality testing is impaired.

Differential diagnosis includes exacerbation of primary psychiatric disorder, toxic, metabolic, or neurologic causes, such as tumors, head trauma, infection, cerebral embolism, seizures, electrolyte disturbances, anoxia, vitamin deficiencies, thyroiditis, and substance-induced psychosis, including that caused by high doses of prescription drugs or recreational drugs.

31.4.3.5 Prognosis

Rate of infanticide associated with untreated postpartum psychosis is estimated to be as high as 4 %. With adequate treatment 95 % women improve within 2–3 months and have a good functional outcome. A 23-year follow-up study showed an increased risk of subsequent episodes in 75 % of patients with an index puerperal episode, most of them unrelated to childbirth. The risk of puerperal recurrence is as high as 30 % (Robling et al. 2000). Medico-legal issues from infanticide secondary to postpartum psychosis can be complicated, as symptoms may remit by the time patient goes for trial.

31.4.3.6 Treatment of Postpartum Psychosis

Postpartum psychosis is a psychiatric emergency and requires major intervention and in most cases hospitalization. Both psychosocial and pharmacologic interventions are necessary. In most cases symptoms should be treated as an affective psychosis. Acute treatment with a mood stabilizer in addition to antipsychotic medication is indicated. Treatment with a mood stabilizer should extend beyond the resolution of active symptoms to reduce the risk of relapse. The infant's clinical status should be regularly monitored if the mother is breastfeeding. A monotherapy regimen should be maintained if possible to minimize side effects and to reduce delayed development from combination treatment. See Lactation and Psychotropic Medications at the end of the Postpartum Psychiatric Disorders section for specific medications.

Electroconvulsive therapy is well tolerated and can work more rapidly than medication in patients with more severe postpartum depression and postpartum psychosis.

In women with a history of postpartum psychosis or bipolar disorder, prophylactic treatment with lithium or other mood stabilizers instituted either prior to delivery (at 36 weeks gestation) or no later than the first 48 h postpartum is found to significantly reduce the relapse rates as well as to diminish the severity of illness (Cohen et al. 1995; Stewart 1988).

31.4.4 Lactation and Psychotropic Medications

Lactation is a unique event during the postpartum period. If the postpartum woman intends to breast-feed, the amount of drug passing into the breast milk becomes an important issue to consider in selecting a psychotropic medication.

Most psychotropic medications pass into breast milk in varying amounts, mostly through the process of passive diffusion. Factors that determine the amount of diffusion into breast milk include maternal dosing and frequency, and the drug's protein binding, lipid solubility, degree of ionization, and molecular weight. The less protein bound, more lipid soluble and more weakly alkaline the drug, the more likely it is to diffuse into breast milk. The higher lipid content of hind-milk makes it likely that the second half of breast milk will have a higher concentration of maternal medication than the first half.

Infant physiology that determines the bioavailability of the drug includes absorption, metabolism, and elimination of drugs. Infants have higher gastric pH, which increases the absorption of basic compounds. They have low serum protein, which would increase the amount of free drug in circulation. Full-term neonatal cytochrome P-450 activity is approximately one half of that found in adults, decreasing the rate of degradation of the medications. Hepatic enzyme immaturity is even more pronounced in premature infants. The newborn kidney is functionally immature, with a glomerular filtration rate (GFR) and tubular secretion

about 20–30 % of adult function, which result in decreased renal clearance. Medications eliminated through the kidneys tend to accumulate in the infant, causing toxic exposure over time. For full-term infants the GFR seen in adults is achieved between the second and fifth months of life. The newborn blood–brain barrier is not fully developed, and lipid soluble agents can be 10–30 times more concentrated in the cerebrospinal fluid (CSF) than in the serum.

The milk to plasma (M/P) ratio is the ratio of medication concentration in milk to the concentration in maternal serum. Compounds that are weakly protein bound, highly lipid soluble, weakly alkaline, and small in molecular size have a higher M/P ratio. Ratios greater than 1 indicate higher milk level than serum level. The higher the M/P ratio, the greater will be the infant's exposure to the medication. A clear correlation between M/P ratio and clinical status has not been established.

31.4.4.1 Treatment Guidelines during Lactation

Before starting psychotropic medications:

1. Explain the potential risks and benefits, ideally to both parents.
2. Refer for a pediatric evaluation to assess the baby's baseline behavior—sleep, feeding, and alertness.
3. Collaborate with the pediatrician and provide education regarding possible infant side effects and interaction with other medications.

The choice of medication is affected by a number of factors, including diagnosis of psychiatric illness, a past history of treatment response, the side-effect profile of the medication, dosing flexibility, and pharmacokinetic characteristics that minimize accumulation of the medication in milk and infant serum. Factors that minimize infant exposure include minimum effective dose, short acting agents, medications without active metabolites, timing the breast-feeding for when the drug levels in milk are lowest, formula supplementation reducing infant exposure while retaining some breast-feeding benefits, and monitoring infant clinical status monthly to ensure general health and normal pediatric development.

31.4.4.2 Specific Drug Use during Lactation

31.4.4.2.1 Antidepressants

SSRIs

From the available data, (Berle and Spigset 2011; Fitelson et al. 2011) SSRIs comprise a relatively safe group of medications that can be used during lactation for postpartum depression and anxiety. Among the SSRIs, sertraline and paroxetine have a uniformly low or non-detectable infant serum level and a lack of reported adverse effects, which makes them good choices for nursing mothers and are usually recommended as first line agents. Paroxetine may have some disadvantages. If the mother needs long-term treatment and subsequently becomes pregnant again, paroxetine is probably not the first choice due to the risk of cardiac defects. Also, among SSRIs, paroxetine has a higher risk for withdrawal symptoms if one or a few doses are missed.

Fluoxetine has an active metabolite-norfluoxetine, with a long half-life which may result in accumulation of the drug in infant serum. It is recommended that when possible, fluoxetine and citalopram should be avoided or used with caution due to the higher infant plasma levels than for other drugs, with the possible risk of adverse effects which are mostly subtle and unspecific and reverse with the discontinuation of the drug. Excessive crying, irritability, decreased feeding and watery stools have been described in a few cases for fluoxetine. For citalopram, hypotonia, colic, decreased feeding and sleep difficulties have been reported in single cases. However, if the mother has been treated with fluoxetine or citalopram previously and the treatment was effective, or if the mother has used one of these drugs during pregnancy, it could also be used in the postpartum period. For venlafaxine, which also result in relatively high infant serum level, no adverse events have been reported. A single case of seizures has been reported in a 6-month-old breast-fed infant after 4 days of maternal bupropion treatment. Also a single case report of necrotizing enterocolitis in a term infant exposed to escitalopram in utero and in breast milk has been published.

No difference in the infant body weight has been reported in several studies of SSRI exposure

through breast milk compared to values from general population (Hendrick et al. 2003). Long-term neurobehavioral data on infant antidepressant exposure through breast milk are lacking. No detrimental long-term effects have been reported in a few studies for factors such as global intelligence quotient, language, behavioral development and neurological development. Little data exist for drugs such as fluvoxamine, venlafaxine, duloxetine, bupropion, and mirtazapine, and these should not be considered as first-line therapies, but they can be used in special cases.

Routine breast milk and/or infant serum sampling for drug concentration analysis is generally not recommended. Clinical monitoring of the infant is indicated if the infant is sick, premature, or has a low body weight.

Tricyclics

The tricyclic antidepressants (TCAs) are useful in the treatment of postpartum depression when the SSRIs have failed, or when the woman has shown a previous good response to these medications. All TCAs are excreted into human breast milk in low concentrations, and a wide range of infant serum levels has been reported. However, no adverse effects have been documented from exposure to amitriptyline, nortriptyline, imipramine, desipramine or clomipramine. Doxepin has an active metabolite with a long half-life and has been reported to cause sedation and respiratory depression in one nursing infant.

31.4.4.2.2 Benzodiazepines

Benzodiazepines are commonly used to treat anxiety and insomnia associated with depression and as an adjunctive treatment for panic attacks, generalized anxiety and obsessive compulsive disorder and psychosis. Mild to moderate postpartum anxiety could be managed with non-pharmacologic interventions such as CBT, relaxation techniques, and environmental stress reduction. For severe anxiety symptoms benzodiazepines may be indicated. Benzodiazepines should be used with caution in lactation because of the risk of sedation, respiratory depression, and withdrawal symptoms. Low doses of medications with no active metabolites like clonazepam, oxazepam, temazepam, and lorazepam are preferred. However, the long half-life of clonazepam may predispose to accumulation in the infant.

In a prospective study of 124 (Kelly et al. 2012) mothers who used benzodiazepines, mainly lorazepam, clonazepam and midazolam while breast-feeding, central nervous system depression including sleepiness, poor latching, limpness or lack of response to stimuli was reported in 2 infants (1.6 %).

31.4.4.2.3 Mood Stabilizers

Lithium

Lithium is secreted into breast milk and levels achieved are nearly half of maternal serum levels. The neonate may be more vulnerable to lithium toxicity because the kidney is relatively immature with decreased renal clearance and high risk for dehydration. Adverse effects reported with lithium include cyanosis, hypotonia, heart murmur, T-wave changes, restlessness, muscle twitches, lethargy and hypothermia. Mild elevation in BUN/Cr and TSH was reported in one study which returned to normal after breast-feeding was discontinued. Long-term effects of sustained lithium levels on the infant are not known. The American Academy of Pediatrics recommends that breast-feeding be undertaken with caution by women undergoing lithium treatment. In a breast-fed infant exposed to lithium, serum concentrations should be monitored (Yonkers et al. 2004; Viguera et al. 2007).

Anticonvulsants

(Chaudron and Jefferson 2000; Yoshida et al. 1999)

Valproic acid

Valproic acid is considered compatible with breast-feeding because of consistent low levels in the breast milk. There is one report of thrombocytopenia and anemia in an infant exposed to mother on valproate. Recent reports on the neurodevelopmental effects, from in utero exposure to valproic acid, increase concern about the long-term effects of valproic acid exposure from lactation on the infant brain. If a nursing mother is taking valproic acid, it is important to monitor maternal and infant serum drug levels and liver function tests every 2 to 4 weeks, or more frequently as indicated by the clinical situation.

Carbamazepine

Carbamazepine is considered compatible with breast-feeding because of low level detected in breast milk. There are two case reports of transient direct hyperbilirubinemia and high concentrations of gamma-glutamyltransferase (GGT). Infants in both cases were exposed to carbamazepine during both pregnancy and through breast milk therefore it is unclear as to whether the adverse effects were the result of in-utero or breast milk exposure. Infants exposed to carbamazepine should be monitored for possible hepatic complications. Maternal and infant serum drug levels and liver function tests should be monitored every 2–4 weeks, or more frequently as indicated by the clinical situation.

Lamotrigine

Lamotrigine is excreted in considerable quantities (60 %) into human breast milk (Newport et al. 2008; Ohman and Vitols 2000; Tomson et al. 1997). Infant serum levels were approximately one-third of maternal levels. None of the infants in these case reports displayed adverse effects. However, lamotrigine has been linked to severe life threatening rashes in children who are treated directly with the drug, and there is a theoretical concern that infants exposed during breast-feeding may also be at risk. Thus, infants exposed to this medication should be observed closely for side effects.

31.4.4.2.4 Antipsychotics

Among the typical antipsychotics haloperidol is excreted in relatively high amounts in breast milk, but also has been shown to have no adverse effects on the infant (Whalley et al. 1981). Chlorpromazine exposure has been associated with drowsiness and lethargy in one infant (Wiles et al. 1978). In one study of seven infants with exposure to chlorpromazine through breast milk, there were no adverse effects reported at 16-month and 5-year follow-up evaluations. Another study showed that infants exposed to haloperidol and chlorpromazine through breast milk exhibited developmental delays at 12–18 months of age (Yoshida et al. 1998a). It is unclear if these delays were due to medication exposure or other factors.

Among the atypical antipsychotics, case reports on risperidone exposure found serum levels to be low to undetectable (Ilett et al. 2004). No adverse effects in any of the exposed infants were reported. With olanzapine exposure, serum levels were low to undetectable in the small number studied. Most infants showed no adverse effects (Croke et al. 2002). In one infant exposed to olanzapine, there was a report of cardiomegaly, jaundice, and sedation. Case reports from quetiapine exposure, breast milk levels were found to be low and there were no reported adverse effects in the exposed infants (Lee et al. 2004). One case report from Clozapine exposure found relatively high accumulation in breast milk (Barnas et al. 1994). Another report attributed delayed speech acquisition to clozapine, after the mother was treated with clozapine both prenatally and during breast-feeding (Mendhekar 2007). Although no cases have been reported of a granulocytosis in nursing infants, it is a theoretical risk.

In a recent meta-analysis (Klinger et al. 2013) of 4 prospective studies, 12 case series, 28 case reports, and 1 pharmaceutical registry, infant outcomes focused on long-term outcome from antipsychotic exposure from breast-feeding. Among 21 antipsychotic drugs used in clinical practice, 7 have no data at all regarding breast-feeding and 6 have data based only on few infant exposures. Only few prospective studies assessing use of haloperidol, chlorpromazine, and olanzapine during breast-feeding were identified. Olanzapine and quetiapine were categorized as acceptable for breast-feeding. Chlorpromazine, haloperidol, and risperidone were categorized as possible for breast-feeding under medical supervision. Breast-feeding cannot be currently recommended for the following medications: aripiprazole, asenapine, clozapine, droperidol, fluphenazine, flupenthixol, iloperidone, lurasidone, paliperidone, perphenazine, pimozide, trifluoperazine, thiothixene, and ziprasidone.

31.4.4.2.5 Hormonal Interventions

Progesterone use has not been supported by randomized controlled studies. Some reports suggest worsening of mood symptoms with synthetic progesterone (Lawrie et al. 1998).

Postpartum estrogen treatment has shown some beneficial effect. Transdermal patch of 17β-estradiol was found to be effective in one double blind placebo-controlled trial ($n=61$)

(Gregoire and Kumar 1996) and sublingual 17β-estradiol was found to be effective in one open-label study ($n=23$) (Ahoka et al. 2001). Effective dosing and the route of administration include using a 200 μg transdermal patch, changed twice weekly, or 1 mg sublingually four times a day. Side effects include changes in breast milk production, thromboembolic events, and endometrial hyperplasia. Efficacy and safety relative to antidepressants have not been established.

31.4.4.2.6 Electroconvulsive Therapy

No randomized controlled trials exist on the use of ECT in postpartum women. It has been advocated by several researchers as an effective treatment option. It is used more commonly in severe drug-resistant psychotic depression. It also has a positive advantage in breast-feeding mothers who do not want to expose their infants to antidepressant medications.

31.4.4.3 Conclusion

The postpartum period increases vulnerability for the development of major psychiatric illness in some women. The consequences of untreated postpartum depression and psychosis can be devastating for the mother, the newborn, and other family members. Screening for risk factors and symptoms can be incorporated into the already existing prenatal and postnatal clinic visits. Instituting effective pharmacologic and nonpharmacologic interventions may limit both maternal and infant morbidity and mortality.

31.5 Special Topics

31.5.1 Hyperemesis Gravidarum

70–85 % of pregnant women develop nausea and vomiting during early pregnancy. In 10 % of these women symptoms may persist throughout pregnancy. Hyperemesis gravidarum is a severe form of nausea and vomiting seen in 0.3–2.3 % of all pregnancies. The condition is defined as uncontrolled vomiting requiring hospitalization for severe dehydration, muscle wasting, electrolyte imbalance (hyponatremia, hypokalemia), low serum urea, ketonuria, and weight loss of more than 5 % of body weight. The symptoms usually peak at 9 weeks of gestation and subside by approximately 20 weeks of gestation. Women who experienced hyperemesis in their first pregnancy have a high risk for recurrence (Trogstad et al. 2005). It can result in a negative pregnancy outcome and can cause considerable distress and disability to the pregnant woman and her family.

Multiple gestation, gestational trophoblastic disease, triploidy, Down syndrome, and hydrops fetalis have been associated with an increased incidence of hyperemesis gravidarum. Multiple medical conditions have been found to play a role in causing or contributing to hyperemesis gravidarum, including gastrointestinal disorders, genitourinary tract diseases, metabolic disorders, neurologic disorders, pregnancy-related conditions like acute fatty liver of pregnancy and preeclampsia, and drug toxicity or intolerance (Quinlan and Hill 2003; Philip 2003)

Negative maternal outcomes associated with hyperemesis gravidarum include splenic avulsion, esophageal rupture, Mallory-Weiss tears, pneumothorax, peripheral neuropathy, and preeclampsia. If not appropriately treated, it may even cause severe adverse effects, including Wernicke encephalopathy, central pontine myelinolysis, and even maternal death.

Negative fetal outcomes include fetal growth retardation, small for gestational age, premature birth, lower birth weight, and low Apgar scores. There are also reports of congenital malformations such as undescended testes, hip dysplasia, Down syndrome, and increased incidence of CNS malformation. Untreated electrolyte disturbance, malnutrition, and maternal weight loss may be the cause for these congenital malformations.

Management of the nausea and vomiting of pregnancy depends on the severity of symptoms and can range from dietary modifications, acupressure, hypnosis, vitamin supplements (pyridoxine), herbal remedies (ginger), and antihistamines (doxylamine) to more aggressive treatments including hospitalization, intravenous fluids, antiemetics (metaclopromide, promethazine, dimenhydrinate, ondansetron), steroids (methylprednisolone), and total parenteral nutrition (Wegrzyniak et al. 2012). There are case reports of positive response to mirtazapine in IV

fluids in treatment resistant cases of hyperemesis gravidarum (Guclu et al. 2005; Leib et al. 2012).

Referral for psychiatric consultation is usually made in cases of repeated hospitalization, multiple medication failures, and presence of significant psychosocial stressors. The role of the psychiatric consultant involves evaluation of the underlying psychosocial stressors, depression, anxiety, or other psychiatric conditions that could be contributing to or worsening the physical symptoms. Appropriate management of the psychiatric comorbidity with medications, weighing the risks and benefits, facilitating support from the staff, family, friends, and support network, and working collaboratively with the treating primary physician can help to alleviate the symptoms.

31.5.2 Fetal Demise

Miscarriage is the most common complication of pregnancy. About one fifth of clinically confirmed pregnancies abort spontaneously. Most women react to this unexpected loss with sorrow and grief. Studies have shown that 22–44 % of these women develop clinically significant levels of depression and anxiety (Thapar and Thapar 1992). Risk for an episode of major depressive disorder among miscarrying women in the 6 months following loss is about 10.9 % compared with 4.3 % of community women (Neugebauer et al. 1997). A majority of women have intense feelings of grief, guilt, and anxiety immediately following miscarriage, which wanes within 4–6 weeks, but some symptoms may persist for longer periods. Miscarriage may represent loss of a pregnancy, a baby, a future child, loss of motherhood, loss of self-esteem, and doubts regarding ability to reproduce. Some women feel responsible for the miscarriage, blame themselves for the loss, and feel excessive guilt and shame.

Clinicians should be aware of the psychological sequelae associated with miscarriage and should provide support and follow-up, as well as access to formal counseling when necessary. Intervention should be focused on grief counseling, support to patients and families, and providing them access to resources in the community. Screening for depression and anxiety initially and at follow-up visits using a general health questionnaire or the Edinburg Postnatal Depression Scale could help with early diagnosis of major psychiatric illness and prompt intervention (Lee et al. 1997).

31.6 Role of Consultation Liaison (CL) Psychiatrist in OB & Gyn Setting

Prevalence of mental disorders in Ob/Gyn practice range from 20 % to 38 % for any psychiatric or substance abuse disorder. Higher rates found in clinics serving low income women. Only 23 % of women diagnosed with depression are adequately treated (Kelly et al. 2001). The CL Psychiatrist can play a major role in consulting and teaching medical students, residents, nursing, and other ancillary staff in recognizing and screening for psychiatric disorders and also to provide supportive care and education to this patient population.

Consultations from the Ob & Gyn service are frequently requested for blunted/flat/odd affect in a pregnant or postpartum woman, lack of bonding with the newborn, bizarre behaviors, depression, anxiety, psychosis, suicidal and homicidal thoughts, suicide attempts, being a victim of abuse or domestic violence, substance abuse, frequent admissions for hyperemesis gravidarum, fetal demise, history of psychiatric diagnosis and psychiatric hospitalization, history of being on psychotropic medications, safety of psychiatric medications during pregnancy and postpartum, involvement of child protective service, safety of the newborn to be discharged with the mother, chronic pain issues and legal/ethical issues related to noncompliance with treatment and capacity to make decisions. Because of the intensity of psychosocial issues involved in these cases collaboration and participation in family meetings, interdisciplinary and ethics committee meetings are sometimes indicated and can help to collaborate care and provide appropriate interventions in a timely manner. This can be a valuable teaching and learning experience.

31.7 Appendix: Postnatal Depression Scale

Edinburgh Postnatal Depression Scale[1] (EPDS)

Postpartum depression is the most common complication of childbearing.[2] The 10-question Edinburgh Postnatal Depression Scale (EPDS) is a valuable and efficient way of identifying patients at risk for "perinatal" depression. The EPDS is easy to administer and has proven to be an effective screening tool.

Mothers who score above 13 are likely to be suffering from a depressive illness of varying severity. The EPDS score should not override clinical judgment. A careful clinical assessment should be carried out to confirm the diagnosis. The scale indicates how the mother has felt ***during the previous week***. In doubtful cases it may be useful to repeat the tool after 2 weeks. The scale will not detect mothers with anxiety neuroses, phobias or personality disorders.

Women with postpartum depression need not feel alone. They may find useful information on the web sites of the National Women's Health Information Center <www.4women.gov> and from groups such as Postpartum Support International <www.chss.iup.edu/postpartum> and Depression after Delivery <www.depressionafterdelivery.com>.

SCORING

QUESTIONS 1, 2, & 4 (without an *)
Are scored 0, 1, 2 or 3 with top box scored as 0 and the bottom box scored as 3.

QUESTIONS 3, 5-10 (marked with an *)
Are reverse scored, with the top box scored as a 3 and the bottom box scored as 0.

Maximum score: 30
Possible Depression: 10 or greater
Always look at item 10 (suicidal thoughts)

Instructions for using the Edinburgh Postnatal Depression Scale:

1. The mother is asked to check the response that comes closest to how she has been feeling in the previous 7 days.
2. All the items must be completed.
3. Care should be taken to avoid the possibility of the mother discussing her answers with others. (Answers come from the mother or pregnant woman.)
4. The mother should complete the scale herself, unless she has limited English or has difficulty with reading.

[1]Source: Cox, J.L., Holden, J.M., and Sagovsky, R. 1987. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry* 150:782-786.

[2]Source: K. L. Wisner, B. L. Parry, C. M. Piontek, Postpartum Depression N Engl J Med vol. 347, No 3, July 18, 2002, 194-199

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Consultation-Liaison with Children and Adolescents

32

Roshni L. Koli and Anthony P.S. Guerrero

Contents

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The field of consultation-liaison child and adolescent psychiatry is an important and vital sub-subspecialty of both child and adolescent psychiatry and psychosomatic medicine. The leading causes of morbidity and mortality among young people [e.g., accidents, homicide, malignancies, and suicide among youth aged 1–19 years (Hoyert et al. 2006)] suggest that there is much that psychiatrists can potentially contribute to general medical physicians striving to provide the best possible preventive and treatment-oriented care to children and adolescents.

This chapter is intended primarily for the benefit of consultation-liaison psychiatrists who encounter children and adolescents on a general medical service, and secondarily for the benefit of child and adolescent psychiatrists who wish to learn more about the practical aspects of working in and administering a pediatric consultation-liaison service.

32.1 General Principles Relevant to Children and Adolescents on a Consultation-Liaison Service

32.1.1 Preparing for the Pediatric Consultation-Liaison Encounter

Before seeing a pediatric patient, as with any other patient on a consultation-liaison service, it is important to discuss the case with the referring provider so as to have a clear idea of the issues to address in the consultation. Where applicable, one should get an idea of the prognosis of the general medical condition. Because children are usually not legally autonomous, it is advisable (except in unusual circumstances) to ensure that the parents have been informed about, and have agreed to, the consultation. The effectiveness of the consultation-liaison psychiatrist is limited if the initial encounter with the parents is awkward or confrontational merely because they had not been informed that a psychiatric consultation was requested. For the purposes of documenting medical necessity (and, in many cases, for billing purposes), the consultant should ensure that the referring medical team has either written an order for the consultation or documented that a consultation is necessary and therefore being requested.

In the interests of maintaining the most optimal relationships with the system of care surrounding a pediatric patient, the consultant should always remember this advice: there is no such thing as an inappropriate consultation request. Even if the identified patient were to seem fine, every consultation request suggests that someone in the system—whether a family member, health care professional, or other stakeholder—is concerned and therefore potentially able to benefit from a systems-sensitive intervention. In our institution's consultation-liaison service, we instruct our residents that even though most of us in the consultation-liaison business operate on fixed salaries, we should nevertheless all take the perspective of bright and eager new physicians who are grateful for the privilege to work in the medical center, and who are always pleased to find work that can support their practice. We find that adopting such an attitude improves the overall quality of the consultation-liaison service and, ultimately, the care the patients and families receive.

32.1.2 The Developmental Perspective

The saying "children are not miniature adults" applies just as well to psychiatry as it does to the rest of medicine. Most prominently, children and adolescents are developing physically and cognitively, so it is very important to consider the developmental level of the patient. Although a comprehensive review of child and adolescent development is beyond the scope of this chapter, we review key aspects of development, particularly as they apply to understanding of and adaptation to general medical illnesses.

One key principle is that development is a continuous process that builds on success in earlier stages. The consultation-liaison psychiatrist working in pediatric settings should therefore recognize the potential disruption that medical illnesses may have on normal child development.

Table 32.1 summarizes the key stages of development (predominantly social and cognitive) that may be of particular clinical importance in the context of general medical illnesses. Children's developmental levels are important to consider when

Table 32.1 A summary of the key stages of development

Age	Social development	Cognitive development	Clinical implications
4–6 months	Increasing awareness and recognition of people, development of attachment		Potential reactive attachment disorders, failure to thrive if inadequate attention to these issues in the context of general medical illness and separation from family
12–15 months		Object permanence	Stranger anxiety; important to consider impact of hospitalization and separation from caregivers
3–6 years	Improved separation (the age when children usually start school)	Preoperational thinking; possible "magical" or otherwise erroneous beliefs	If there is ongoing severe separation anxiety, need to consider differential possibilities, for this child's reactions and emotions are still very much connected to the family's
7–11 years	Generally good coping with separation	Concrete thinking	Relatively favorable age for elective surgery Increasing ability to be involved in explanations of illness and treatment, though need to adjust to concrete thinking
11–20 years	Challenging authority	Formal operations: morals, ethics, self-control, humanitarian/global concerns	Need to anticipate/address potential impacts on compliance May be able to give more detailed explanations of illness and implications

discussing coping with illness (and associated treatments) and death and dying. For example, 6-year-olds may have erroneous (though developmentally age-appropriate) beliefs about human physiology, believing that they can lose all of their blood from a blood draw on injection, in spite of well-meaning reassurances that the pain will not be severe. As another example, 6-year-olds might believe that justice can emanate from inanimate objects, and thus (unknown to their parents or caregivers) blame themselves for a personal illness or otherwise be afraid of reporting symptoms. Older children, in spite of more accurate perceptions about the causation of illness, may still not be able to appreciate all of the mechanisms that lead to illness. Hence, relatively straightforward explanations about the need for certain treatments (including medications) may be most appropriate.

Beyond just the cognitive understanding of illness, the emotional adjustment to illness is heavily influenced by developmental level. For example, it is likely that a preadolescent who must cope with a physical deformity may be more vulnerable to emotional difficulties, compared to a younger child, who may have a less developed body image, or an older adolescent, who may be more cognitively mature.

In order for children to optimally adjust to issues related to death and dying, they need to understand that death is irreversible, final, inevitable, and causally explained. Children facing death (whether their own or in a family member) at a developmental age earlier than that when these principles are understood are vulnerable to experiencing adjustment difficulties. For example, a child who does not realize that death is inevitable or causally explained may consider death to be a punishment for wrongdoing. Therefore, parents and caregivers often benefit from briefings about how to discuss challenging topics, such as death and illness, in a developmentally appropriate manner, and are often best able to gauge their child's cognitive development.

32.1.3 The Family and Systems Perspective

Children, both legally and developmentally, are not autonomous beings, and therefore are part of a complex system (whether explicit or not) that includes the family and other professionals involved in the child's care. While state laws may differ somewhat on the degree to which adolescents can consent to

certain aspects of medical care (e.g., related to family planning, sexually transmitted diseases treatment, and substance abuse treatment), most states require parental consent for most types of behavioral health care. Additionally, most child and adolescent psychiatrists would agree that conscientious, systems-sensitive involvement of the family in the care of a child or adolescent (or even adult), whether legally mandated or not, usually constitutes the most optimal clinical care.

Consultation-liaison psychiatrists who are not primarily child and adolescent psychiatrists often wonder what is the best way to approach child or adolescent patients and their family: should the patient be interviewed first, or should the family be interviewed first, or should the patient and family be interviewed together? In our clinical experience, we have found that there is no correct answer to this question. We recommend that (1) the patient and available family at bedside can be introduced to the context of the consultation and then asked about how they would like to proceed; (2) time may be set aside to interview the patient and parents separately (particularly if there are concerns about abuse or other sensitive issues); and (3) a solid biopsychosocial formulation with attention to family and systems perspectives should guide the titration of the amount of time spent with the patient alone, with the parents alone, and with the patient and parents together (for instance, if improving communication between the patient and parents is an important focus of the intervention).

Children and adolescents rarely request psychiatric consultations on their own. The requests for psychiatric assistance and the reporting of psychiatric symptoms are therefore often seen through the lens of the family or requesting health care providers. It is therefore of utmost importance to (1) build and maintain solid working relationships with the health care team (through rounds and other collaborative meetings with pediatric medical, nursing, social work, chaplain, and other staff); and (2) determine why the consultation is being requested, which facilitates deciding which aspects of the system warrant attention and intervention. For example, was it someone other than the child or family who requested the consultation, in which case part of an effective consultation must include directly addressing that person's concerns. Consultation-liaison psychiatry is the perfect venue to practice the biopsychosocial formulation, which can guide the intervention on multiple levels.

Many requests for consultation arise from concerns about emotional or behavioral symptoms in a parent or other family member involved in the child's care. These are entirely appropriate reasons to consult psychiatry, since the family is part of the whole system affecting the child's health. Therefore, while it is certainly appropriate to clarify the intent of the consultation with the referring provider, we recommend against "hassling" the medical team about the fundamental request for help. In such situations, it is important to document the consultations from the perspective that the child is the identified patient, even though observations about the parent or other caregiver may also be included. If a parent or other family member needs follow-up as an identified patient, then this can be part of the recommendation.

Common family-related situations and the potential role for the consultation-liaison psychiatrist are summarized in Table 32.2.

32.1.4 Psychopharmacologic Principles

The consultation-liaison psychiatrist in pediatric settings should have basic knowledge of child and adolescent psychopharmacology. Once again, children are not "miniature adults" when it comes to responses to medications. It is important to note that most psychotropic medications are not approved by the Food and Drug Administration (FDA) for children and adolescents. Also, children and adolescents generally metabolize medications differently (usually faster) than adults. Finally, the responses of children and adolescents to medication are such that the risk–benefit profile (for instance, in the case of certain antidepressant medications) may not necessarily be the same as what it is for adults.

Given these differences, it is of utmost importance for psychiatrists treating children and adolescents to engage in solid psychopharmacologic practice, which includes the following:

1. Clearly defining and monitoring target symptoms (and utilizing collateral information where appropriate)

Table 32.2 Common family-related situations and the potential role for the consultation-liaison psychiatrist

Consultation-liaison scenario	Potential tasks for the consultation-liaison psychiatrist	Possible pitfalls to be aware of
Family adjustment (e.g., depression, anxiety, "denial") to a child or adolescent's illness	Provide family-oriented support and psychoeducation. Evaluate for the need for further mental health services for family members, and provide referrals as appropriate. Educate the medical team on possible emotional reactions to a child's illness, including what may be initial "denial."	Providing long-term or in-depth care for a specific family member, without making it explicit to the family (or explicit in the medical record) that you have assumed this role, separate from your consultation/liaison role to the identified patient. Not adequately recognizing where what may initially be adaptive "denial" may interfere with optimal medical care and possibly constitute medical neglect.
History or possibility of mental illness (including substance abuse) in the parent and/or other caregiver adult	Evaluate for any acute dangerousness in the parent, or possible abuse/neglect of the child. Evaluate for the need for further mental health services for family members, and provide referrals as appropriate.	Providing long-term or in-depth care for a specific family member, without making it explicit to the family (or explicit in the medical record) that you have assumed this role, separate from your consultation/liaison role to the identified patient. Giving the appearance of having performed a forensic assessment of the adult's parenting capacity, whereas such a function might better be performed by another mental health provider (using standardized assessment tools and usually affiliated with child protective services).
Possible parental abuse/neglect, including Munchausen-by-proxy	Evaluate for the need for further mental health services for family members, and provide referrals as appropriate. Assist the team in making referrals to child protective and hospital risk management services, where indicated. Assist the team in formulating a crisis plan (e.g., with hospital security) where indicated.	Providing long-term or in-depth care the parent (see above). Giving the appearance of having performed a forensic assessment of the adult's parenting capacity, whereas such a function might better be performed by another mental health provider (using standardized assessment tools and usually affiliated with child protective services).
Angry, abusive, potentially litigious family	Listen closely to parents' concerns (including what they are most concerned about with their child's condition). Consider all possible reasons for the family's anger (including factors that may be within the medical team's control). Evaluate for the need for further mental health services for family members, and provide referrals as appropriate. Evaluate for the need for other referrals (e.g., domestic violence help). Assist the team in making referrals to child protective and hospital risk management services, where indicated. Assist the team in formulating a crisis plan (e.g., with hospital security) where indicated.	Not adequately helping the medical team to avoid unnecessary medicolegal risk via: • "Splitting" • Inappropriate documentation • Indiscreet conversation
Failure to thrive	Provide a thorough assessment that considers child variables (e.g., temperamental and other behavioral conditions), caregiver variables, and interactional variables; encourage multidisciplinary approaches. Evaluate for the need for further mental health services for the child or family members, and provide referrals as appropriate.	Failing to recognize the multifactorial nature of failure to thrive or inadequately managing general medical conditions coexisting with psychosocial conditions (see Guerrero, 2004)

2. Carefully considering the existing standards of care and treatments that are best supported by evidence, whether FDA approved or not
3. Determining and considering the patient's and family members' previous responses to medications
4. "Starting low and going slow" in the titration of the medication
5. Continuing to raise the dose until one has satisfactorily treated all symptoms, reached the recommended upper dose limit of the medication, encountered side effects that make further titration intolerable, or reached a plateau in improvement or worsening of symptoms with an increase in dose
6. Following recommended guidelines in monitoring vital signs, other physical parameters, and laboratory values
7. Recognizing medically ill patients' potential sensitivity to medication side effects

Table 32.3 summarizes the usual first-line medications and recommended doses for common diagnoses and scenarios encountered in pediatric consultation-liaison psychiatry.

Because of the likelihood that patients in pediatric consultation-liaison settings will have general medical comorbidities and may be on other medications, the reader is referred to specific chapters in this book on psychopharmacology in the context of specific general medical illnesses and to tables on drug–drug interactions.

Finally, specific to the pediatric population, we recommend the following "rules":

1. Very carefully consider the evidence for medication safety and efficacy in children and adolescents.
2. One medication is (generally) better than two medications, which is (generally) better than three medications, which is (generally) better than four medications, etc.
3. Although FDA approval is not necessarily everything, pay attention to the various categories of medications:
   (a) FDA-approved for treating children/adolescents with the condition you are prescribing the medication for (e.g., stimulants for attention-deficit hyperactivity disorder, fluoxetine for major depressive disorder)
   (b) FDA-approved for treating adults with the condition but also approved for treating children/adolescents with a different condition (e.g., valproic acid for pediatric bipolar disorder)
   (c) FDA-approved for treating adults with the condition, and with some evidence for safety/efficacy for children/adolescents with the condition (e.g., certain atypical anti psychotics for pediatric psychotic disorders)
   (d) Not FDA-approved either for the condition being treated or for children/adolescents for any indication
4. When multiple conditions amenable to psychopharmacologic treatment are possibly present, consider a rough (and potentially modifiable, depending on new evidence) hierarchy of evidence for safety and efficacy: stimulants > serotonin-selective reuptake inhibitors > mood stabilizers > antipsychotics.
5. Finally, "it's more than just medication." Particularly in pediatric settings, where a complex network of people surrounds the patient, it is important to realize that good psychopharmacology depends on various other components, arranged in the form of a pyramid (Fig. 32.1).

32.2 Specific Consultation-Liaison Scenarios That Are Common or High-Risk

32.2.1 Suicide Attempts

Suicide attempts or concerns about suicidality are likely to be among the more common concerns presented to a consultation-liaison psychiatrist on a pediatric service (Shaw et al. 2006).

First, it is important to follow whatever policies exist in the medical center regarding the management of patients who are suicidal or potentially suicidal. For many medical centers, doing so includes assigning a risk level (e.g., low, moderate, high) and implementing orders appropriate to the assigned risk level. The orders may address the following areas:

- Psychiatry consultation—optional or mandatory
- Whether or not the patient may leave the unit, and if so, under whose supervision

Table 32.3 First-line medications and recommended doses for common diagnoses and scenarios

Condition	Reasonable first-line medications	FDA approval?	Initial dose	Important precautions (should always advise patients on "rare, serious, potentially life-threatening reactions")	Labs and other physical parameters to monitor	References
Acute agitation	Antihistamines	No	Diphenhydramine: For infants over 20 pounds and older children: 5 mg/kg/day divided q6 h, up to 50 mg per dose (po, IM, IV) Hydroxyzine: 2 mg/kg/day divided q6 h, up to 25 mg per dose (po, IM)	Avoid diphenhydramine if there is delirium or if there is risk of anticholinergic toxicity		Allen et al. (2001) Green (1995) Johnson (1993)
Aggressive behavior refractory to treatment of the primary disorder, aggressive behavior in autism, and psychotic disorders	Atypical antipsychotics	Risperidone: >5k >13 for psychosis Aripiprazole >6, >13 for psychosis Olanzapine >13 for psychosis Paliperidone >12 for psychosis Quetiapine >13 for psychosis	Olanzapine: 2.5 mg daily (po, IM) Quetiapine: 12.5 mg daily (child) 12.5 mg bid (teen) (po) Risperidone: 0.25 mg daily (<20 kg) 0.5 mg daily (≥20 kg) (po)	Weight gain, metabolic syndrome, extrapyramidal symptoms	Fasting blood sugar and lipids at baseline and every 6 months, Abnormal Involuntary Movement Scale every year Consider baseline electrocardiogram for ziprasidone	Blair et al. (2005) Janssen (2006) Pappadopulos et al. (2003)
Attention-deficit hyperactivity disorder (ADHD)	Stimulants	Yes	Methylphenidate: 2.5–5 mg daily (po) Dextroamphetamine or amphetamine/dextroamphetamine: 2.5 mg daily (po)	Family history of tics	Tics on physical examination Pulse, blood pressure, height, weight every 3 months or with medication change	AACAP (2002)

(continued)

Table 32.3 (continued)

Condition	Reasonable first-line medications	FDA approval?	Initial dose	Important precautions (should always advise patients on "rare, serious, potentially life-threatening reactions")	Labs and other physical parameters to monitor	References
Bipolar disorder	Lithium or valproic acid	Lithium >12 Risperidone >10 Aripiprazole >10 Olanzapine >13 Quetiapine >10	Lithium: 30 mg/kg/day or according to Weller protocol (po) Valproic acid: 15 mg/kg/day divided bid (po)	Weight gain, metabolic syndrome, hepatic and hematologic effects	Lithium: Baseline CBC, basic metabolic profile with renal function tests, urinalysis, thyroid function, electrocardiogram Valproic acid: Baseline CBC, comprehensive metabolic profile with hepatic function tests Both medications: Medication levels (appropriate to rate of titration) and periodic follow-up labs	Weller et al. (1986) Green (1995)
Delirium with agitation or psychotic features	Haloperidol Risperidone Olanzapine	No	Oral: 0.01–0.1 mg/kg q12 h IV: 0.005–0.07 mg/kg every 30 min; once stable, use ½ of needed dose divided q12 h. Should not exceed 0.15 mg/kg/day. Risperidone 0.25 mg BID Olanzapine 2.5 mg BID	Vigilance to extrapyramidal symptoms, which children may be more at risk for	Rigidity, tremor, other abnormal involuntary movements Consider baseline and follow-up electrocardiogram to evaluate QT_c interval	Lavid and Budner (2000)
Major depressive disorder	Fluoxetine Escitalopram	Yes, >8 Escitalopram 12–17	10 mg per day (po)	Unmasking of mania, akathisia, increase in suicidal thoughts		March et al. (2004)
Obsessive-compulsive disorder	Sertraline fluvoxamine Fluoxetine	Yes, Sertraline >6 Fluvoxamine >8 Fluoxetine >7	Sertraline: 25 mg per day (po) Fluvoxamine: 25 mg qhs (po) Fluoxetine 10 mg per day (po)	Unmasking of mania, akathisia, increase in suicidal thoughts		Fleming (2003)

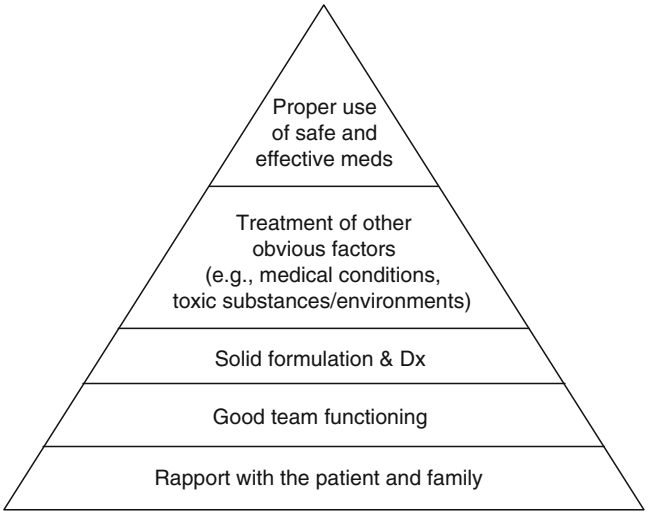


Fig. 32.1 Specific consultation-liaison scenarios that are common and/or high-risk

- Allowed clothing (e.g., hospital clothing)
- Patient/room search for dangerous articles
- Allowed visitors
- Need for 1:1 staff supervision
- Frequency of nursing checks

Next, while keeping close contact with the referring medical team and nursing staff, the consulting psychiatrist should seek opportunities for crisis intervention where appropriate. As suggested previously, the psychiatrist, particularly when working with children and adolescents, should ask, "Why did this crisis happen now, on this day, at this time of day?" and "What are all of the biologic, psychological, and social stressors that led to this crisis?" The answers to these questions often help determine what should be done to resolve the crisis. Examples of common precipitating factors are shown in Table 32.4.

Once the patient is cleared for discharge from the medical unit, a decision needs to be made on whether or not the patient should be discharged home or admitted to an inpatient psychiatric unit. This decision can often be approached by considering the preferences of the patient and the family, since the benefit from inpatient hospitalization is often dependent on the patient's and family's openness to treatment. If neither the patient nor the family wants psychiatric admission, and if the patient is not acutely dangerous (wherein state-specific involuntary commitment criteria are met), the patient should be discharged following medical stabilization, but with an appropriate follow-up plan.

Overall, in planning for disposition options, the consulting psychiatrist should match clinical need with location of service (Table 32.5). Also, in keeping with the American Academy of Child and Adolescent Psychiatry's (2001) practice guidelines, the clinician should make sure to do the following prior to discharging any patient for whom suicidal risk had been a concern:

- Ask the family about any unsupervised access to firearms or other dangerous materials in the home.
- Give the patient and family resources for after-hours emergencies.
- Ensure timely follow-up.

32.2.2 Eating Disorders

At our institution, because of the inherently higher risks involved, we instruct trainees to ensure that consultations for suicidal patients or patients with potential eating disorders are set up as soon as possible regardless of whether or not the requesting physician has described the consultation as being urgent.

Consultation-liaison psychiatrists typically encounter patients with eating disorders in the context of relatively brief medical hospitalization

Table 32.4 Common precipitating factors of suicide attempts

Biologic		Psychological		Social	
Factors	Potential interventions	Factors	Potential interventions	Factors	Potential interventions
Neuropsychiatric effects of general medical illness (including even minor viral illnesses)	Evaluation and treatment of general medical illness	Acute psychological stressor (e.g., breakup with significant other)	Crisis-oriented supportive psychotherapy	Acute interpersonal stressor (e.g., with family)	Crisis-oriented family or conjoint intervention
Neuropsychiatric effects of medications (e.g., steroids for immunologic disorders)	Adjustment of medication regimen	Limited coping ability	Discussion of coping strategies and crisis resources	Volatile relationship with family or caregiver, or family or caregiver in need of respite	Respite placement (e.g., with a relative)
Neuropsychiatric effects of substance of abuse (e.g., alcohol intoxication)	Supportive environment while intoxication clears	Loss of hope	Psychoeducation, instill hope where appropriate	Family or anyone else in the system (e.g., other professional) distressed over patient's behavior	Psychoeducation, instill hope where appropriate
Neuropsychiatric effects of starvation	Medical refeeding, improvement of nutrition			Family feeling unable to meet caregiving demands because of potential missed work	Physician's note to "prescribe" temporary caregiving role
Neuropsychiatric effects of sleep deprivation	Recovery of lost sleep				
Noncompliance with psychiatric medications	Restart medications				

Table 32.5 Location of psychiatric services

	Inpatient	Outpatient	Other community services and creative solutions
Individual psychotherapy	Yes	Yes	
Family psychotherapy	Yes	Yes	
Medication management	Yes	Yes	
Group psychotherapy	Yes	Not usually	Yes
Respite from stressful environment	Yes	No	Yes
Locked observation and management of acute dangerousness or potentially serious medical complication	Yes	No	Not usually

for general medical sequelae (e.g., cachexia, autonomic instability, or electrolyte abnormalities).

According to the *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition (American Psychiatric Association 2013), diagnostic criteria for each of the eating disorders, the key features of anorexia nervosa include a restriction of energy intake relative to requirements, leading to significantly low body weight in the context of age, sex, developmental trajectory, and physical health, intense fear of gaining weight or persistent behavior that interferes with weight gain, and body image distortion or persistent lack of recognition of the seriousness of the low body weight. There are two subtypes of anorexia nervosa, the restricting and the binging–purging type. The key features of bulimia nervosa include binging (defined as eating in a discrete period of time an amount of food that is definitely larger than what most individuals would eat in similar circumstances) with a sense of lack of control coupled with inappropriate compensatory behaviors, including purging, starvation, laxative abuse, or excessive exercise (at least once a week for 3 months) and body image concerns. The disturbances that might otherwise suggest bulimia nervosa should not occur exclusively in the context of anorexia nervosa. Because of the generally more serious complications associated with anorexia nervosa than with the other eating disorders, we believe it is particularly important to identify the diagnosis of anorexia nervosa, binge-eating–purging type, when, on the surface, the clinical presentation may suggest a diagnosis of bulimia nervosa. Binge Eating Disorder is a newly recognized distinct eating disorder that is characterized by recurrent episodes of binge eating accompanied with a lack of sense of control. The episodes may be associated with eating more rapidly than normal, eating until uncomfortably full, eating large amounts of food when not hungry, eating alone due to embarrassment, and having feelings of prominent guilt following the episode. The binge eating episodes occur at least once a week for a period of 3 months. It is differentiated from bulimia nervosa in that there is an absence of inappropriate compensatory behaviors.

To thoroughly assess both the type and severity of an eating disorder, we recommend that the consulting psychiatrist obtain a careful history and physical examination as detailed below.

32.2.2.1 History

The history should address the following issues:

- Restricting behaviors (duration, context, etc.)
- Exercise history (duration, context, etc.)
- Binging behaviors (duration, context, etc.)
- Purging behaviors (duration, context, etc.)
- Menstrual history
- Physical symptoms (light-headedness, palpitations, fatigue, syncope, bloating, constipation, swelling)
- Mood symptoms
- History of abuse/harm/threats

32.2.2.2 Physical Examination

Generally, the physical examination will have been done by the time the psychiatric consultation is requested, and it should be consulted for the following information:

- Height (in centimeters)
- Weight (in kilograms)
- Body mass index (BMI)
- Vital signs, including temperature and sitting/standing pulse and blood pressure
- Physical stigmata of eating disorders
- Swelling

In deciding whether or not the patient should be admitted and what the eventual disposition should be, it is important to carefully review existing standards of care, particularly the American Psychiatric Association Practice Guidelines (American Psychiatric Association, Work Group on Eating Disorders 2006). It is especially important to be familiar with recommended criteria for inpatient hospitalization; if the patient meets these criteria, listed below, then discharge to a lower level of care may not be feasible:

- Heart rate in the 40s
- Orthostatic blood pressure changes (>20 bpm increase in heart rate or >10–20 mmHg drop)
- Blood pressure below 80/50 mmHg
- Hypokalemia
- Hypophosphatemia
- Suicidal intent and plan
- Weight <75 % of ideal body weight (for children and adolescents: acute weight decline with food refusal even if not <75 % below healthy body weight)
- Very poor to poor treatment compliance/motivation: preoccupied with ego-syntonic thoughts, cooperative only in highly structured environment
- Presence of any existing psychiatric disorder that would require hospitalization
- Needing supervision during and after all meals or needing nasogastric/special feeding
- Complete role impairment: inability to eat by oneself and gain weight; structure required to prevent patient from compulsive exercising
- Needing supervision during and after all meals and in bathrooms
- Severe family conflict, problems, or absence, thus precluding the provision of structured treatment at home, or patient lives alone without adequate support system
- Lives too distantly from treatment setting to make intensive treatment feasible

Because "ideal weight" is determined not only by height but also by stage of physical development, we recommend the following steps in determining the ideal weight for the patient:

1. Determine what the ideal (approximately 50th percentile) BMI should be for the patient's age, by referring to appropriate growth charts from the Centers for Disease Control and Prevention (http://www.cdc.gov/nchs/data/nhanes/growthcharts/set2clinical/cj41l074.pdf)
2. Determine, for the patient's height, what weight should correspond to the ideal BMI, by referring to a BMI normogram or table (http://www.cdc.gov/nccdphp/dnpa/bmi/00binaries/bmi-checkbook.pdf)

Slow, steady weight gain (for example, 2 lb per week in inpatients and 1 lb per week in outpatients) is the goal for medical treatment of an eating disorder—typically anorexia nervosa—with cachexia and other physiologic complications. Weight gain, achieved through medical refeeding, is important to address not only the physiologic complications of the eating disorder but also the behavioral and emotional symptoms, which often improve dramatically with restoration of nutrition. During medical hospitalization for an eating disorder, it is extremely important to monitor for signs and symptoms of refeeding syndrome, which may include bloating and abdominal distress, edema, and, in severe cases, hypophosphatemia and cardiac failure. We recommend that the clinician perform a daily review of systems in order to assess these symptoms.

It is also very important to tailor psychotherapeutic interventions to the immediate goal of restoring normal physiologic functioning. While the clinician should convey significant support for the patient and acknowledge how emotionally challenging the "refeeding" stage is, it is important not to view apparently in-depth psychological revelation and discussion (on the patient's part) as an adequate substitute for the needed goal of weight gain. In working with the patient, the family, and other health care providers, the clinician needs to be aware that patients may not like the requirement to gain weight and may therefore (with the support of their families and possibly other health care providers) "doctor shop."

Because of the significant risks involved with both the eating disorder itself as well as its medical treatment, we recommend that consultation-liaison teams consider the use of pathways of care and standard orders for the management of eating disorders—typically anorexia nervosa with cachexia. The standard orders used at our institution are as follows:

- Dietary consult
- Electrocardiogram with rhythm strip
- Urinalysis
- Blood: erythrocyte sedimentation rate, thyroid-stimulating hormone with reflex, chemistry panel with calcium, phosphorus, and magnesium (these are not necessarily part of the panels typically ordered)
- Cardiorespiratory monitor
- Vital signs with orthostatic blood pressures
- Daily weights (after first void, dressed in hospital gown)
- Strict assessment of input/output
- Chemistries every other day or as appropriate (to evaluate for metabolic complications of refeeding syndrome, such as hypophosphatemia)
- No outside food
- Limited fluids
- Modest starting diet
- Postmeal restriction from using the bathroom
- Limited activity

32.2.3 Possible Somatoform Disorder to Explain General Medical Symptoms

It is not unusual for children and adolescents to have somatic symptoms associated with emotional distress. It is likewise fairly common for the pediatric team to request a consultation to address the issue of differential diagnosis of a somatoform disorder (Shaw et al. 2006). When the psychiatric team is consulted, the medical team is not infrequently frustrated by a symptom or sign that does not seem to have a clear organic etiology, and the team wants an additional blessing from psychiatry to make sure that an organic etiology has not been missed.

Koranyi (1979) described how a substantial number of patients in a psychiatric setting may have serious general medical illness that is either undiagnosed or labeled as psychosomatic. Of interest, even Freud (1901) described how a 14-year-old girl, who reportedly "fell ill of an unmistakable hysteria, which did in fact clear up quickly and radically under [his] care," died 2 months later "of sarcoma of the abdominal glands." He admitted that he "had perhaps overlooked the first signs of the insidious and incurable disease."

We believe that the consultation-liaison psychiatrist has a potentially important role in helping the general medical team cautiously approach the challenge presented by patients who present with possible psychosomatic symptoms in a pediatric hospital setting. To appropriately rule in or rule out psychiatric causes for general medical symptoms, we suggest that the consultation-liaison psychiatrist go through the following steps (adapted from Guerrero 2003):

(A) Adequately consider differential diagnoses:
   1. Correctly identify the chief complaint (without being inappropriately biased toward psychiatric etiologies at the exclusion of general medical etiologies).
   2. Identify mechanisms behind the chief complaint to establish an initial list of differential diagnoses (again, to avoid being narrowly focused on only psychiatric etiologies).
   3. Carefully elicit and examine other coexisting signs and symptoms to test the hypotheses.
   4. Ask "Why now?" to evaluate further which hypotheses best explain why the patient is having the symptoms *at this time.*

(B) Specifically consider life-threatening conditions:
   5. Observe the vital signs and specifically consider the most life-threatening explanations (e.g., unexplained hypertension and bradycardia, possibly associated with a space-occupying brain lesion; unexplained tachycardia, possibly associated with substance or medication toxicity).

(C) Consider child development and specific pediatric conditions:
   6. Apply knowledge of child development to the interpretation of presenting symptoms (e.g., preverbal children may manifest pain as unusual behavioral symptoms such as head-banging).
   7. Consider specific pediatric illnesses in the differential diagnosis (e.g., genetic syndromes associated with particular behavioral phenotypes; infections that are statistically probable in children and adolescents such as Epstein-Barr virus infections for depression, streptococcal infections for obsessive-compulsive spectrum disorders).

(D) Advocate for optimal general medical care:
   8. Consider the rarity of certain psychiatric conditions relative to the general medical conditions being ruled out (e.g., many of the specific somatoform disorders are, from a statistical standpoint, relatively rare compared to other general medical conditions).
   9. Consider other general medical conditions that may be comorbid or underrecognized in the context of a psychiatric condition or challenging psychosocial circumstance (e.g., sexually transmitted diseases in homeless or runaway youth).
   10. Use liaison skills in managing bias and countertransference and working with the general medical team.

(E) Effectively communicate and listen:
   11. Consider asking families what they fear may happen to their child to guide supportive explanation.
   12. Listen to other people's suggestions about diagnostic possibilities.

Given the complex nature of many of these cases, we recommend that the consulting psychiatrist follow these patients closely and work closely with the medical team. Even if it is obvious that a patient does not need psychiatric hospitalization, it is not sufficient to see the patient only once and then recommend "outpatient follow-up" without addressing the issue of the unexplained somatic symptom. Finally, in determining whether or not a patient with a possible somatoform disorder can be safely discharged, we recommend performing a final checklist:

1. Have general medical conditions been adequately ruled out?
2. Have patient/family concerns about what they are most worried is causing these symptoms been addressed?
3. Have threats to the patient's safety, including abuse/neglect, been adequately ruled out through individual and family interview?
4. Has the patient and family been "prescribed" a face-saving expected course of recovery?
5. Is there a follow-up plan?

32.2.4 Chronic or Severe Medical Illness

Often, consultations are requested for pediatric patients with chronic or severe medical illnesses, including congenital heart disease, cystic fibrosis, asthma, chronic renal failure, immunodeficiency, diabetes mellitus, cancer, seizure disorders, and various rheumatologic illnesses. We refer the reader to other chapters in this textbook for discussions of the specific illnesses. However, we believe that, in consults on pediatric patients with these conditions, it is often helpful to keep a checklist of the possible individual, family, and staff issues that may need to be addressed (while still being mindful of the specific consultation question and context of the consultation request). The checklist that we use at our institution is shown in Table 32.6.

32.2.4.1 Delirium

Delirium is a well-recognized phenomenon in the critically ill adult population. However, it has only recently been studied and characterized in the pediatric population. It has been reported in children and adolescents with CNS infections (i.e., encephalitis, lupus cerebritis), metabolic abnormalities, seizures, cancer, organ failure, critical care settings, and surgical settings. As in adults, delirium is associated with longer hospital stays and higher rates of morbidity and mortality in children and adolescents (Turkel and Tavare 2003).

Table 32.6 Checklist of the possible individual, family, and staff issues

Discussion with referring physicians:

Biologic/medical issues:

- Specific psychiatric symptoms (depression, anxiety, delirium)?
- Prognosis of medical illness, and what is child/family's understanding?
- Potential end-of-life issues?
- Potential decisional capacity concerns?
- Possibility of brain/neurologic involvement with this illness; any neuroimaging or other neurodiagnostic tests done?
- Medications (including those with neurobehavioral effects, e.g., steroids)?
- Medication and other compliance issues and real/potential barriers?
- Medical symptoms that likely impact on emotions (e.g., pain, nausea, pruritus)?
- Concern about physical symptoms not fully explained by general medical causes?
- Possibility of transplant or other major procedure in the near future?

Psychosocial issues:

- What is known about family structure and coping?

Discussion with nursing staff:

- Specific psychiatric symptoms (see above)?
- Medical symptoms that likely impact upon emotions (see above)?
- Staff responses, including possible splitting, burnout, etc.?

Discussion with family:

- Specific psychiatric symptoms (see above)?
- Medical symptoms that likely impact on emotions (e.g., pain, nausea, pruritus)?
- Perception of underaddressed medical conditions and symptoms?
- Past psychiatric and developmental history, including history of learning difficulties?
- Family members' coping? (consider administering rating forms)

Discussion with patient:

- Safety concerns?
- Screening cognitive exam, assessment of decisional capacity if applicable
- Consider administering rating forms for specific symptoms

Potential interventions:

Biologic/medical	Individual	Family	Team
• Labs/neurodiagnostics • Medications (PRN, palliative, or other medications) • Change in medications • Frequent reorientation for confusion	• Relaxation training • Coping with procedural pain and other discomfort (guided imagery, hypnosis) • Education regarding healthy and unhealthy coping	• Discussing illness with child and siblings • Education regarding healthy and unhealthy coping • Problem-solving around barriers to compliance	• Education regarding healthy and unhealthy coping • Management of countertransference, splitting; risk management • Liaison forums • Family conferences • Who is following the patient, mechanisms for follow-up and contact

Potential other consults and resources:

Mental health related	In-hospital	Other community
• Psychiatry (medications, general medical considerations) • Psychology (testing, specialized behavioral interventions) • Specific evaluation (e.g., pretransplant) • DOH/DOE services • Referrals for family members	• Social work • Chaplain • Rehabilitation (occupational therapy, physical therapy, SLT) • Risk management	• Condition-specific organizations • Hospice

Mortality rates of up to 20 % have been reported in specific pediatric subgroups such as transplantation and autoimmune diseases (Turkel and Tavare 2003).

Psychiatric consultants are often asked to assess acute mental status changes in the pediatric hospital population. The clinical presentation of delirium in the pediatric population is similar to that of adults. The DSM-V describes delirium as a disturbance in awareness, attention, and cognition that develops acutely and tends to fluctuate in severity throughout the day. Delirium usually has an acute onset (usually hours to days) and represents a significant change from baseline functioning. There are two main subtypes: hyperactive type which presents as psychomotor agitation often accompanied by emotional lability, confusion, and refusal to cooperate with medical care. The hypoactive type is more often missed as it presents with psychomotor retardation and can be accompanied by lethargy and may be accompanied by tearfulness and confusion. Individuals are usually cooperative with care. Hypoactive delirium can sometimes be mistaken for depression.

The following principles can be helpful in guiding the consultant in management of delirium:

Look for the underlying medical etiology. The mnemonic "I WATCH DEATH" can be helpful in discerning the various medical etiologies of delirium.

Use medications judiciously. Often the psychiatric consultant is called to help manage the agitation associated with hyperactive delirium. In these settings, while psychotropic medications can be helpful, it is just as important to identify the other medications that may be exacerbating delirium, such as sedatives/hypnotics (benzodiazepines), pain medications, and anticholinergic medications.

Non-pharmacological interventions can be very helpful. At our institution, we recommend memory boards (with date, name, brief one-line description of why a child is in the hospital) to help with orientation, bringing in familiar things from home (blankets, pictures, etc.), trying to keep bedtime routines (for younger children), if possible.

Rating Scales

Rating scales are useful both in the evaluation of delirium and to assess treatment response. While most scales have been designed for the adult population and adapted for use in pediatrics, there are a few scales that have been created specifically for use in the pediatric population.

The Pediatric Confusion Assessment Method for the ICU (pCAM-ICU) was developed by the Vanderbilt Pediatric Delirium Group and has been validated to assess delirium in children greater than 5 years of age. It uses a two-step approach to diagnose delirium: (1) assessment of level of consciousness (using a standardized sedation scale), (2) assessment of content of consciousness (using the pCAM-ICU). It takes into account the inherent challenges of developmental expressions of cognition by creating an Attention Screening Examination (ASE) that uses pictures of non-threatening figures that are easily recognized by children. One of the advantages of this particular scale is that is able to be given at the bedside to ventilated and non-ventilated critically ill pediatric patients by non-psychiatric trained caregivers.

The Delirium Rating Scale (DRS-98) is a valid and reliable tool created to assess delirium in a critically ill adult population and has been found to be applicable to the pediatric population as well (Trzepacz et al. 1999). The DRS-98 is a clinician-rated scale divided into a 13-item severity section and a 3-item diagnostic section. The sum constitutes the total score and a score of 10 or greater identifies delirium. The severity scale can be repeated to further measure a patient's clinical status within an episode of delirium.

MoCA

The Montreal Cognitive Assessment (MoCA) was created in 1996 and validated for assessment of mild cognitive impairment in adults. It can be useful for older adolescents, as it assesses a variety of cognitive domains, including memory, visuospatial abilities, attention, concentration, and working memory. It is a one-page 30-point test and can be administered in approximately 10 min. It has three variations and is available free of charge in numerous languages.

Management of Delirium

It is important to note that delirium may often be under-recognized in the pediatric setting and thus psychoeducation regarding the identification of delirium and appropriate steps to take to help with appropriate management is essential. Once the psychiatric consultant is called to help with management of delirium, the first step will be obtaining a thorough medical and psychiatric history as well as a comprehensive assessment of mental and cognitive status.

Environmental interventions can be very helpful in the management of delirium. Patients with delirium should be placed close to the nurses' station with a familiar staff member or family member in the room at all times. If the delirium is severe, one should consider a 1:1 sitter at all times to ensure the safety of the patient. Additionally, every effort should be made to help to restore the sleep–wake cycle as quickly as possible. Interventions in this regard can be keeping lights on and curtains open during daytime hours and lights off during nighttime hours. One may also consider the use of melatonin to help with further regulating the sleep–wake cycle. If possible, it is helpful to reduce the activity at nighttime and consolidating medical procedures, including the taking of vital signs. Further, one should consider having a clock or memory board with the date, hospital, nurse, and reason for hospitalization present in the room. Familiar objects and pictures from home can also help to make the hospital environment more comfortable for patients that have delirium.

Pharmacological Interventions

While obtaining a thorough medical history, the psychiatric consultant should also do a thorough review of medications to help identify particular medications that may be exacerbating delirium. Several medications used commonly in the critical care setting have the potential of exacerbating delirium, with some of the most common being benzodiazepines, anticholinergics, opiates, and corticosteroids. While some of these medications may be essential for the treatment of the underlying illness or to help manage specific symptoms, such as pain, or seizures, every effort should be made to reduce the frequency and dosage of these classes of medications, so as to reduce any potential adverse effects on the mental status. Benzodiazepines in particular may have different effects in children and adolescents than in adults. They may cause a paradoxical reaction, which can look like an increase in agitation and emotional lability or may also cause further disinhibition.

Antipsychotic Medications

While there are currently no FDA approved medications for delirium in the adult or pediatric population, literature does indicate that antipsychotic medication can be helpful in reducing the symptoms of agitation and confusion associated with delirium as well as reducing the psychotic symptoms that are often present with delirium (Martini 2005). In pediatric delirium, similar to adult delirium, haloperidol has been one of the most commonly used agents. It has the advantage of being available in oral, intravenous, and intramuscular formulations. However, there are certain adverse side effects that one must be cautious with, including the risk of prolongation of the QTc interval with IV formulations of haloperidol, extrapyramidal symptoms, dystonic reactions. These side effects may be more common in younger children.

Given the potential for adverse side effects with typical antipsychotics and the improved tolerability of atypical antipsychotics, one may also consider the use of atypical antipsychotics in pediatric delirium. Until recently, there was little available literature looking at the use of atypical antipsychotics in the management of delirium in children and adolescents. However, over the past 5–10 years, there have been several studies looking at the utility of atypical antipsychotics in the management of pediatric delirium. Olanzapine, risperidone, and quetiapine have all been shown to be effective in managing symptoms of delirium in the pediatric population without significant adverse side effects (Turkel 2012). While olanzapine and risperidone are available in orally disintegrating tablets, there are no atypical anitpsychotics that are available in parenteral formulations, which may, at times, limit their use in severely critically ill patients.

At our institution, we use atypical antipsychotics, including olanzapine, risperidone, and quetiapine, as first-line medications for the management of pediatric delirium.

Clinical characteristics of delirium
Fluctuating disturbance in attention and awareness
Disorientation
Impaired memory
Acute onset of change in mental status
Sleep–wake cycle disturbance
Perceptual disturbances (may have visual hallucinations, delusions)
Arousal disturbance (hyperactive, hypoactive, or mixed)
EEG findings (generalized slowing)

Differential diagnosis of pediatric delirium "I WATCH DEATH"	
*I*nfection	Encephalitis, sepsis
*W*ithdrawal	Methamphetamine, Alcohol, Benzodiazepines
*A*cute Metabolic	DKA, renal failure, electrolyte abnormalities
*T*rauma	Head injury, burns
*C*NS Pathology	Intracranial hemorrhage, abscess, tumors
*H*ypoxia	Cardiac failure, pulmonary failure, carbon Monoxide poisoning
*D*eficiencies	Vitamin B12, folate, niacin, thiamine
*E*ndocrinopathies	Hyperglycemia/hypoglycemia, hyperparathyroidism
*A*cute Vascular	Stroke, hypertensive encephalopathy
*T*oxins/Drugs	Medications, pesticides, illicit drugs
*H*eavy Metals	Lead, mercury

Adapted from Clinical Manual of Pediatric Psychosomatic Medicine (Shaw 2006).

32.3 Other Issues in Pediatric Consultation-Liaison Psychiatry

32.3.1 Outpatient Child and Adolescent Consultation-Liaison Psychiatry

A discussion of the entire specialty of child and adolescent psychiatry is beyond the scope of this handbook, but it is important for administrators of consultation-liaison psychiatric services to recognize their potential role in the provision of quality preventive and treatment-focused behavioral health care in primary care settings, including pediatric and family practice clinics.

Table 32.7 lists the suggested screening areas where consultation-liaison psychiatrists may be a helpful resource for primary care clinicians who primarily practice in outpatient settings.

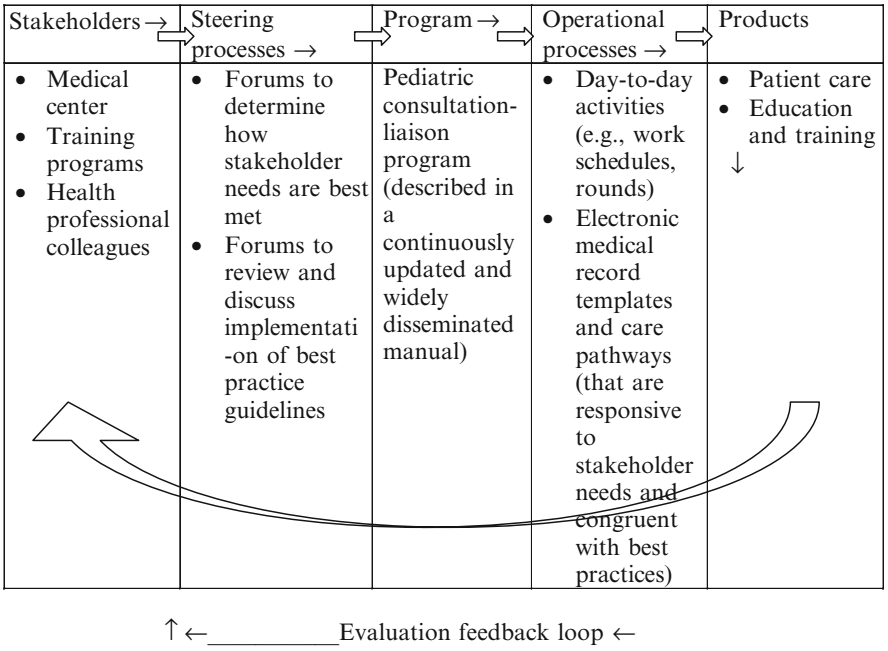
When acting as a resource for outpatient primary care providers for children and adolescents and their parents, the psychiatrist should be mindful of the major causes of morbidity and mortality in children and adolescents, including accidents (often related to childhood behavioral problems or psychosocial adversities in the family), homicide, and suicide (Guerrero et al. 2003). We recommend that consultation-liaison psychiatrists should be prepared to take the following steps in preventing violence-related causes of morbidity and mortality:

- Early identification and intervention for children, adolescents, and families at risk for or involved in violence

Table 32.7 Screening tools to address specific conditions

Age group	Condition	Potential screening tools	References
Newborn to age 1 year	Maternal postpartum depression	Edinburgh Postnatal Depression Scale (EPDS)	Cox et al. (1987)
Toddler, e.g., 12–18 months	Autism and the pervasive developmental disorders	Checklist for Autism in Toddlers (CHAT)	Baron-Cohen et al. (2000)
Preschool to adolescence	Internalizing, externalizing, and attentional conditions	Pediatric Symptom Checklist (PSC)	Borowsky et al. (2003)

Table 32.8 A process for continuous improvement of the quality and value of the consultation-liaison service



- Facilitation of families' access to mental health care services
- Reduction of youth's unsupervised access to firearms
- Education of parents on alternatives to corporal punishment for behavior management (American Academy of Pediatrics 1999; Commission for the Prevention of Youth Violence 2000)

32.4 Educational and Administrative Aspects

Pediatric consultation-liaison may often not be financially viable based on direct revenue. According to Shaw et al. (2006), collection rates for professional billing for pediatric consultation-liaison services appear to average around 30 %. Nevertheless, pediatric consultation-liaison services can prove their significant value to the sponsoring medical center (which often provides a substantial "coverage contract" to the service) by enhancing the overall quality and efficiency of care that children and adolescents receive and by contributing to the education and training of pediatric and other health care providers. We believe that it is of utmost importance to maintain collaborative attitudes with, and financial and administrative accountability to, all stakeholders in a pediatric consultation-liaison service. Given Campo et al.'s (2000) finding that financial viability of pediatric consultation-liaison services is correlated with integration of the psychiatry program within the medical center and adequate fiscal information being provided to the psychiatry chair, we recommend regular meetings with hospital administration and the establishment of a process that allows for financial and revenue cycle issues to be regularly reviewed. We also recommend a process that allows for continuous improvement of the quality and value of the consultation-liaison service (Table 32.8).

32.5 Summary

A checklist before doing a pediatric consultation should include the following:

- Understand the context, including the general medical condition and its prognosis
- Ensure parent/guardian consent, and documentation of consultation request

The differences between pediatric and adult consultation/liaison encounters are as follows:

- The psychiatrist needs to more prominently consider the developmental level of the patient, in assessing the psychological impact of the general medical condition and its treatment.
- The psychiatrist needs to more prominently consider the family context in assessment and management, but being careful not to assume inappropriate or inadvertent roles (e.g., forensic investigator, psychiatrist providing individual treatment for a family member).
- The psychiatrist needs to appreciate the differences in responses to medications, and to become familiar with commonly used medications in pediatric consultation-liaison psychiatry.

Tips for managing suicidal or potentially suicidal patients:

- Follow hospital policies (e.g., risk assessments, standard orders).
- Ask "why now?" and use the biopsychosocial approach to crisis intervention and determination of disposition.
- Use checklists (e.g., no unsupervised access to firearms) to optimize the safety of patients being discharged.

Tips for managing *eating disorders*:

- Utilize existing practice guidelines to determine optimal site of treatment.
- Medical refeeding and slow, steady weight gain is the cornerstone of treatment in anorexia nervosa.
- Consider using standard orders or pathways of care to implement practice guidelines.

Tips for managing possible *somatoform disorders*:

- Help the team to thoroughly and conscientiously consider general medical etiologies or comorbidities.
- Help the parents to express what they are most concerned about.
- Assess the risk situations (e.g., abuse/neglect).

Tips for consultations on patients with *chronic or severe medical illnesses*:

Ensure a comprehensive approach that anticipates potential areas of intervention to benefit the patient, family, and staff.

Overall tips:

- Remember the leading causes of morbidity and mortality in children and adolescents (including accidents, homicide, suicide) and the prevalence of mental health conditions in children and adolescents.
- Remember our duty and our potential value to our stakeholders

32.6 An Illustrative Case: Eating Disorder

The patient is a 17-year-old girl, a cosmopolitan 11th grader, who was initially brought to the outpatient clinic by her mother, who was concerned about "depression." She was subsequently admitted to the inpatient pediatric unit, and a psychiatric consultation is requested for a likely eating disorder (labeled as "anorexia/bulimia.")

She reports that, ever since a breakup 1 year ago, her life has been "headed downhill." For the past 3 or 4 months, she has experienced depression, anhedonia, difficulty concentrating, and intermittent suicidal thoughts. Previously a straight-A student, she has experienced a marked decline in grades this past semester, which is nearly complete.

There is no history of any symptoms suggestive of mania or hypomania. In terms of any substance abuse, she endorses tasting alcohol at a party "once or twice," trying marijuana once, and (because she learned that it could help her to lose weight) "focusing pills," supplied by a friend. "But it was only a few times… I know better than to get hooked on pills."

Upon specific questioning, the patient reluctantly discloses that, for the past 5 or 6 months, she has been skipping meals, using her fingers to induce vomiting, and running several miles per day. She also has been consuming large amounts of water and caffeinated beverages. She says that, for her body type, she thinks her ideal weight should be around 90 lb. She has lost 25 lb since 5 or 6 months ago. She admits to thinking

constantly about her weight, and to being overwhelmed with feelings of needing to lose more weight to avoid becoming fat.

Around 1½ years ago, for a few months after quitting cross-country running, she would consume large quantities of food in a short period of time and then induce vomiting by using her fingers. She denies any history of consuming emetics, laxatives, or diuretics. "But I researched them at one point." She has been amenorrheic since 3 months ago, and has not been sexually active since her breakup.

Past medical history is negative for any significant illnesses. She is on no chronic medications and has no allergies.

32.6.1 Family History

The patient has two older brothers, ages 21 and 25. Her mother is 50 years old and in good health, and her father is 57 years old, with a history of hypertension. Family history is also significant for lupus in a maternal aunt, hypothyroidism in the paternal mother, and leukemia in her brother's infant daughter.

32.6.2 Social History

Patient had previously been involved in numerous extracurricular activities, and she had been popular among her friends. Also, her mother reports a good mother–daughter relationship throughout most of her daughter's life. However, recently, the patient has been more isolative. The patient denies any past history of physical or sexual abuse.

32.6.3 Examination

A review of systems is significant for fatigue, cold sensitivity, and episodes of light-headedness. The patient also tends to be constipated.

On examination, her vital signs are as follows: temperature 96.8 °F, sitting pulse 44 per minute, sitting blood pressure 84/54, weight 92 lb, and height 5 ft 5 in. She is dressed in thick clothing and makes fair eye contact. Her mood is depressed, and her affect is congruent and restricted. Her thoughts are linear, without delusions. There are no auditory or visual hallucinations. She denies any current suicidal or homicidal ideations. She is alert and oriented. Attention and concentration is intact. Registration is intact; however, she needs prompting to recall one of three objects after 5 min. Insight is questionable regarding her ability to connect her eating behaviors to her medical and psychological symptoms.

32.6.4 Questions

1. Calculate body mass index (BMI) (answer: 41.8 kg/1.65 m^2 yields a BMI of 15.4). Calculate 50th percentile BMI for age (answer: 21). Calculate weight for height, corresponding to 50th percentile BMI for age (answer: 126 lb). Calculate percentage of ideal body weight (answer: 92/126 = 73 %).
2. Present a biopsychosocial formulation, followed by a five-axis differential diagnosis (Table 32.9).
3. Work with the medical team to ensure appropriate management orders:

Table 32.9 A biopsychosocial formulation for eating disorders

	Biologic	Psychological	Social
Precipitating	Physiologic effects of starvation on the brain	Recent breakup	
Predisposing		Distorted body image	
Perpetuating			Isolation from family and friends

Axis I: Anorexia nervosa, binging–purging type.
Axis III: Cachexia, hypothermia, symptomatic bradycardia, and hypotension.

Admit:	To medical team care
Diagnosis:	Cachexia, hypothermia, symptomatic bradycardia with hypotension
Condition:	Fair
Vital signs:	Per routine, with orthostatic blood pressures once per shift; cardiorespiratory (CR) monitor; daily weights (after first void, hospital gown)
Allergies:	None
Activity:	Bedrest
Nursing:	Postmeal observation and restriction from using the bathroom
Diet:	Dietary consultation ASAP
	No outside food
	Begin 1,500-calorie diet
	No fluids outside of agreed-upon diet
I/O:	Strict monitoring
Meds:	
Labs:	CBC with differential
	Comprehensive metabolic profile with phosphorus and magnesium
	Erythrocyte sedimentation rate
	Thyroid-stimulating hormone with reflex to free thyroxine (T_4)
	Urinalysis
	Electrocardiogram with rhythm strip
	Daily basic metabolic profile with calcium, phosphorus, and magnesium
Consults:	Psychiatry

The patient is admitted to the medical unit for further management and refeeding. You see her daily. You provide individual and family psychoeducation, and work closely with the general medical team. With adequate stabilization of her physiological parameters and weight gain according to targeted goals, she is ready for discharge 1½ weeks later. You plan for close outpatient follow-up.

32.6.5 Further Questions

1. During the inpatient hospitalization, what complications of refeeding would you make sure to assess for on a frequent basis? (Answer: bloating, edema, hypophosphatemia.)
2. During the inpatient hospitalization, what would be the appropriate content of individual and family psychotherapy? (Answer: psychoeducation and building therapeutic alliance around primary importance of medical stabilization and weight gain.)
3. What would be the targeted rate of weight gain in an inpatient setting? (Answer: approximately 2 lb per week.)
4. How would you assess readiness for discharge? (Answer: refer to APA practice guidelines.)

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The Geriatric Patient

33

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33.1 Vignette

An 85-year-old woman, with a history of moderate dementia (with an MMSE of eighteen 6 months ago), hypertension, hyperlipidemia, coronary artery disease was admitted to the hospital because of altered mental status. History reveals worsening agitation after a fall about a week ago. Her current medications include oxybutynin for urinary incontinence, cimetidine for acid reflux, and citalopram 40 mg daily for depression, in addition to her antihypertensive and cardiovascular medications. Because she was agitated she had also been started on haloperidol (5 mg total daily) and 1 mg lorazepam every 6 h as needed a week ago with no improvement in behavior, but with further decrease in her eating and self-care. On physical exam she was noted to have cogwheeling, restlessness, and bruises on her arms and her left hip area. When palpating and performing range of motion of her left lower extremity, it was noted that she pulled back and got more agitated. Mini-Mental Status Exam was 12/30 with difficulties with orientation, spelling "WORLD" backwards, and recall. During the interview she stated that she wants to go home and dislikes medications. Staff reported

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that she has been refusing some of her medications. Labs were performed which indicated sodium 120, urinalysis positive for leukocyte esterase and nitrites, an EKG with QTc 490, and X-ray indicating ankle fracture. The patient was started on ciprofloxacin for urinary tract infection. A psychiatric consultation is requested for management of altered mental status and agitation, as well as for assessment of capacity to refuse treatment.

33.2 Introduction

The elderly or geriatric population—comprising people over the age of 65 years—is rapidly growing in the USA and throughout the world. According to the United Nations World Prospects (2012), the global population of people over age 60 years in 2013 was estimated to be 841 million or 12 % of the population. They are expected to reach two billion, or 21 % of the population, by 2050. In 2010, the US Census Bureau estimated that the elderly population over age 65 years was 40.3 million, or 13 % of the total US population. Of this group, those over the age of 90 nearly tripled in the past 30 years to 1.9 million.

This growing elderly population correlates with the increasing utilization of health services by the elderly. The 2006 National Hospital Discharge Survey conducted by the US Department of Health and Human Services (DeFrances et al. 2006) found that 38 % of inpatient beds were occupied by patients ages 65 and older compared to 20 % in 1970. A prospective study (Fulop et al. 1998) found that 44.5 % of geriatric inpatients met criteria for a psychiatric comorbidity. Studies have shown that treatment of these psychiatric comorbidities can actually impact health care spending because of the correlation between psychiatric comorbidities and length of stay in the hospital (Fulop et al. 1998). Levitan and Kornfeld (1981) also found that elderly patients receiving psychiatric consultations after being admitted for hip fractures spent 12 fewer days in the hospital and were also more likely to be discharged home rather than to a nursing home.

Table 33.1 Most frequently occurring conditions of the elderly in 2009–2011 (US Department of Health and Human Services, Administration on Aging 2012)

Arthritis (51 %)
Cardiac disease (31 %)
Cancer (24 %)
Diagnosed diabetes (20 %)
Hypertension (72 %)

Table 33.2 Common diagnoses seen in geriatric inpatients by the consultation-liaison service: (Ruskin 1985; Levitte and Thornby 1989; Grossberg et al. 1990; Scott et al. 1988)

Dementia[a]
Delirium[a]
Mood disorders (particularly depression[a])
Psychosis
Personality disorder
Adjustment disorder
Anxiety disorder

[a]Indicates the most common

33.3 Principles of Geriatric Assessment and Treatment

The geriatric population on the Consultation-Liaison service is a distinct and challenging group because high rates of medical comorbidity and biological changes associated with aging can impact treatment. Most elderly patients have at least one or more chronic medical conditions (Table 33.1). In addition, the psychiatric problems and stressors elderly patients deal with are vastly different from their younger counterparts (Table 33.2) with higher rates of dementia, delirium, and depression (Downing et al. 2013). They are also unique because of issues related to death, dying, and palliative care.

Many of the unique developmental issues facing geriatric patients can be understood from a biopsychosocial perspective (Table 33.3, Ahmed and Takeshita 1997). From a biological perspective, understanding normal age-related changes is important to distinguish them from pathological ones. For example, there are age-related cognitive changes such as reduced mental processing speed, perceptual-motor tasks, memory, and the performance of novel tasks. Vocabulary, compre-

Table 33.3 Issues facing the geriatric population

Biological aging issues	Psychological aging issues	Sociological aging issues
Age-related changes of the body and organ systems.	Changing roles and relationships: family, friends, society, occupational.	Societal and cultural attitudes towards aging.
Changes in the brain: Gross structural changes. Loss of neurons which can affect mood, behavior, and cognition. Decreased adaptive capacity. Neurotransmitter and receptor changes.	Issues and fears of dependency. Coping with physical and cognitive limitations.	Changes in socioeconomic status, marital status, occupation.
Sensory changes (vision, hearing).	Coping with loss and end of life issues. Preparing for death.	Changing and decreasing sources of support. Increasing emphasis on the extended family.
Higher rates of medical comorbidities.	Erik Erikson's developmental stage of Ego Integrity versus Despair.	Intergenerational issues including role reversals.
Changes in pharmacokinetics and pharmacodynamics. Brain having increased vulnerability to side effects of medications.		Institutionalization.

hension, knowledge, reasoning, and judgment, however, should remain the same (Albert and Moss 1988; Christensen 2001). Also, understanding the concept of young-old (65–75) versus old-old (85+) helps emphasize that elderly patients cannot all be categorized as one homogenous group. The old-old tend to have more comorbidities, functional problems, and poor prognostic conditions. From a psychological and social perspective, there are changes in self-concept and roles, particularly increasing dependency issues. Age-related biopsychosocial issues make elderly patients more vulnerable to psychiatric disorders.

The assessment of the geriatric patient should also pay attention to their medical co-morbidities as well as their level of cognition and functioning. Geriatric patients more likely have medical illnesses that coexist with or cause psychiatric symptoms. Therefore understanding patterns of onset, associated medical/psychiatric symptoms, recent changes to health status, and medications can help differentiate medical versus psychiatric causes. The presentation of psychiatric disorders may also be different than that seen in the younger population. They often present with more somatic and cognitive symptoms and may report psychiatric symptoms less often (Jeste et al. 2005).

Compared to their younger counterparts, there also may be barriers to communication due to their sensory loss (vision, hearing), slower processing time, and varying degrees of cognitive decline (Stubbe 2013). In addition, because there may be capacity issues, assessment often includes speaking with family members or caregivers. Allowing extra time for these assessments and limiting the distractions in the room can be helpful. Speaking slowly, simply, using visual/hearing devices if necessary, and having caregivers involved can also improve communication.

33.4 Pharmacological issues in the Elderly

Pharmacokinetic changes occur with both normal aging and with the diseases that increase with aging such as cardiac, renal and liver diseases (Table 33.4). In addition, age-related changes in the various organ systems render them more susceptible to the adverse effects of the medications. The changes in the brain with aging are particularly significant (Table 33.5) and have an impact on both the therapeutic and adverse effects of the drugs.

Adhering to the principles of pharmacotherapy outlined in Table 33.6 should help ensure the optimal therapeutic benefit of medications in the elderly while avoiding the risks of adverse reactions. Specific considerations in choice of agents should include caution in the use of drugs with anticholinergic effects and those with cardiovascular effects. Because of increased medical comorbidities, the elderly are at increased risk for adverse outcomes with medications. In addition, with the increased use of both prescribed and over-the-counter medications, there is a greater risk of drug–drug interactions. The choice of agents used should factor in the associated medical/neurologic comorbidity. For example, in patients with specific disorders such as Parkinson's disease, agents with minimal extrapyramidal effects such as quetiapine may be preferred.

In a prospective study conducted by Hamilton et al. (2011) of hospitalized patients 65 years or older, 26 % had adverse drug reactions. 66.6 % of the total adverse drug reactions either contributed to or were the cause of the admission. The Beers criteria was developed and updated (American Geriatrics Society 2012 Beers Criteria Updated Expert Panel 2012) to evaluate for potentially inappropriate medication use in the older adults. Examples of potentially inappropriate medications (PIMs) in the elderly include: tertiary tricyclic antidepressants (such as amitriptyline, doxepin) and first generation antipsychotics such as thioridazine and mesoridazine because of their high anticholinergic effects. Other PIMs include benzodiazepines

Table 33.4 Effects of age related physiologic changes on pharmacokinetics (Turnheim 2003)

Physiologic change	Pharmacokinetic effect
Increased body fat	Slower elimination of fat soluble drugs
Decreased total body water	Increased concentration of water soluble drugs
Decreased serum albumin	Higher percent of unbound active drug
Decreased hepatic blood flow	Delayed clearance of drugs through the liver
Decreased phase I metabolism	Decreased effectiveness of metabolism of most psychotropic drugs
Decreased renal excretion	Increased concentration of renally excreted drugs

Table 33.5 Biological changes in aging brain

Brain size decreases 10–15 %, with the most dramatic changes occurring in frontal lobes and hippocampus
Increased blood–brain barrier permeability
Decrease in horizontal dendritic components
Formation of neurofibrillary tangles and amyloid plaques
Decrease in neurons and neurotransmitters, particularly dopamine, and acetylcholine
Altered receptor sensitivity

Table. 33.6 Principles of pharmacotherapy in the elderly (Ahmed and Takeshita 1997)

1. Rule out medical etiologies for psychiatric symptoms.
2. Review the patient's medication list (both before admission and during admission) and ask about over-the-counter or herbal medications.
(a) Avoid polypharmacy
(b) Watch for drug–drug interactions
3. Consider removing psychiatric/psychoactive medications that may be causing symptoms.
4. Use behavioral interventions first and minimize use of medications.
5. If medications are used, determine what symptoms are to be targeted.
6. Ensure adequate hepatic or kidney function depending on the medication used.
7. Start low and go slow (half the usual dose and rate). Use the lowest effective dose.
8. Change one medication at a time. Utilize blood levels if possible.
9. Monitor for side effects, particularly anticholinergic/cardiovascular/hyponatremic effects, orthostasis, falls, and confusion.
10. Laboratory monitoring for adverse effects from psychotropics that could include complete blood count, electrolytes, lipid profile, fasting glucose, and EKG.

and nonbenzodiazepines, which can increase fall risk, produce prolonged sedation, and diminished cognition. It is also recommended that first and second generation antipsychotics be avoided for behavioral disturbances of dementia, unless non-pharmacological treatment has failed, due to its increased stroke and mortality risk. Medications that can cause or worsen SIADH and are thus to be used with caution are antipsychotics, carbamazepine, mirtazapine, SSRIs, SNRIs, and tricyclic antidepressants.

33.5 Specific Disorders in the Elderly

33.5.1 Dementia/Major Neurocognitive Disorders (NCD)

With the rapidly growing elderly population, dementia (renamed major NCD in DSM5) is a commonly encountered issue in the medical unit. (See Chap. 13 for further details regarding change in criteria from Dementia to Major NCD.) According to Alzheimer's Association Report (2013), 11 % of those age 65 and older have Alzheimer's Disease, and the prevalence reaches 32 % by age 85 years or older.

The presence of dementia can directly affect the care of an elderly patient in the hospital setting. A study conducted by Erkinjuntti et al. (1986) reported that patients suffering from dementia had increased lengths of stay and required more daily nursing care upon discharge than those without it. The distinction between delirium and dementia is a frequent subject of inpatient consults. Taking a proper history of patients' cognitive symptoms from a reliable caregiver and recognizing the fluctuating level of consciousness that characterizes delirium may help distinguish between the two conditions. Using a cognitive screening instrument such as the Saint Louis University Mental Status (SLUMS), Montreal Cognitive Assessment (MOCA), Mini-Mental State Examination (MMSE, although now copyrighted), or Mini-Cog may be helpful in both the diagnosis of cognitive impairment and in determining if cognition is fluctuating with serial examinations (Feliciano et al. 2013; Ismail et al. 2010) (see Chaps. 12 and 13 for additional discussion of delirium and dementia).

Table 33.7 Common behavioral problems in Dementia Patients: (Dillon et al. 2013; Wyszynski and Wyszynski 2005)

Depression, anxiety, irritability, mood lability
Apathy, social disengagement
Psychosis: hallucinations, delusions, paranoia
Physically nonaggressive behaviors:
Restlessness, pacing, wandering
Repetitive behaviors, hoarding, hiding things
Inappropriate/disinhibited social interactions and regressive behavior (neediness)
Physically agitated/aggressive behaviors:
Resistance to care
Biting, hitting, kicking
Verbally nonaggressive behaviors:
Repetitive vocalizations/questions
Verbally agitated/aggressive behaviors:
Yelling, swearing, calling out

Additionally, assisting the treatment team with problematic behaviors that arise with dementia is also a common role for CL psychiatrists. Some of these behavioral problems are included in Table 33.7.

33.5.1.1 Treatment of Dementia

When approaching treatment of behavioral problems, it is important to first investigate the following (American Psychiatric Association 1997):

1. New medical problems
2. Medication side effects, recently added medications
3. Pain issues
4. Sleep deprivation
5. Recent environmental changes (e.g., transition to hospital, changes in caregivers)_
6. "ABC's" (antecedent → behavior → consequence)

Considering these factors can aid in not only determining the etiologies for these problematic behaviors, but can also give clues to what interventions can help in the future.

Before considering pharmacologic treatment of behavioral problems, non-pharmacologic interventions must first be attempted. Some general recommendations in dealing with agitated dementia

Table 33.8 Recommendations in dealing with agitated dementia patients

Sensory interventions:
Use relaxation techniques, massage, or music during nursing activities to promote ease of care
Use glasses, dentures, and hearing aids
Provide adequate lighting
Adequate pain assessment
Light exercise
Environmental interventions:
Minimize noise in the environment
Provide adequate personal space
Limit interventions during most agitated times of the day (often times after late afternoon/early evening)
Allow safe places for patients to wander
Behavioral interventions:
Calm and soothing tones
Use simple sentence directions
Use distraction and redirection.
Minimize arguing, scolding. Understand that insight into their illness may be limited-Praise for positive behavior
Limit use of restraints for problematic behaviors
Caregiver support:
Providing caregiver support
Monitoring for caregiver burnout

patients are listed in Table 33.8 (American Psychiatric Association 1997; Cohen-Mansfield 2001; Wyszynski and Wyszynski 2005).

Side effects and drug interactions must be considered when administering medications for elderly patients with medical comorbidities. Acetylcholinesterase inhibitors such as donepezil, rivastigmine, or galantamine are routinely used for those with mild to moderate dementia, with donepezil labeled for the severe stage as well (Patel and Holland 2011). These medications frequently have gastrointestinal side effects such as nausea, vomiting, diarrhea, and anorexia therefore slow titration and administering with food can be helpful. Although less common, other side effects to consider include gastrointestinal bleeding, urinary incontinence, fatigue, muscle cramps/weakness, insomnia, abnormal dreams, tremors, seizures, dizziness, bradycardia, orthostatic hypotension, and syncope. Thus they should be used with caution in those with a history of bradycardia, heart block, sick sinus syndrome, syncope, seizure disorder, peptic ulcer disease, low body weight, or severe asthma/chronic obstructive pulmonary disease.

Memantine, an NMDA receptor antagonist can also be used to treat moderate to severe dementia. Often used in combination with cholinesterase inhibitors in the past (Tariot et al. 2004), a recent study by Howard et al. (2012) indicated no significant advantage of using combination treatment compared to donepezil alone.

The decision whether to discontinue these medications in the inpatient setting may be considered when the patient has reached the end-stage of dementia or when other medical comorbidities make continued treatment burdensome or futile. It is the role of the clinician with input from the caregiver and family members to make that assessment.

For the treatment of agitation and psychosis in dementia patients when non-pharmacologic approaches fail, medications such as SSRIs or antipsychotics may need to be used (Keenmon and Sultzer 2013; Barak et al. 2011, and Pollock et al. 2007). A greater number of studies indicate atypicals, particularly risperidone as having the best evidence of efficacy for agitation (Corbett et al. 2012). However, in the studies by Pollock (2007) and subsequently Barak (2011), there was no statistically significant difference in efficacy of citalopram or escitalopram respectively compared to risperidone.

The FDA has, however, recently issued warnings about antipsychotic use in dementia patients. In 2003 a safety alert was issued when patients participating in risperidone trials were found to have increased incidence of cerebrovascular accidents (FDA 2003). Other sources, however, indicate this is probably a class effect (Corbett et al. 2012; FDA 2003). Later in 2005, the FDA issued an advisory declaring an increase in overall mortality in elderly patients with dementia being treated with any atypical antipsychotic medication (FDA 2005). The advisory then expanded to include typical antipsychotics in 2008 with typicals likely having a greater mortality risk (FDA 2008; Wang et al. 2005). Of note, none of these agents are approved by the FDA for treating

psychotic and behavioral symptoms associated with dementia.

33.5.2 Delirium

Delays in recognizing and treating delirium can have significant complications from both a medical and economic standpoint. Nearly 12.5 million elderly patients are admitted to US hospitals each year (Inouye 2006). The development of delirium complicates at least 20 % of these hospitalizations, contributing to over 49 % of all hospital days and increasing hospital costs by as much as $2,500 per patient. These effects in the elderly are further magnified in the postoperative setting (15–53 %), in the intensive care setting (70–87 %) and in the end of life setting where the incidence is estimated at nearly 83 %. A meta-analysis by Witlox et al. (2010) found that there are long term consequences to delirium post-discharge. Those with delirium were at higher risk for mortality (38 % compared to 27.5 % for controls), institutionalization (33.4 % vs. 10.7 %), and dementia (62.5 % vs. 8.1 %).

Elderly patients are more prone to delirium because of the increased prevalence of risk factors such as chronic medical illness, dementia/cognitive impairment, sensory impairment (visual and hearing), structural brain disease, age-related central nervous system changes, and changes in pharmacokinetics and pharmacodynamics (Inouye 2006; Goy and Ganzini 2003). The presentation of delirium in the elderly shares many of the same characteristics as in the younger population (see Chap. 12 for DSM-5 diagnostic criteria for delirium).

Although priority should always be placed on non-pharmacological treatment and on treating the underlying etiology, a meta-analysis by Meagher et al. (2013) found 75 % clinical response rate in those with delirium that received short-term, low dosage antipsychotics. Historically treatment guidelines have generally recommended haloperidol when an antipsychotic is considered for agitation or psychosis due to its minimal anticholinergic effects, its wide therapeutic window, and its multiple routes of delivery. This meta-analysis, however, found no difference in response rates between atypicals (such as risperidone, olanzapine, and quetiapine) versus haloperidol except for the later having higher extrapyramidal rates.

If haloperidol is used in elderly patients, haloperidol can be administered at 0.25–1.0 by mouth (po) twice to three times daily with 0.25–1.0 mg po or intramuscularly (IM), repeated every 30–60 min if needed (Mittal et al. 2011). Similarly, dosing schedules were also reported for the atypicals as well. It should be noted that for delirium attributed to seizures or alcohol/sedative withdrawal, benzodiazepines are the first line agents for therapy. Lorazepam may have advantages for the elderly because of its rapid onset, shorter ½ life, more predictable bioavailability, lack of active metabolites, and decreased risk of accumulation (see Chap. 20 for a discussion of the controversy over lorazepam versus long acting benzodiazepines for alcohol withdrawal).

There have also been studies that have looked into whether prophylactic antipsychotic use would be beneficial for those at high risk for delirium. A meta-analysis by Teslyar et al. (2013) found that prophylactic antipsychotics had a 50 % reduction in relative risk for delirium compared to placebo.

33.5.3 Mood Disorders

33.5.3.1 Depression

The prevalence of major depression is higher in disabled, medically ill elderly patients at 10–12 % compared to their community-dwelling counterparts with an even larger number having less severe forms of depression (Alexopoulos and Kelly 2009). Elderly patients that have depression combined with chronic medical issues have higher disability rates, cost of inpatient services, and rates of readmission, nursing home placements, and mortality (Ellison et al. 2012; Shanmugham et al. 2005). Geriatric patients have unique risk factors for depression that are discussed in Table 33.9. Their clinical presentation of depression can also be different

Table 33.9 Risk factors for depression in the elderly: (Burke and Wengel 2003)

Death of a spouse or loved one (increased risk by 24.3 over 1 year)
Medical illness/injury (increased risk by 3.0 over 1 year) including: Parkinson's disease Cardiovascular disease Alzheimer's disease Cerebrovascular disease (including stroke and white matter infarcts)
Disability and functional decline (increased risk by 4.2 over 1 year)
Limited social support

Table 33.10 Differences in depressive characteristics in the elderly compared to younger populations: (Alexopoulos et al. 2002; Alexopoulos et al. 2005; Burke and Wengel 2003; Wise and Rundell 1996; Shanmugham et al. 2005)

"Masked" depression: patients that appear depressed but deny that they are depressed.
Higher threshold for reporting depressive symptoms.
Less likely to express feelings of guilt or suicidal ideations
Less personality disorders or family history of depression.
More anorexia, weight loss, insomnia, anger, psychotic symptoms, melancholic symptoms.
More cognitive impairment/executive dysfunction (with more anhedonia, psychomotor retardation, poorer insight)
More structural brain abnormalities such as ventriculomegaly and white-matter hyperintensities (particularly frontal/temporal regions)
Higher rate of medical comorbidities, mortality from medical illness or suicide
More preoccupation with somatic symptoms
Poorer response to treatment

as they may complain of more somatic symptoms and sometimes deny feeling depressed. Table 33.10 describes some of the differences in characteristics of geriatric depression.

Some medical illnesses have been implicated in causing depression in the elderly, including cerebral vascular disease and dementia. Greater than 30 % of stroke patients develop depression (Hackett et al. 2005) but the relationship between vascular disease and depression is actually thought to be bidirectional—vascular disease predicting the onset of depression and preexisting depression predicting the onset of stroke and cardiovascular disease (O'Brien et al. 2006). Major depression has been found in 20–25 % of those with dementia with another 20 % categorized as having other depressive syndromes (Burke and Wengel 2003). The difficulty in diagnosing depression in dementia patients lies in the fact that the diagnostic process can often be hindered by poor cognitive functioning and many of the symptoms of dementia and depression overlap. Further complicating early detection is the fact that depressive symptoms may not fit the diagnostic criteria for a major depressive disorder and may be more intermittent and associated with other psychological and behavioral disturbances. Because of this diagnostic dilemma, alternative approaches have been aimed at (1) using an "inclusive approach" where symptoms are counted regardless of the presumed etiology of those symptoms or (2) focusing primarily on the "psychological symptoms" of depression. The Geriatric Depression Scale has been validated for inpatients with mild-moderate cognitive impairments and medical comorbidities with its emphasis placed on cognitive symptoms of depression rather than somatic (Ellison et al. 2012). In addition, features that are more suggestive of depression rather than dementia include (1) acute onset of symptoms, (2) improvement with antidepressants, and (3) complaints of memory problems exceeding actual memory impairment during neuropsychological testing (Small et al. 1986). While it is helpful to make the distinction of cognitive impairment due to depression because of potential treatment with antidepressants, from a long term perspective these patients remain at an increased risk of developing irreversible dementia later on (Ownby et al. 2006).

Treatment of depression in the elderly

While selective serotonin reuptake inhibitors (SSRIs) have been widely used as first line agents, there is no specific evidence demonstrating superior efficacy of any particular class of antidepressants for late-life depression (Ellison et al. 2012). Citalopram and escitalopram were often used in the past for geriatric patients

because they carried the lowest risk of drug interaction (Burke and Wengel 2003). In 2012, however, the FDA came out with a safety warning stating citalopram should not be dosed higher than 20 mg in those over the age of 60 because of increased risk of QTc prolongation and should avoid combining with other QTc prolonging medications (FDA 2012). Other risks to consider with SSRIs include hyponatremia, falls, gastrointestinal intestinal side effects, and risk for bleed (Allan and Ebmeier 2013; Coupland et al. 2011).

Reviews of tricyclic antidepressants (TCAs) versus SSRIs found that TCAs had different side effect profiles and possibly higher withdrawal rates due to side effect experience but with mixed results (Cochrane 2006, Shanmugham et al. 2005). The potential adverse effects however, may be more serious for TCAs including higher risk toxicity in overdose as well as anticholinergic (dry mouth, constipation, urinary retention, cognitive impairments) and cardiovascular side effects (Ellison et al. 2012).

Mirtazapine is a good alternative when SSRIs are contraindicated or not tolerated, especially for patients with anorexia or insomnia (Allan and Ebmeier 2013). It also has a weaker association with hyponatremia (Jung et al. 2011).

Treatment of non-major depression such as dysthymia, and minor depression has been shown to have moderate benefits (Burke and Wengel 2003). In terms of treatment of geriatric psychotic depression, expert consensus guidelines recommend the use of an antidepressant medication in addition to an antipsychotic medication or electroconvulsive treatment (ECT) (Shanmugham et al. 2005).

In the elderly ECT has been recommended as an initial treatment for those with (1) psychotic depression, (2) catatonia, (3) severe depression with functional impairment, (4) medical comorbidities, or (5) acute suicidality or inadequate nutrition where a quick response is needed (Ellison et al. 2012; Shanmugham et al. 2005). Although there are no absolute contraindications, relative contraindications in the elderly are similar to younger patients including cerebrovascular conditions such as aneurysms, recent stroke, space occupying lesions, increased intracranial pressure, cardiovascular comorbidities (uncontrolled hypertension, recent myocardial infarction), as well as patients who are deemed high anesthetic risks (Ellison et al. 2012; Greenberg and Kellner 2005). Another consideration in the elderly is the risk of transient anterograde and retrograde amnesia as well as less frequent persistent cognitive disturbances.

Although there are few studies with elderly patients, transcranial magnetic stimulation (TMS) shows promise and appears safe in those with late-life depression (Jorge and Robinson 2011). Because it is a noninvasive outpatient procedure without the use of anesthesia and limited complications, it is a viable alternative for the frail elderly.

In patients with shortened life expectancy (<2 months), psychostimulants such as methylphenidate are recommended (Goy and Ganzini 2003). Psychostimulants can also be used adjunctively for the depressed, apathetic, medically ill geriatric patient until the primary antidepressant can reach maximal efficacy; however, evidence is limited (Ellison et al. 2012). Response to psychostimulants can be seen in 2 days and discontinuation side effects are uncommon (10 %), although blood pressure and pulse should be monitored because of the possibility of tachycardia and hypertension (Goy and Ganzini 2003; Rosenberg et al. 1991). The starting dose of methylphenidate can be 2.5 mg every morning with breakfast and can be increased by 2.5–5 mg every 2–3 days (Jacobson et al. 2002). A typical daily dose is between 5 mg BID and 10 mg BID. Drug interactions have been noted with warfarin, tricyclic antidepressants, MAOIs, and venlafaxine. Tachycardia and hypertension can occur when combined with the latter agents.

Elderly Suicide

It has been estimated that 20–50 % of elderly patients that commit suicide see their general practitioner within the week preceding their suicide (Cattell 2000). The difficulty in evaluating elderly patients for suicide is that they give fewer warnings, use deadlier methods (71 % using firearms) and have smaller attempts to completion ratios (4:1 versus 200:1 in adolescence). Because

Table 33.11 Risk factors for suicide in the elderly: (Cattell 2000; Burke and Wengel 2003; Shanmugham et al. 2005)

Male: Age > 75
Widowed/divorced/single, social isolation, bereavement
Psychiatric illness Prior suicide attempts Depression, alcohol, "vulnerable" personality traits Hopelessness best predicts suicidal ideation in the presence of depressive symptoms
Physical illness Inadequate treatment of depression: Most studies indicate an inadequate use of antidepressant use prior to death (around 10–25 %)
Access to firearms (71 % use guns)

Table 33.12 Differential diagnosis of manic symptoms in older adults: (Burke and Wengel 2003)

Hyperthyroidism
Sympathomimetic agents, stimulants, and steroids
Frontotemporal dementia (which can present with changes in behavior, disinhibition)
Cerebrovascular disease particularly with lesions in the right hemisphere
Various neurologic diseases

of these alarming statistics, earlier detection and treatment is advised to decrease the rates of suicide (refer to Table 33.11 for Risk factors for elderly suicide).

33.5.3.2 Bipolar Disorder

When an elderly patient presents with manic symptoms but has an unclear history of bipolar disorder, it is important to first rule out medical etiologies for those manic symptoms such as those listed in Table 33.12. For those with a prior diagnosis, the natural history of bipolar disorder is for the frequency and duration of affective symptoms to increase with age. Elderly bipolar patients with manic symptoms frequently present differently from their younger counterparts, often typified by a mixed state (Burke and Wengel 2003). They tend to be more irritable and argumentative with less euphoria and racing thoughts. Geriatric patients also have higher rates of psychotic symptoms and cognitive deficits, often mimicking delirium.

In terms of treatment of acute mania, lithium is an option; however, there is a higher risk for lithium toxicity in the elderly including cognitive impairments, ataxia/gait abnormalities, worsening kidney dysfunction or urinary frequency, and hypothyroidism (Sajatovic and Chen 2011). Drug interactions are more likely to be seen in the elderly because of higher rates of medications such as nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, calcium antagonists, and thiazide/loop diuretics.

Valproate is another option for geriatric mania; however, the free and total serum valproate level should also be ordered since protein displacement can occur with medications such as warfarin, digoxin, phenytoin, and aspirin. Carbamazepine is another option but there are no controlled studies in the geriatric population.

While atypical antipsychotics (except clozapine) are FDA approved for bipolar mania, their use in geriatric patients is limited and as described previously, carry risks including weight gain, metabolic abnormalities, increased risk of falls, sedation, extrapyramidal symptoms, and neuroleptic malignant syndrome.

For geriatric bipolar depression, lamotrigine, quetiapine, and olanzapine are possible options. Maintenance therapy may include lamotrigine, olanzapine, aripiprazole, or quetiapine. ECT is used in severe mania unresponsive to medications or in those who are acutely suicidal or nutritionally compromised.

33.5.4 Psychosis

In a geriatric patient without a history of psychosis, it is important to rule out medical or medication etiologies of psychosis by reviewing medication lists, performing a neurologic exam, and obtaining laboratory tests such as blood counts, liver function tests, basic chemistry panel, vitamin B12/folate levels, serum TSH, RPR, and imaging studies including MRI or CT scan of the brain.

For the elderly patient with schizophrenia, a major difference when compared with the younger patient with schizophrenia lies in the reduction of positive symptoms and an increase in negative symptoms and cognitive deficits (referred to as "burning out").

For those patients without a prior history or evidence of a medical etiology, the diagnosis of late onset psychosis can be entertained. Symptoms often begin after 40 years of age and present with delusions (mostly persecutory) and hallucinations. There is a higher prevalence in females, and these patients have often functioned moderately well in the past (Agronin and Maletta 2006). They present less often with thought disorders, negative symptoms, and severe cognitive impairments, and they may respond to lower doses of antipsychotics (Jeste et al. 2005).

Patients with various dementias can also develop psychotic symptoms. In these cases, the onset of psychosis usually occurs after or coincides with the onset of dementia (Jeste et al. 2005). While patients with schizophrenia do have generalized cognitive impairments, their learning capacity is relatively intact, unlike patients with dementia.

33.5.4.1 Treatment of Psychosis in the Elderly

Rather than typical antipsychotics, atypical antipsychotics are the treatment of choice due to efficacy and superiority of side effect profiles. Atypical antipsychotics can be used to treat negative symptoms and have less EPS (to which the elderly are more susceptible), but their use requires vigilance for orthostatic hypotension, sedation, and impaired glucose tolerance/diabetes, and FDA concerns for increased mortality and cerebrovascular accidents in patients with dementia (Carson et al. 2006).

33.5.5 Anxiety disorders

Common themes of anxiety in the geriatric medically ill patient include worries about physical illness and their impact on quality of life including pain, disability, and the possibility of death. These fears can often be exacerbated by feelings of isolation and dependence in the hospital environment.

In certain instances, it is in the hospital setting that an underlying anxiety disorder is exacerbated. In other instances, anxiety symptoms are secondary to a medical etiology including various diseases, medications, or substances. It is therefore important to differentiate the causes by evaluating for: (1) history of anxiety symptoms; (2) current medications especially analgesics, cold remedies, anticholinergics, herbal medications, and vitamins; (3) history of drug or alcohol use; (4) medical history including endocrine diseases (thyroid/diabetes), pheochromocytoma, cardiac/pulmonary disease; and (5) family history of anxiety. Various rating scales including HAM-A, Beck Anxiety Inventory, Hospital Anxiety and Depression Screen, and Brief Symptom Inventory are tools to help screen for and monitor the diagnosis (Agronin and Maletta 2006; Goy and Ganzini 2003). A combination of psychotherapy (cognitive–behavioral approach) and medications are appropriate interventions for those motivated and have the cognitive capacity to engage in therapy. For those receiving palliative care, the focus of therapy is teaching anxiety management skills such as progressive muscle relaxation, controlled respiration, and guided imagery rather than insight-oriented psychotherapy. Reassuring patients that their symptoms will be addressed, that familiar nursing staff members will be available, and that their spiritual needs will be met by offering pastors services, can help alleviate anxiety in the medically ill elderly (Goy and Ganzini 2003). In addition to therapy, benzodiazepines are considered first-line treatment but caution is used because they can cause confusion and falls in the elderly and can potentially suppress respiration in patients with pulmonary disease or those on high doses of narcotics (Goy and Ganzini 2003). If longer term anxiety treatment is needed, then the traditional use of SSRIs or SNRIs would be more appropriate.

33.5.6 Substance Use Disorders/ abuse/dependence

Alcohol and substance abuse is often unrecognized in the elderly. According to community-based epidemiologic studies, the 1-year prevalence rate for alcohol abuse and dependence is 2.75 % for elderly men and 0.51 % for elderly women. The prevalence rates are higher, however, in primary care settings,

where at-risk drinking has been estimated to be 5–15 % (Oslin 2005).

The prevalence of substance use disorders, however, may actually be underestimated because of limited applicability of DSM-5 criteria to the geriatric population. For example, elderly patients may have difficulty fitting the "tolerance" criteria because age-related changes in pharmacokinetics and pharmacodynamics lower drugs tolerance. In addition, the criteria addressing the inability to fulfill occupational obligations may be less applicable because a large portion of these patients no longer work (Jeste et al. 2005). At-risk drinking may also go unrecognized because physicians may not realize that the allowable intake for an elderly patient is different than for a middle-aged adult. The National Institute on Alcohol Abuse and Alcoholism and the Center for Substance Abuse Treatment recommends that patients ages 65 and older should consume no more than one standard drink per day or seven standard drinks per week (Oslin 2005).

While the geriatric population can face similar substance abuse problems as their younger counterparts, a particularly unique problem facing the elderly is the misuse of prescription and over-the-counter medications. The two most commonly misused prescribed drugs by geriatric patients are benzodiazepines and opioids, both of which can cause problems of tolerance, withdrawal, and cognitive changes. According to Oslin (2005), approximately 32 % of community-dwelling geriatric patients take analgesics and 10.4 % take benzodiazepines. In addition, geriatric patients often use over-the-counter cold and allergy medications which can increase the risk of delirium because of their anticholinergic effects.

Helpful diagnostic tools to assess alcohol use disorders in the elderly include: (1) the CAGE questionnaire in which one positive response is an indicator of a disorder, and (2) The short Michigan Alcoholism Screening Instrument—Geriatric version (Beresford 1992; Ewing 1984). In addition to assessing for substance use, it is important to assess for alcohol related problems such as (1) medication interactions, particularly warfarin and digoxin, (2) medical problems such as uncontrolled diabetes, poor nutrition, cardiovascular disease, hypertension, osteoporosis, hyperuricemia, and peripheral neuropathy, (3) insomnia, (4) withdrawal, and (5) accidents/falls (Agronin and Maletta 2006). To assess for potential abuse of opioids or benzodiazepines, the Dupont Checklist is a useful tool (Blow et al. 1992).

Treatment of alcohol and substance withdrawal in the elderly is similar to regimens used in younger populations. Although elderly patients have been shown to have a longer duration of withdrawal symptoms, there is no evidence suggesting that older patients are more prone to alcohol withdrawal or need a longer duration of treatment for withdrawal symptoms (Oslin 2005). Treatment with a smaller than usual dosage of short-acting benzodiazepine such as lorazepam has been recommended in treating alcohol withdrawal in the elderly because of the increased half-life in this populations and risk of oversedation (Caputo et al. 2012).

For the treatment of opioid withdrawal, symptomatic treatment is used for mild to moderate withdrawal (Agronin and Maletta 2006). Methadone or buprenorphine can be used with caution for elderly patients with significant opioid addiction.

For non-pharmacologic maintenance treatment of substance abuse, day programs and senior centers can be useful. According to Agronin and Maletta (2006), age-related group activities have been found to be superior to mixed-aged group activities.

In terms of pharmacological agents for alcohol, naltrexone has been shown to be safe and beneficial in older adults (Agronin and Maletta 2006; Caputo et al. 2012). It now is available in an extended release injection. This may be beneficial for those who forget to take their medications. It should, however, be avoided in opioid dependent patients or those currently taking opioids for pain. Treatment can be initiated at 25 mg daily and can either be maintained or increased to 50 mg daily. Studies on acamprosate have indicated some efficacy in adults; however, there are no studies focused on the elderly (Caputo et al. 2012). Disulfiram use in the elderly is generally not recommended because of the risk that

the patient may drink alcohol while taking it, especially in those with hepatic or cardiovascular disease.

33.6 Specific Issues in Caring for the Elderly

33.6.1 Palliative Care/End of Life Issues

Palliative care has been extensively covered in Chap. 27, but it is an important topic when working with the medically ill geriatric population. It is important to recognize that progressively ill patients also have progressively higher rates of major depressive disorder. The prevalence of depression during terminal illness has been estimated to be between 1 % and more than 40 % with approximately 25 % of cancer patients developing a significant mood disturbance (Goy and Ganzini 2003). Addressing depression even in this setting is crucial because patients who are depressed tend to make more restricted advance directives and change them after remission of their depression (Ganzini et al. 1994). In those with end-stage cancer, pharmacological treatment approach is symptom management and to use medications with lower drug–drug interactions since many chemotherapy medications are metabolized through CYP3A3/4 (Rosenstein 2011). Mirtazapine is particularly useful in this population because of its limited drug interactions, weight gaining/sedating properties, and antiemetic effects since it is a partial 5HT3 receptor antagonist.

Another key end of life issue is differentiating hypoactive delirium from depression since prescribing an antidepressant or psychostimulant can worsen delirium. In the last days of life, the prevalence of delirium can reach 90 %. Although it would be tempting to see a calm, confused state at the end of life as desirable, hypoactive delirium can be distressing to patients and their families. It can also hamper their ability to tell their loved ones goodbye.

Focus should also be given to caregiver stress. Support can be provided through inpatient staff (social workers, pastoral care, nurses, and psychiatrists) and community resources. Helping families understand what to expect through each stage of the patients' course, up the final hours of life, can help alleviate distress. It can also serve to improve communication with the primary care provider (Goy and Ganzini 2003).

33.6.2 Capacity

Capacity is a common consultative question for geriatric patients on the medical and surgical unit. In order to be deemed as having capacity, the patient must demonstrate that they have sufficient understanding to make or communicate responsible decisions concerning one's condition (Appelbaum and Grisso 1988). This is not to be confused with competence, which is legally determined.

Prior to interviewing the patient, it is important to learn the facts of the situation from the treatment team and whether the patient has been informed of these facts. The treatment team should also understand that just because a patient lacks capacity, does not mean that they cannot later regain capacity. This is particularly true with reversible conditions such as delirium, psychoses, and mood disorders.

For a person to have capacity, there are four basic principles which state that the patient must: (1) communicate a choice, (2) understand the information given, (3) understand the situation and its consequences, and (4) manipulate the information rationally (Appelbaum and Grisso 1988). Table 33.13 lists specific question prompts to these principles. A sliding scale approach can be taken to making a determination of capacity. This means that a lower standard can be used if a patient refuses a high risk to low benefit procedure but a higher standard is used if a patient refuses a low risk high benefit procedure.

If a patient has been determined to lack capacity, then their advanced directives can be activated and their durable power of attorney (DPOA) can begin to be involved in making decisions. If there are no advanced directives, then a surrogate decision maker can be sought, either by

Table 33.13 Capacity questions: (based on Appelbaum and Grisso 1988)

1. Communicate a consistent choice: Have you decided whether or not to go along with your doctor's suggestion for treatment? Can you tell me what your decision is?
2. Factual understanding of issues:
Please tell me in your own words what your doctor told you about:
(a) The nature of your condition
(b) The recommended treatment
(c) Benefits and possible risks (or discomfort) from the treatment
(d) Alternative treatments that could be used and their risks/benefits
(e) The possible risks and benefits of no treatment at all
You mentioned that your doctor told you of a ___% chance the (named risk) might occur with the treatment. How likely do you think the occurrence of (named risk) might be?
3. Appreciation of the situation and consequences: Please explain to me what you really believe is wrong with your health now? Do you believe that you need some kind of treatment? What do you believe will happen if you are not treated? Why do you think your doctor has recommended (specific treatment) for you?
4. Rational manipulation of information: Tell me how you reached the decision to accept/reject the recommended treatment? What were the factors that were important to you in reaching the decision? How did you balance those factors?

having a capable patient designating someone, or by having involved parties (such as family members) stepping in. If a surrogate decision maker is not available, then a guardian can be appointed by the court once there is a legal determination of incompetence.

33.6.3 Functional Ability and Disposition Planning

In the elderly, a key focus is evaluating and optimizing function and quality of life, and not just illness or treatment focus. In the hospital every effort should be made to optimize functional ability, as the elderly are vulnerable to loss of function due to aging physiology as well as due to medical, psychiatric, and iatrogenic factors (Creditor 1993). The level of function is determined by assessment of basic activities of daily living (ADLs) and instrumental ADLs (IADLs). Basic ADL evaluation focuses on activities such as feeding, bathing, toileting, grooming, and transfers. Evaluation of IADLs focuses on cooking, cleaning, shopping, use of telephone, and managing of finances and medications. This functional assessment will often determine the level of care an older person may need. Once this is determined, it is important to involve family and caregivers in the patient's life in the decision making process about what additional supports they may need including future living arrangements. There should be a balance between patient safety and respect of their autonomy. Decisional capacity assessment may be needed if the patient does not appear to show good judgment decisions about living arrangements or following through with medical recommendations.

33.6.4 Elder Abuse and Undue Influence

A possible reason for consultation to psychiatry may be to provide an evaluation of elderly abuse. According to a systematic review by Cooper et al. (2008), 6 % of older persons reported abuse in the past month. Although reporting of suspected elder abuse was mandated in 44 states, actual reporting remains low. According to the 2004 survey of state adult protective services, of those states that separated out those aged 60+, health care professionals (not including social services agencies) made 14.5 % of the reports with physicians making only 1.4 % Teaster et al. (2007).

According to the National Aging Resource Center on Elder Abuse (NARCEA) there are seven suggested categories of elder abuse which include the following listed in Table 33.14. Undue influence (UI) is another concern when dealing with elderly, particularly those that are dependent or impaired. UI becomes an issue when "caregivers use their role or power to exploit the trust, dependency, or fear of another to

gain psychological control over the patient's decision-making, usually for financial gain" (Quinn 2002). Physicians should be aware of signs of elderly abuse (Table 33.1) and report any incidents according to state laws.

33.6.5 Discussion of vignette

The vignette described earlier illustrates some of the challenges of caring for elderly patients, including recognizing delirium superimposed on dementia and the various possible etiologies for delirium including urinary tract infections, pain, anticholinergic medications and hyponatremia. Agitation could occur from the delirium, as well as from pain secondary to an occult hip fracture from a fall, in a vulnerable older woman with possible osteoporosis. In addition, it is important to recognize the potential adverse effects of psychotropics in the elderly such as extrapyramidal symptoms with antipsychotics, and hyponatremia with selective serotonin reuptake inhibitors. Also, being aware of increased fall risk and QTc prolongation issues with both antidepressants and antipsychotics is important. One also has to be mindful of potential psychiatric adverse effects from medical treatments such as ciprofloxacin. In addition, ciprofloxacin may add to the QTc prolongation that the patient has. Because of changes in cognition, extra consideration is needed to look for signs of elderly abuse and capacity to make medical decisions. In this case, the observable bruises and fall should raise the index of suspicion for abuse and neglect. Caregiver burden in a patient with agitation increases the risk for abuse.

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Table 33.14 Categories of elder abuse (NARCEA) (Kleinschmidt 1997)

Physical
Psychological/Emotional: insults, humiliation, threats to institutionalize or abandon
Financial: theft, misuse of funds, and coercion (e.g., changing a will)
Neglect: basic care not provided
Self-neglect: conduct by a patient that threatens his/her own health/safety
Sex abuse
Miscellaneous: rights violations, medical abuse, and abandonment

Table 33.15 Observations suggestive of elder maltreatment (Kleinschmidt 1997)

General	Caregiver	Patient
Medication problems such as duplications and questionable dosages	Indifference towards patient Recent conflicts	Fearful of caregiver or indifferent Recent conflicts
Numerous hospitalizations or health care visits with different physicians and hospitals.	Mental health problems: History of alcohol or drug problems History of violence or legal problems Depressed	Mental Health problems: Depressed
Delays in seeking medical care.	History is vague or does not corroborate with evidence Attempts to prevent patient from interacting with health care providers	History is vague or does not corroborate with evidence, reluctant to answer questions
Unexplained injuries/fractures, labs/radiographic inconsistencies	Provides poor supervision or noted abandonment	
	Overly concerned with medical costs, financially dependent on patient	
	Limited understanding of patient's medical problems	

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Special Procedures: Intravenous Sedative Interviews, Hoover Test, Waddell Tests, and Hypnosis

34

Hoyle Leigh and Jon Streltzer

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An interview with the patient under an intravenous (IV) sedative, the Hoover test, Waddell tests, and hypnosis are some of the specialized techniques useful in the consultation-liaison (CL) setting for rapid diagnosis of potential psychological factors affecting a physical condition and for behavioral control of pain and anxiety.

This chapter presents an example of an IV sedative interview using lorazepam and describes the procedure in detail, and discusses the Hoover test and the indications, precautions, and procedure of hypnosis in the CL setting.

34.1 Case Presentation: Patient Interviewed Under Lorazepam

A 42-year-old Arabic woman, married to a part-time Protestant minister, was admitted to the hospital with chest pain. Myocardial infarction was promptly ruled out, but the patient developed neck pain and left-sided weakness of her arms and legs and paresthesia of her left side. Magnetic resonance imaging showed moderate cervical stenosis without any evidence of spinal compression. The deep tendon reflexes were normal, and the paresthesia was confined to the left side at midline. Psychiatric consultation was requested to rule out "malingering, factitious disorder, or conversion." The patient was dressed in hospital attire, of medium build, with brown hair; she spoke fluent English, showed labile affect, and was moderately

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depressed about her physical condition. Cognitive exam was normal. She was one of eight children born of Muslim Arab parentage in Israeli-occupied territory. She was rather independent, and upon finishing school, enrolled to be trained as an Israeli police officer. She met her future husband who was an American evangelical missionary traveling in the Middle East. They eloped, married, and came to the USA, where she became a housewife with two children. Her husband developed back pain attributed to a herniated disk and was placed on permanent disability, though he continued to preach on and off. She had never applied for permanent residence or citizenship, and was worried about her status, as she might not be eligible for disability should she become permanently paralyzed. Her oldest daughter, now 18, had just left home to attend college out of town. The consultant felt that an interview with the patient under lorazepam was indicated as her symptoms were disproportionate to objective findings, and there seemed to be a potential psychological overlay to her physical symptoms.

The consultant explained to the patient that an interview using an antianxiety, muscle-relaxant medication sometimes helps patients to talk about stresses that may worsen physical symptoms, and that in a state of relaxation patients might be able to regain some control over muscles and nerves that have been affected by stress. The patient wished to discuss it with her husband, who turned out to be an imposing bearded man with a booming voice, who seemed to be very controlling. Initially, he would not consent to the interview unless he could be present, but it was explained that a psychiatric interview of this type has to be confidential even to the spouse. Eventually, the patient consented to the interview, which would be videotaped, provided that she would be able to watch it afterward. A standardized consent form for special procedures was signed, and an additional video interview consent was obtained.

34.1.1 The Interview

Five ampules of lorazepam 2 mg solution were ordered and a crash cart with emergency breathing equipment was on standby in case of a respiratory arrest. If the patient does not have an IV running already, the ampules may be pooled and diluted so that a 10-cc syringe contains 4 mg of lorazepam. The patient was instructed to count backward from 100 as the first syringe with 2 mg of lorazepam was slowly injected into an existing IV line. Her speech became slurred and she made mistakes in counting about halfway into the second syringe (3 mg lorazepam), at which point she was asked to relax, imagine something pleasant, and to describe it. She imagined being back in Palestine, playing in the fields as a child, running and singing. She missed home, but could not visit as she was afraid of her family, and besides she might not be able to reenter the USA.

She was quite tearful at this point. Another 2 mg of lorazepam was slowly injected as the consultant gently refocused her on the present, and told her to talk about anything that was on her mind. She talked about her daughter, Sarah, who just left for college, who is an all-American girl, who plays basketball, and who wants to be a criminologist. She will miss her, but she is happy for her. The consultant then asked her to empty her mind of all thoughts, just concentrate on a feeling of relaxation all over her body, gentle, pleasant, comfortable, relaxation, beginning from the feet, up the legs, thighs, abdomen, chest, hands, arms, shoulders, neck, face, and head. Then the consultant asked her to first gently lift her right hand (the unaffected side), which she did easily, and then the left, affected, hand, which she had initial difficulty doing, but with reiterated suggestions of relaxation and concentration she was able to raise it halfway. Then she was asked to raise her unaffected leg, and then, the affected leg, which she was, again, able to do halfway.

The consultant reassured the patient that with relaxation and concentration she was able to overcome her symptoms at least part of the way, which proved that she could expect eventual improvement of her symptoms. She was told that she would remember what was said and what happened during the interview to the extent that she felt comfortable doing so, and that she would regain some of the function of her limbs to the extent she might be ready to do so. Then she was asked again to relax and, if she wished, to sleep a little. Another 1 mg of lorazepam was injected.

The patient was on a monitor for heart rate and respiration, and the nurses were instructed to observe her frequently for the next 2 h. The patient slept for about an hour after the interview.

For medical documentation purposes, the consultant listed the diagnosis as psychological factors affecting medical condition, for pain and weakness, with conversion features (we use "psychological factors affecting medical condition" to cover all somatic symptom disorders; see Chaps. 21–23).

34.1.2 Subsequent Events

Following the lorazepam interview, the patient regained some use of her extremities, but continued to complain of neck pain. She was discharged with prescribed physical therapy as an outpatient, and recommended follow-up by a psychiatrist, which she refused. She was lost to follow-up until about 2 years later, when the consultant happened to see the patient in the hospital lobby. She was happy to see the consultant, told him that she was visiting a friend who was in the hospital. When the consultant asked her about her health, she said, "Well, all the paralysis and pain disappeared after I had surgery for the narrowing of the spinal canal. I am now working full time, and doing very well." Apparently, about 3 months after her lorazepam interview, she had gone to a university hospital in another city, where they decided to operate on the cervical stenosis. She had obtained her permanent residence status since then, and was now fully recovered.

34.1.3 Discussion

Like many patients with physical symptoms with psychological overlay, this patient had cervical stenosis that might have contributed to some of her symptoms, but the paralysis and paresthesia were not fully consistent with an organic pathology. Psychodynamically, she seemed to have considerable conflict over dependence versus independence and a conflicted relationship with her controlling husband. Proximal stressors might have included her daughter's gaining independence, and her chronic concerns about her immigration status with her pathologic procrastination over doing something about it. The surgery on the cervical spine seems to have provided two things: relief from whatever physical symptoms it caused, and, perhaps more importantly, a psychological rationale to assume a different aspect of her personality, specifically a resurgence of the frustrated drive for independence, as she straightened out her immigration status and found a full-time job, emancipating herself from her controlling husband. Now, as an American permanent resident, and perhaps as a citizen in the future, she might even be able to visit her homeland.

34.2 Intravenous Sedative Interview

The above case illustrates the use of the lorazepam interview in which partial function of a paralyzed limb was restored through relaxation and concentration. Intravenous lorazepam causes frontal lobe disinhibition and muscle relaxation at the same time, producing a dissociative state where the patient may be more amenable to suggestions given by the consultant. In the past, sodium Amytal was frequently used for such interviews; in fact, any intravenous relatively short-acting sedative may be used. In attempting such interviews, it is essential that patients be prepared well beforehand so that they will feel relaxed and at the same time will be able to concentrate, and that medical personnel are available should there be any untoward effect. Prior to attempting such interviews independently, the consultant should observe and practice them under supervision by an experienced CL psychiatrist.

The intravenous sedative interview may be particularly useful in patients who seem to be catatonic or mute in the CL setting. Under IV sedation, as described above, mute patients can often vocalize with the suggestion of vocal cord relaxation, and then talk. Then the consultant may be able to differentiate among catatonia/mutism secondary to depression (quite common), psychosis, or brain damage. If patients are depressed, they are likely to talk about depressive thoughts

and delusions; if psychotic, the verbalizations may be loose, bizarre, or delusional; and in brain damage, patients may simply fall asleep.

At times, patients may become emotional during a sedative interview and abreact or live through a traumatic event. The consultant should take care that such abreaction does not adversely affect the medically ill patient through judicious questions, suggestions of relaxation, and, if necessary, additional administration of the sedative. It is always important to give the suggestion that patients will remember just as much as they may wish to after the session.

34.3 Hoover Test

This is a neurologic test to ascertain whether the paralysis of a lower extremity is primarily psychological (conversion, somatization, factitious, malingering) or organic. Facing the patient at the foot of the bed, the tester places both palms under the heels of the supine patient. Then the tester asks the patient to raise the unaffected limb. The patient should have no difficulty in doing this. Then the tester asks the patient to raise the affected paralyzed limb. If the paralysis is organic, the tester should feel pressure on the palm under the unaffected limb as the patient attempts to raise the affected limb. If the tester feels no pressure, then the paralysis is presumptively caused by psychological factors or conscious malingering.

While this test is reasonably reliable, there are occasions when the patient may have an organic lesion, but also has motivational reasons not to cooperate with the test. The tester should interpret the results in the light of other findings, such as reflexes, spasticity, and imaging studies.

34.4 Waddell Tests

Waddell tests were first described by an orthopedic surgeon and are commonly used in orthopedic evaluations of back pain (Main and Waddell 1998). They are simple to perform and take little time. They are considered non-organic or non-physiological findings. Waddell did not consider them to be diagnostic of malingering. Rather, they are likely to indicate that psychological factors are significant in the symptomatic complaints of low back pain (Waddell et al. 1980). As such, the psychiatric consultant may find them useful in evaluating chronic pain patients. In one study of patients claiming injury and persistent pain, positive Waddell tests for nonphysiological findings were present in the majority of patients who had suffered trivial injuries in contrast to very few of those who had suffered significant injuries (Streltzer et al. 2000)

There are several categories of Waddell tests related to distraction, simulation, overreaction, non-anatomical sensory disturbances, and superficial tenderness. A particularly useful test is performed by asking the patient to stand up keeping the spline as straight as possible. This can also be performed in a sitting position. The patient is then told that pressure is going to be placed on the spine. The patient is asked to report any pain that develops at which point the test is immediately stopped. Then the examiner places his hand on the top of the patient's head. Pressure is then gradually increased by pressing downwards. A positive test occurs when the patient says this produces or increases back pain. In fact, it is physiologically impossible for this maneuver to produce any sensation in the back. This test is not recommended if neck pain is also present as a complaint.

Another easily performed Waddell test is that of simulated rotation. The patient is asked to stand straight with his arms at his side. The examiner holds the arms next to the hips and rotates the body to either side, keeping the arms steady at the sides of the body. This keeps the shoulders and the hips in the same plane, simulating spine rotation without any actual twisting of the spine. If the patient states that this causes back pain, it is considered a positive test.

Touching the back in the area of the pain with very light pressure so that sensation is only felt by the skin with no pressure on the muscles is the technique for testing superficial tenderness. If this elicits complaints of back pain, it is considered a positive test.

Other simple tests for non-physiological back pain and also neck pain have been described (Blom et al. 2002; Sobel et al. 2000)

34.5 Hypnosis in the Consultation-Liaison Setting

Historically, hypnosis was used extensively by psychiatrists to diagnose and treat hysteria (see Chaps. 1 and 21). Since Freud abandoned hypnosis in favor of free association, the use of hypnosis in psychotherapeutic settings declined, but it continued to be used in treating dissociative syndromes (e.g., multiple personalities) and in some CL settings. In the CL setting, hypnosis can be used in place of the intravenous sedative interview discussed above, provided the patient is willing and hypnotizable. Despite Charcot's historical claim that hypnotizability was pathognomonic of brain degeneration in hysteria, our modern understanding of hypnotizability is that it represents an ability to concentrate intensively, to be absorbed in a task, and to be able to dissociate under cue.

Patients who are unable to concentrate, such as delirious, demented, and psychotic patients, are usually unable to use hypnosis. Persons who have a natural tendency to dissociate, as in borderline personality, posttraumatic stress disorder (PTSD), and dissociative disorders, may be particularly good subjects for hypnosis. There is evidence that hypnotizability is associated with differential electroencephalograph (EEG) patterns (Graffin et al. 1995; Ray 1997; Ray et al. 2002; Williams and Gruzelier 2001), and, in highly hypnotizable subjects (about 8 % of the population), hypnosis can induce perceptual changes (hallucinations) with corresponding activation of brain sensory and association areas (Kogon et al. 1998; Kosslyn et al. 2000).

There are gradations of hypnotizability; about 75–80 % of the general population can make use of hypnosis at least to an extent, particularly for anxiety and pain control.

34.5.1 Indications

Hypnosis in the CL setting can be used for the following reasons:

1. Relaxation and anxiety control
2. Pain control
3. Habit control (e.g., smoking)
4. Exploration of psychological factors affecting physical condition

34.5.2 Contraindication: Unprepared Patient

An unprepared patient is one whose expectations and motivations for hypnosis deviate from the stated purpose of the procedure. This can be explored in the preparation phase for hypnosis.

34.5.3 Preparation

Before any hypnotic procedure, the patient should be informed about what to expect. Ask whether the patient had previous experience with hypnosis or had seen hypnosis being performed, and then explain that medical hypnosis is not like stage hypnosis, in that the patient will not be told to do things that are foolish or unwarranted. Explain that hypnosis is not magic; it is simply a way of concentrating attention and causing profound relaxation through concentration. It is a way of utilizing an inherent ability of the patient to concentrate and relax; there is nothing that the hypnotist does to the patient. It is performed solely for the purpose of helping the patient to relax (or reduce anxiety, to control pain, to help with diagnosis and control stress, etc.). Patients under hypnosis will not do anything against their will during the hypnotic session; in fact, they will never lose control, and they will be able to remember everything that happened during the session.

Hypnosis for relaxation, anxiety, and pain control is particularly useful in the CL setting using the procedure presented below. A similar procedure may be used to explore psychological factors affecting a physical symptom as in an intravenous sedative interview, discussed above, substituting the relaxation and concentration achieved through hypnosis for that of the intravenous sedative. For hypnosis to stop smoking, see Herbert Spiegel's (Spiegel 1970) classic article. A more intensive form of hypnotic treatment for smoking has shown a success rate of 40 % in a 6-month follow-up (Elkins et al. 2006).

34.5.4 Procedure for Hypnosis for Relaxation, Anxiety, or Pain Control

First, the consultant should explain the purpose of the hypnotic session, have an informed consent form signed for a special procedure (hypnosis), and prepare the patient as discussed above. Then the consultant should ask the patient to think about a particularly relaxing place where the patient would like to go in his/her imagination, and, if it is for pain control, what the patient would like to imagine to control the pain, for example, a novocaine injection to the painful spot, a block of ice numbing the pain, a warm electric blanket surrounding the painful area, or something else—patients can be creative here. During the hypnotic session, the consultant will suggest to the patient to imagine exactly what the patient wants. The most important aspect of hypnosis for relaxation and pain control is to teach self-hypnosis, so that the patient can use it at any time it is needed. Thus, a patient who was in the intensive care unit with multiple fractures and multiple tubes inserted was able to imagine sunning himself in a beautiful beach looking at relaxing sailboats with a grin on his face, which was puzzling to the nursing staff.

Below is a procedure for teaching self-hypnosis that may be modified as indicated or desired. For example, if the patient's left arm or hand is not available for levitation as instructed, this part may be skipped (as may the other parts in parentheses below), and the patient may simply proceed to looking down on a favorite spot while still floating in air.

The CL psychiatrist should learn to use hypnosis under supervision to gain confidence with its use.

34.5.5 Hypnotic Procedure for the Consultation-Liaison Psychiatrist

This procedure is modified from Herbert Spiegel's induction technique. With the patient sitting or lying comfortably in bed, first discuss hypnosis experiences and prepare the patient as outlined above. Second, have the patient determine a favorite relaxing spot. Third, ask the patient to look all the way up while keeping the head level, and while still looking up, close the eyelids slowly. Then have the patent take a deep breath while still looking up with eyes closed, hold, and exhale and relax the eyes. Then ask the patient to open the eyes, and say, "This is the first step we will be using to get you into a relaxed state. As you can see, this is not difficult to do. Are you ready?" If the patient answers yes, proceed. If the patient has questions, discuss them. The better prepared the patient, the better the hypnotic experience will be.

Then read aloud (or say, if the procedure is familiar) the following instructions:

Lie or sit comfortably in an open position as you are doing now. Relax. Look all the way up, take a deep breath, close your eyelids slowly. Exhale and relax your eyes.

Concentrate on a feeling of floating, floating, floating … Imagine yourself floating. Floating among soft, white clouds, floating, floating, floating … And now you begin to see scenery under you as you are floating, buildings in the distance, fields, trees, hills. [If the patient's left hand is unavailable, skip to the end of the next parenthesis:]

(While you concentrate on this sensation of floating, now also concentrate on your left hand, and imagine that it is becoming lighter and lighter and lighter, like a huge buoyant balloon … Getting lighter and lighter and lighter … Imagine that the middle finger of the left hand is attached by a string to a huge, helium-filled balloon, and it is pulling the finger up, and let the finger and the hand go up … feeling very, very light … in a smooth motion, let your elbow bend, and let the hand go up until your forearm is in an upright position … Let your hand go up feeling very, very light … Sometimes this is an amusing sensation as your hand becomes so light that it floats up like a huge buoyant balloon. If your hand is not up yet, imagine it being pulled up by a huge buoyant balloon, and put it up in a smooth motion, until your forearm is in an upright position Now, when your hand is up in this position feeling very, very light, and …)

When you feel so light that you can imagine yourself floating, and you imagine and see scenery below you, this is the signal that you are in a state of concentrated attention and relaxation, a state of self-hypnosis, when you can concentrate your attention and by concentrated attention, what you imagine feels real. In the state of concentration, concentrate on the sensation of floating, floating, floating, and imagine yourself floating among soft, white, clouds, floating, floating, floating, and …

Concentrate on the feeling of relaxation all over your body, (read the following body parts very slowly) your legs, thighs, hips, abdomen, back, chest, shoulders, arms, neck, head, all over your body, and as you float among the soft white clouds, you look down and see, under the clouds, peaceful scenery, trees, fields, towns, mountains, the sea coast …

Now you see your favorite relaxing spot, and gently land on the spot, and look around, soak in the peaceful surroundings, the fresh air, feel the breeze, and enjoy the scenery and the sounds … and you feel yourself relaxing, your legs, thighs, hips, abdomen, back, chest, shoulders, arms, neck, face, head, all over your body … and you can stay here, relaxing, enjoying the scenery … If you want, you can sit up, walk around, whatever relaxes you.

[For pain control, add the following: While you are here, very relaxed and very comfortable, you can also imagine that your painful area is (given an injection of novocaine … Now, you feel the pinch, and the numbness spreading) [or] (wrapped in a warm electric blanket, and the warmth is spreading, neutralizing the pain) [or] (in a block of ice, you feel the cold, and the numbness caused by the ice, spreading and neutralizing the pain) and as long as you are here, you can continue this sensation as long as you like, feeling relaxed at the same time.]

And when you are ready to come out of this relaxed state, all you have to do is count backward, from 3 to 1, don't do this yet, and at the count of three, look all the way up with your eyes still closed, at the count of 2, relax your eyes, and at the count of 1, make a fist with your left hand and open your eyes, (and all the normal sensations of the hand and arm will return), and you will be out of the state of self-hypnosis, feeling refreshed, clear-headed, and energetic. From now on, whenever you want to come to this state of concentrated attention and relaxation, all you need to do is just what you did just now: Sit or lie down in a comfortable position, look all the way up, take a deep breath, close your eyelids slowly, exhale, and relax your eyes, then concentrate on a feeling of floating, floating, floating, (and imagine that your left hand is getting lighter and lighter, and let it go up in an upright position), and let yourself float among soft, white clouds, relax all muscles of your body, then locate your relaxing spot, gently land, and enjoy … When you are ready to come back, count backward from 3 to 1, at the count of 3, look all the way up, at the count of 2, relax your eyes, and at the count of 1, (make a fist with your left hand and) open your eyes slowly (and all the normal sensations and control will return to the hand), and you will be out of the state of self-hypnosis, feeling refreshed and relaxed. Ok. Now, I'll count backwards from 3 to 1. 3—look all the way up, 2—relax your eyes, 1—(make a fist with your left hand and) open your eyes slowly. Now you are out of the state of hypnosis. Do you feel relaxed?

Suggest to patients that they do this self-hypnosis as many times a day as possible. Discuss the following points and any other questions the patient might have. Here are some example questions:

"What if I am interrupted while in self-hypnosis?" "Just quickly count backward, 3-2-1, and make a fist with your left hand, and you will be out of the hypnotic state, feeling relaxed and refreshed."

"What if I see images I did not plan on?" "As long as it is pleasant, enjoy! Some people can use hypnosis creatively, and may be able to do various pleasant things in vivid imagination. If anything unpleasant happens, simply come out of the hypnosis by counting backward, 3-2-1, and open your eyes while making a fist."

"What if I still seem to be in a trance after I come out?" "Simply reenter hypnosis quickly by looking all the way up, close your eyes, take a deep breath, hold, and exhale, and then look up again, count backward, 3-2-1, make a fist, and open your eyes. You will definitely be out of the trance."

34.6 Other Techniques

In addition to the techniques described in this chapter, there are other techniques that may be equally useful in CL psychiatry, such as relaxation training without hypnosis, mindfulness training, and meditation, which the reader is encouraged to explore.

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