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13 Mood Disorders

▲ 13.1 Mood Disorders: Historical Introduction and Conceptual Overview

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CLINICAL AND PUBLIC HEALTH SCOPE OF MOOD DISORDERS

Prevalence

Depressive disorders afflict one of five women and one of ten men at some time during their lives. Depressive episodes alternating with mania or hypomania represent the domain of bipolar disorders. Increasingly, the conventional figure of 1 percent for bipolar disorders in the general population is being challenged, and there are now convincing data that this group of disorders may account for 5 percent of the population and up to 50 percent of all depressions. The enlargement of the boundaries for bipolar disorder is largely due to better detection of the bipolar II subtype (depression plus hypomania rather than mania). The current evidence for clinical, therapeutic, and public health implications of such a broadened bipolar concept has been summarized in a World Psychiatric Association monograph.

Despite the availability of effective treatments, many persons with mood disorders are disabled, and rates of suicide (which occurs in approximately 15 percent of depressive patients) are high in young and, particularly, elderly men. An alarming increase of suicide rates among middle-aged women has been recently reported. Although depressive disorders are more common in women, the traditional view that more men than women die of suicide may therefore need revision in light of these data. High-profile cases of infanticide publicized on television have brought into the public’s awareness the role of the reproductive cycle in severe postpartum psychosis and, more generally, the high burden of all forms of depression.
in women. It is therefore relevant that psychiatric journals targeting clinicians are increasingly devoting larger space to reproductive-related mood disorders in women. Obviously, more than hormones and physiology are involved in the morbidity and mortality of women, and broader developmental and life cycle–related traumatic, social, and economic factors should be addressed in the research and clinical literature.

The suboptimal outcome of mood disorders documented in recent research reports cannot be ascribed to underdiagnosis and undertreatment alone, for several reasons. First, Gerald Klerman and colleagues suggested that the incidence of mood disorders may be increasing in younger age groups, especially in cohorts born in the 1960s, and may be associated with rising rates of alcohol and substance abuse. Second, mood disorders, once believed to be essentially adult disorders, are increasingly being diagnosed in children and adolescents. Third, clinical studies suggest higher rates of chronicity, recurrence, and refractoriness than previously believed. For instance, chronicity, reported by Emil Kraepelin to occur in no more than 5 percent of this population in the early 20th century in Germany, is now seen in varying degrees in one of three affectively ill patients. Nonetheless, outcome studies coming from university centers tend to overestimate the proportion of cases with less favorable prognosis, and, undeniably, many patients seen in private practice experience a favorable outcome. In addition, not unexpectedly, current data indicate that depressed patients treated by psychiatrists in private settings receive much better care than those in other settings.

**Concepts of Mood Disorders**

In the European tradition, the broader rubric of *affective disorder* (which subsumes mood and anxiety disorders) has been conceptualized along two influential schools. Aubrey Lewis and his followers from the Maudsley school have promoted a continuum model—from anxiety disorders to mild neurotic depressions to severe endogenous and psychotic depressions. The Newcastle school, led by Martin Roth, has sharply demarcated those conditions from one another. Although vestiges of both approaches are still influential in clinical and basic research, their significance is now overshadowed by European studies in German-speaking countries that subdivide mood disorders on the basis of polarity: unipolar (depressive episodes only) and bipolar (depressive episodes plus manic, hypomanic, or mixed episodes). That subdivision, in part supported by studies in the United States, has served as the basis for much recent research into the biology, treatment, and classification of mood disorders, and is reflected in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) and the tenth revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10). Despite such official sanction, many authorities continue to see considerable continuity between recurrent depressive and bipolar disorders. This has led to widespread discussion and debate about the bipolar spectrum (BPS), which incorporates classic bipolar disorder, bipolar II, and recurrent depressions.

Childhood bipolarity, too, is receiving increasing clinical attention, thanks to the seminal work of Elizabeth Weller and colleagues, originally conducted at Ohio State University. In addition, clinical observations at the University of Tennessee on the juvenile offspring of adult patients with bipolar disorder have led to a greater appreciation of the bipolar nature of complex clinical presentations of affective illness in the juvenile offspring and kin of adult bipolar probands. More recent work by Biederman’s group at Harvard suggests intriguing links between pediatric bipolar disorder and attention-deficit/hyperactivity disorder (ADHD).
Current concepts of mood disorders in the United States embrace a wide spectrum, including many conditions previously diagnosed as schizophrenia, personality disorder, or neurosis. The diagnostic shift occurred in part as a result of the U.S.–U.K. Diagnostic Project, which demonstrated that schizophrenia was being diagnosed at the expense of mood disorders (Fig. 13.1-1). Conceptual boundaries were further broadened by the availability of new and effective treatments and by the unacceptable risk for tardive dyskinesia and suicide in persons with misdiagnosed mood disorders. More generally, present research interest in mood disorders in the United States emanated from a landmark 1969 NIMH conference on the psychobiology of affective illnesses. The NIMH Collaborative Depression Study—a long-term prospective project deriving directly from recommendations made at the conference—has legitimatized the broader perspective.

**Morbidity and Mortality**

Unfortunately, findings published by Martin Keller and colleagues in the 1980s documenting gross undertreatment of mood disorders continue to describe the current treatment landscape worldwide. Whatever changes have occurred in diagnostic practice do not appear to have significantly affected the morbidity and mortality of mood disorders. This is all the more scandalous because the 1990s saw new classes of user-friendly antidepressant and mood-stabilizing agents, as well as depression-specific psychotherapies. Thus state of affairs results, in part, from the fact that clinical exposure to mood disorders in both specialized (psychiatric) and primary care (general medical) training is suboptimal. Mood disorders, as highly prevalent and lethal disorders, must command a greater share in the clinical curriculum of both psychiatrists and general medical practitioners. Because most mood disorders are
chronically relapsing conditions, long-term exposure to patients with these disorders in mood or bipolar clinics should be obligatory training for young doctors. Unfortunately, few academic centers have such clinics, and those that exist are largely devoted to research. The primary goal of these clinics is the execution of research protocols rather than the acquisition of clinical experience in caring for such patients.

Nearly half of all cases of depression, just like those with adult-onset diabetes, remain undetected for years or inadequately controlled—both of which seem to lag behind hypertension, in which early detection and treatment have significantly reduced complications such as stroke. Efforts by patient-advocacy organizations—often in concert with national psychiatric organizations and governmental mental health agencies—appear to be increasing public and government awareness of mood disorders. Ultimately, however, the challenge is to provide all primary care physicians with the requisite hands-on experience in caring for this prevalent group of disorders. User-friendly tools to detect suicidal patients in the general medical sector would further enhance preventive efforts. These would require significant changes in the structure of health care, including, but not limited to, the greater participation of nurses and social workers as liaisons in primary mental health and continuity of care for depressed or suicidal patients.

Because mood disorders underlie 50 to 70 percent of all suicides, effective treatment of these disorders on a national level should, in principle, drastically reduce this major complication of mood disorders. That elderly depressed patients, often with medical comorbidity, constitute the highest-risk group for suicide yet escape clinical detection and treatment is particularly problematic for public health. A small-scale prospective Swedish study undertaken by Rihmer and Rutz, although not specifically targeted to the elderly, yielded promising results in this regard. In addition, clinical findings in recurrent mood disorders have clearly shown the value of lithium prophylaxis in the prevention of suicide and overall mortality. Emerging data suggest that such benefits may accrue from all efficacious treatments for mood disorders. Suicide prevention at the national level, attributed to the widespread use of selective serotonin reuptake inhibitors (SSRIs) and primary care physician education, has been achieved in many but not all European countries. Such prevention does not have a tradition in the United States and, as mentioned earlier, suicide rates have actually increased in the United States in the last few years, from 10.5 percent to 11 percent, a net increase of 5 percent.

**DEFINITIONS**

Mood disorders encompass a large group of psychiatric disorders in which pathological moods and related vegetative and psychomotor disturbances dominate the clinical picture. Known in previous editions of DSM as *affective disorders*, the term *mood disorders* is preferred today because it refers to sustained emotional states, not merely to the external (affective) expression of the present emotional state. Mood disorders are best considered as syndromes (rather than discrete diseases) consisting of a cluster of signs and symptoms, sustained over a period of weeks to months, that represent a marked departure from a person’s habitual functioning and tend to recur, often in periodic or cyclical fashion.

**Major Depressive Disorder and Bipolar Disorder**

Major depressive disorder (MDD) (unipolar depression) is reported to be the most common mood disorder. It may manifest as a single episode or as recurrent episodes. The course may
be somewhat protracted—up to 2 years or longer—in those with the single-episode form. Whereas the prognosis for recovery from an acute episode is good for most patients with major depressive disorder three of four patients experience recurrences throughout life, with varying degrees of residual symptoms between episodes. Bipolar disorders (previously called manic-depressive psychosis) consist of at least one hypomanic, manic, or mixed episode. Mixed episodes represent a simultaneous mixture of depressive and manic or hypomanic manifestations. Although a minority of patients experience only manic episodes, most bipolar disorder patients experience episodes of both polarity. Manias predominate in men, depression and mixed states in women. The bipolar disorders were classically described as psychotic mood disorders with both manic and major depressive episodes (MDEs) (now termed bipolar I disorder), but recent clinical studies have shown the existence of a spectrum of ambulatory depressive states that alternate with milder, short-lived periods of hypomania rather than full-blown mania (bipolar II disorder). Bipolar II disorder, which is not always easily discernible from recurrent major depressive disorder, illustrates the need for more research to elucidate the relation between bipolar disorder and major depressive disorder.

The border with schizophrenia continues to be fuzzy. The Kraepelinian dichotomy of dementia praecox and manic-depressive illness has been challenged in favor of a spectrum concept that goes beyond mood-incongruent mood episodes and might spill over into “good-prognosis” schizophrenia.

**Dysthymia and Cyclothymia**

Clinically, major depressive episodes often arise from a low-grade, intermittent, and protracted depressive substrate known as dysthymic disorder (called persistent depressive disorder in DSM-5, but the terms are interchangeable). Likewise, many instances of bipolar disorders, especially ambulatory forms, represent episodes of mood disorder superimposed on a cyclothymic background, which is a biphasic alternating pattern of numerous brief periods of hypomania and numerous brief periods of depression. Dysthymic and cyclothymic disorders represent the two prevalent subthreshold mood conditions roughly corresponding to the basic temperamental dysregulations described by Emil Kraepelin and Ernst Kretschmer as predisposing to affective illness.

It is not always easy to demarcate full-blown syndromal episodes of depression and mania from their subthreshold counterparts commonly observed during the interepisodic periods. The subthreshold conditions appear to be fertile terrain for interpersonal conflicts and postaffective pathological character developments that may ravage the lives of patients and their families. In North America and some Western European countries many such patients end up being labeled with borderline personality disorder, which, unfortunately, often tends to obscure the affective origin of the presenting psychopathology.

Cyclothymic and dysthymic conditions also exist in the community without progression to full-blown mood episodes. As such, they are best considered, respectively, as trait bipolar and trait depressive conditions. Understanding the factors that mediate transition from trait to clinical state is important for preventing manic and major depressive episodes.

A fascinating development related to these temperaments pertains to the “positive” attributes of the depressive and related temperaments in subserving sensitivity to human suffering, thereby playing a role in altruistic behavior. The more tempestuous cyclothymic, based on recent data from different centers, appears to be the temperament involved in poetry, the arts,
architecture, and other forms of creative human endeavor. In other words, the “dilute” forms of affective illness may have evolved as traits of fundamental importance for human culture.

**Other Subthreshold Mood States**

Epidemiological studies in both Europe and North America have also revealed other subsyndromal conditions with depressive and hypomanic manifestations with few symptoms (oligosymptomatic mood states) and of short duration (brief episodes). Variousy referred to as *minor, subsyndromal, brief, or intermittent*, these descriptions do not merely represent arbitrary lowering of diagnostic thresholds, but they also herald increasing realization of their importance in early detection of at-risk individuals, as has happened in other medical fields (e.g., diabetes mellitus and essential hypertension). If disabling mood disorders afflict 5 to 8 percent of the general population (Epidemiologic Catchment Area [ECA] study), milder but still clinically significant mood disorders would raise lifetime rates to 17 percent (National Comorbidity Study [NCS]); if subclinical mood states are added, that figure doubles to involve one-third of the general population (as reported, e.g., by Kenneth Kendler and colleagues). New evidence from both Europe and the United States has shown that BPS conditions (bipolar I, bipolar II, and unspecified bipolar disorder in formal diagnostic manuals such as the DSM-5 and the ICD-10) may account for at least 50 percent of all mood disorders in the community and in psychiatric practice.

Comorbidity in mood disorders involves considerable overlap with anxiety disorders. As summarized in an NIMH monograph, anxiety disorders can occur during an episode of depression, may be a precursor to the depressive episode, and, less commonly, may occur during the future course of a mood disorder. Those findings suggest that at least some depressive disorders share a common diathesis with certain anxiety disorders. More recent clinical experience suggests intriguing comorbidity patterns between bipolar II disorder on one hand and panic, obsessive-compulsive, and social phobic states on the other. Furthermore, bipolar I and II disorders are particularly likely to be complicated by the use of alcohol, stimulants, or both. In many cases, the alcohol or substance abuse represents attempts at “self-treatment” of the depression and associated anxiety or insomnia (or both) and, in the case of mania and hypomania, attempts to maintain or enhance the positive moods and energy. Finally, physical illness—both systemic and cerebral—occurs in association with depressive disorders with a greater frequency than expected by chance alone. Unless properly treated, such depression negatively affects the prognosis of the physical disorder. More provocatively, there is current reawakening to the contribution of cerebral and cardiovascular factors to the origin of late-onset psychotic depressions (previously classified as *involutional melancholia*).

An integrated framework of pathogenesis is necessary for understanding psychopharmacological, somatic, and psychotherapeutic approaches in the clinical management of patients with mood disorders. A historical perspective on current developments is also a valuable lesson in the study of mood disorders.

**ANCIENT GREEK AND ROMAN DESCRIPTIONS**

Much of what is known today about mood disorders was described by the ancient Greeks and Romans, who coined the terms *melancholia* and *mania* and noted their relation. The ancients also hypothesized a temperamental origin for those disorders. Much of modern thinking about mood disorders (e.g., the work of French and German schools in the middle and latter
parts of the 19th century, which influenced current British and U.S. concepts) can be traced back to these ancient concepts.

**Melancholia**

Hippocrates (460 to 357 Before the Common Era [bce]) described melancholia ("black bile") as a state of "aversion to food, despondency, sleeplessness, irritability, and restlessness." Thus, in choosing the name of the condition, Greek physicians (who may have borrowed the concept from ancient Egyptians) postulated the earliest biochemical formulation of any mental disorder. They believed that the illness often arose from the substrate of the somber melancholic temperament, which, under the influence of the planet Saturn, made the spleen secrete black bile, ultimately leading to mood darkening through its influence on the brain.

One Hippocratic aphorism recognized the close link between anxiety and depressive states: "Patients with fear of long-standing are subject to melancholia." Hippocrates, who described the first historical case of melancholia, may have also been the first to describe a depressive mixed state, an activated form of depression:

> A woman of Thasos became morose because of a justifiable grief, and although she did not take to her bed, she suffered from insomnia, loss of appetite . . . she complained of fears and talked much; she showed despondency and . . . talked at random and used foul language . . . many intense and continuous pains . . . she leapt up and could not be restrained. [Emphasis added]

According to Galen (131 to 201), melancholia manifested in "fear and depression, discontent with life, and hatred of all persons." A few hundred years later, another Roman, Aurelianus, citing the now-lost works of Soranus of Ephesus, amplified the role of aggression in melancholia (and its link to suicide) and described how the illness assumed delusional coloring: "Animosity toward members of the household, sometimes a desire to live and at other times a longing for death, suspicion on the part of the patient that a plot is being hatched against him."

In addition to natural melancholia, which, presumably, arose from an innate predisposition to overproduce the dark humor and led to a more severe form of the malady, ancient medicine recognized such environmental contributions to melancholia as immoderate consumption of wine, perturbations of the soul due to the passions (e.g., love), and disturbed sleep cycles. Autumn was considered the season most disposing to melancholy.

**Mania**

A state of raving madness with exalted mood was noted by the ancient Greeks, although it referred to a somewhat broader group of excited psychoses than that in modern nosology. Its relation to melancholia was probably noted as early as the first century bce, but, according to Aurelianus, Soranus discounted it. Nonetheless, Soranus had observed the coexistence of manic and melancholic features during the same episode, consisting of continual wakefulness and fluctuating states of anger and merriment and, sometimes, of sadness and futility. Thus, Soranus seemed to have described what today are called mixed episodes. Natural melancholy was generally considered a chronic disorder, but Soranus noted the tendency for attacks to alternate with periods of remission.
Although others before him hinted at it, Aretaeus of Cappadocia (ca. 150) is generally credited with making the connection between the two major mood states: “It appears to me that melancholy is the commencement and a part of mania.” He described the cardinal manifestations of mania as it is known today:

> There are infinite forms of mania, but the disease is one of them. If mania is associated with joy, the patient may laugh, play, dance night and day, and go to the market crowned as if a victor in some contest of skill. The ideas the patients have are infinite. They believe they are experts in astronomy, philosophy, or poetry.

Aretaeus described the extreme psychotic excitement that could complicate the foregoing clinical picture of mania:

> The patient may become excitable, suspicious, and irritable; hearing may become sharp . . . [and they might] get noises and buzzing in the ears; or may have visual hallucinations; bad dreams and his sexual desires may get uncontrollable; aroused to anger, he may become wholly mad and run unrestrainedly, roar aloud; kill his keepers, and lay violent hands upon himself.

Noting the fluctuating nature of symptoms in the affectively ill, Aretaeus commented: “They are prone to change their mind readily; to become base, mean-spirited, illiberal, and in a little time extravagant, munificent, not from any virtue of the soul, but from the changeableness of the disease.” Aretaeus was thus keenly aware of the characterological distortions so commonly manifested during the different phases of cyclical mood disorders.

Finally, consolidating the knowledge of several centuries, Aretaeus described mania as a disease of adolescent and young men given intermittently to “active habits, drunkenness, lechery” and an immoderate lifestyle (what today might be called *cyclothymic disorder*). Exacerbations were most likely to occur in the spring.

**Affective Temperaments**

The concept of health and disease in ancient medicine was based on harmony and balance of the four humors, of which sanguine humor was deemed the healthiest. Even a desirable humor, however, such as blood, which made persons habitually active, amiable, and prone to jest, could, in excess, lead to the pathological state of mania. The melancholic temperament, dominated by black bile and predisposed to pathological melancholia, was described as lethargic, sullen, and given to brooding or contemplation; its modern counterpart might be persistent depressive disorder as defined in DSM-5. A long tradition dating back to Aristotle (384 to 322 bce) attributed creative qualities to the otherwise tortured melancholic temperament in such fields as philosophy, the arts, poetry, and politics. The remaining two temperaments—choleric and phlegmatic—were less desirable, in that yellow bile made persons choleric (irritable, hostile, and given to rage) and phlegm made them phlegmatic (indolent, irresolute, and timid). The choleric and phlegmatic temperaments would probably be recognized today as borderline personality disorder and avoidant or schizoid personality disorder, respectively.

Many of the original Greek texts on melancholia were transmitted to posterity through medieval Arabic texts such as those of Ishaq Ibn Imran and Avicenna (and their Latin renditions by Constantinus Africanus). In describing different affective states, Avicenna developed the theory of the temperaments to its fullest. He speculated that a special form of melancholia supervened “if black bile be mixed with phlegm,” when the illness was “coupled
with inertia, lack of movement, and quiet.” Furthermore, mania was not necessarily linked to the sanguine (what today is termed hyperthymic) temperament, in that many forms of excited madness were believed to represent a mixture of black and yellow bile.

Avicenna further observed that the mixture of anger and restlessness in melancholia indicated that the disease was manic in nature and that the appearance of such signs and symptoms along with violence heralded the transition from melancholia to mania. Those elaborations on Galen’s temperamental types might be considered the forerunners of current personality dimensions, deriving mood states from various mixtures of neuroticism and introversion-extroversion. (What both the ICD-10 and the DSM-5 describe as cyclothymic disorder represents the intense mood lability of high neuroticism coupled with cyclic alternation between extroversion and introversion.) Speculation on how diverse depressive phenomena could be understood as a mix of humors anticipated modern multiple-transmitter hypotheses of depression. Ishaq Ibn Imran summarized the existing knowledge of melancholia by considering the interaction of genetic factors (“injured prenatally as the result of the father’s sperm having been damaged”) with a special temperament given to “mental overexertion”—although not necessarily physical overactivity—that, in turn, was associated with “disruption of the correct rhythms of sleeping and waking.” Those views, too, have a very modern ring to them.

MODERN ERA

The first English text (Fig. 13.1-2) entirely devoted to affective illness was Robert Burton’s Anatomy of Melancholy, published in 1621. A scholarly review of medical and philosophical wisdom accumulated in past centuries, it also anticipated many modern developments. The concept of affective disorder endorsed by Burton was rather broad (as it always has been in the United Kingdom), embracing mood disorders and many disorders that are today considered somatoform disorders, including hypochondrias. Although he described “causeless” melancholias, Burton also categorized the various forms of love melancholy and grief. Particularly impressive was his catalogue of causes, culminating in a grand conceptualization:

> Such as have Saturn misaffected in their genitures such as are born of melancholy parents as offend in those six non-natural things, are of a high sanguine complexion, are solitary by nature, great students, given to much contemplation, lead a life out of action, are most subject to melancholy. Of sexes both, but men more often. Of seasons of the year, autumn is most melancholy. Jobertus excepts neither young nor old.
Burton’s six non-natural things referred to such environmental factors as diet, alcohol, biological rhythms, and perturbations induced by passions such as intense love. Burton did not definitively indicate age prevalences. Like nearly all of his predecessors, he favored male (rather than the currently reported female) preponderance.

Finally, Burton considered both the melancholic (contemplative) and the sanguine (hot-blooded) temperaments to be substrates of melancholia. Burton’s work thus linked certain forms of depression with the softer expressions of the manic disposition, or bipolar II disorder, from which he appears to have suffered.

The 18th and 19th centuries introduced humane hospital care of the mentally ill, thereby permitting systematic clinical observation of the psychopathology and outcome of mood disorders.
Concept of Affective Disorder

Although Celsus (ca. 30) had described “forms of madness that go no further than sadness,” the French alienist Jean-Philippe Esquirol (1840) may have been the first psychiatrist in modern times to suggest that a primary disturbance of mood might underlie many forms of depression and related paranoid psychoses. Until Esquirol’s work, melancholia had been categorized as a form of insanity (i.e., ascribed to deranged reasoning or thought disturbance). Esquirol’s observations on melancholic patients led him to postulate that their insanity was partial (dominated by one delusion, a monomania) and that “the symptoms were the expression of the disorder of the affections. The source of the evil is in the passions.” He coined the term lypemania (from the Greek, “sorrowful insanity”) to give nosological status to a subgroup of melancholic disorders that were affectively based. Esquirol cited Benjamin Rush (1745 to 1813), the father of American psychiatry, who had earlier described tristimania, a form of melancholia in which sadness predominated.

Esquirol’s influence led other European psychiatrists to propose milder states of melancholia without delusions, which were eventually categorized as simple melancholias and, ultimately, as primary depressions. Such descriptions culminated in the Anglo-Saxon psychiatric term affective disorder, coined by Henry Maudsley (1835 to 1918), the renowned British psychiatrist after whom a London hospital is named.

Manic-Depressive Illness and the Question of Psychogenic Depressions

Although the connection between mania and depression had been rediscovered sporadically since it was first described 2,000 years ago, the clinical work that finally established circular insanity (Jean-Pierre Falret’s term) and folie à double forme (Jules Baillarger’s term) as discrete nosological entities with both depressive and manic poles was undertaken by these two Esquirol disciples in the 1850s. That accomplishment built on Philippe Pinel’s reforms, which championed humane treatment of the mentally ill in Paris around the turn of the 18th century and emphasized systematic clinical observations of patients, which were detailed in case records. French alienists made longitudinal observations on the same patient from one psychotic attack into another. Furthermore, Esquirol had introduced the practice of chronicling events in statistical tables. Thus, the Hippocratic approach to defining a particular case by its onset, circumstances, course, and outcome was applied by French alienists in studying the affectively ill. The humanitarian reforms introduced in the 19th century ensured that standards of general health and nutrition would improve the outlook for the mentally ill—especially those with potentially reversible disorders such as affective disorders, who could now be discharged from the asylums. The French school, by segregating the nondeteriorating mood disorders from other types of insanity, then paved the way for the Kraepelinian system.

Kraepelin’s (1856 to 1926) unique contribution was not so much his grouping together of all the forms of melancholia and mania, but his methodology and painstaking longitudinal observations, which established manic-depressive illness as a nosological entity and (he hoped) a disease entity. His rationale was based on the following: (1) the various forms had a common heredity measured as a function of familial aggregation of manic and depressive cases, (2) frequent transitions from one to the other occurred during longitudinal follow-up of patients, (3) a recurrent course with illness-free intervals characterized most cases, (4) the superimposed episodes were commonly opposite to the patient’s habitual temperament—that is, mania could be superimposed on a depressive temperament and depression on a
hypomanic temperament—and (5) both depressive and manic features could occur during the same episode (mixed states). Kraepelin’s synthesis was developed as early as the sixth (1899) edition of his Lehrbuch der Psychiatrie and most explicitly stated in the opening passages of the section on manic-depressive psychosis in the eighth edition (published in four volumes, 1909 to 1915):

Manic-depressive insanity includes on the one hand the whole domain of so-called periodic and circular insanity, on the other hand simple mania, the greater part of the morbid states termed melancholia and also a not inconsiderable number of cases of confusional insanity. Lastly, we include here certain slight and slightest colorings of mood, some of them periodic, some of them continuously morbid, which on the one hand are to be regarded as the rudiment of more severe disorders, on the other hand, pass over without boundary into the domain of personal predisposition.

For Kraepelin, the core pathology of clinical depression consisted of lowered mood and slowed (retarded) physical and mental processes. In mania, by contrast, the mood was elated, and physical and mental activity were accelerated. His earlier observations on what he termed involutional melancholia (referring to 40- to 65-year-old patients with extreme anxiety, irritability, agitation, and delusions) had led him to separate that entity from the broader manic-depressive rubric. In the eighth edition of Lehrbuch der Psychiatrie, however, he united melancholia with the manic-depressive group, with the justification that it was a special form of mixed state and that follow-up conducted by his pupil Dreyfus had demonstrated unmistakable excited phases.

The classification of mood disorders is still evolving. Karl Leonhard in 1957, Jules Angst in 1966, Carlo Perris in 1966, and George Winokur, Paula Clayton, and Theodore Reich in 1969, working independently in four different countries, proposed that depressive disorders without manic or hypomanic episodes (unipolar depressive disorder) that appear in middle age and later are distinct from depressive episodes that begin at earlier ages and alternate with manic or hypomanic episodes (bipolar disorder). The main difference between the two affective subtypes is the greater familial loading for mood disorder—especially for bipolar disorder—among bipolar disorder probands.

Kraepelin had conceded the occurrence of psychogenic states of depression occasioned by situational misfortune. However, he believed that manic-depressive illness was hereditary, although he could not document postmortem anatomopathological findings in the brains of manic-depressive patients. Therefore, manic-depression had to be considered a functional mental disorder in which brain disturbances were presumed to lie in altered physiological functions. Such biological factors were deemed absent in the psychogenic depressions. Thus, Kraepelin’s classification of mood disorders is both dualistic and unitary. It is dualistic to the extent that he designated them as either psychologically occasioned or somatically caused. It is unitary with respect to disorders in the latter group, which have been termed endogenous affective disorders (i.e., due to internal biological causes). In other words, Kraepelin restricted the concept of clinical depression to what the DSM-5 terms major depressive disorder with melancholic features. Moreover, he postulated a continuum between that condition and what the DSM-5 and the ICD-10 now term bipolar disorders.

Cartesian thinking in 17th-century France conceptually separated mind from body, thereby providing physicians autonomy over the somatic sphere, free from interference by the Church. The dichotomous paradigm ensured that the study of the two aspects of the human organism would not be confounded by the complexities of mind–body interactions. That is one reason Kraepelin’s descriptive observations have proved valuable to subsequent
generations of clinicians. Furthermore, his approach exemplifies the best tradition of scientific humanism in medicine: Description and diagnostic categorization of an individual patient are necessary for the physician to apply the knowledge gained from past observation of similarly described and diagnosed patients. One limitation to the Kraepelinian approach is that because of its biological reductionism, it is not sufficiently articulate to account for mind–body interactions in the genesis of mental disorders.

Depressions as Psychobiological Affective Reaction Types

It was the ambition of Swiss-born Adolf Meyer (1866 to 1950) to bridge the divide between psyche and soma. Meyer, who dominated psychiatry from his chair at Johns Hopkins University during the first half of the 20th century, coined the term psychobiology to emphasize that both psychological and biological factors could enter into the causation of depressive and other mental disorders. Because of the nascent state of brain science during Meyer’s time, he was more adept at biography than biology and therefore paid greater attention to psychosocial causation. He preferred the term depression (pressed down) to melancholia because of its lack of biological connotation. He conceived of depressive states in terms of unspecified constitutional or biological factors interacting with a series of life situations beginning at birth or even at conception. From that viewpoint arose the unique importance accorded personal history in depressive reactions to life events.

Meyer’s terminological revision left a somewhat confusing legacy, in that the term depression is now applied to a broad range of affective phenomena ranging from sadness and adjustment disorders to clinical depression and bipolar disorders. Nosological nuances to which Meyerians paid little attention, such as the difference between melancholic depression and more mundane depressions, are not just a matter of semantics. To the extent that those two forms of depression are seen in different clinical settings, hypotheses based on one population may not apply to the other. For instance, uncontrollable traumatic events may have taught study participants to feel helpless or to view the world in a negative light, but that does not equate with clinical depression; nor does the process appear to be specific to depression. Failure to make such nosological distinctions further clouds interpretations of the results of trials comparing psychotherapy and pharmacotherapy for depressive disorders.

On the other hand, the Meyerian emphasis on biographical factors for the patient represented a more practical approach to depth psychology. Recent sociological interpretations of depression can also be traced to Meyer’s work. In final analysis, however, the Meyerian concern for the uniqueness of the individual has proved heuristically sterile. It de-emphasizes what is diagnostically common to different individuals, thereby obscuring the relevance of accrued clinical wisdom for the index patient. For that reason, the Meyerian approach, after enjoying clinical popularity for several decades in North America, has given way to neo-Kraepelinian rigor. However, the psychobiological vision of bridging biology and psychology, one of the major preoccupations of psychiatric thought and research today, owes much to Meyer’s legacy.
CONTEMPORARY MODELS OF DEPRESSION

Aggression-Turned-Inward Model

Sigmund Freud was initially interested in a psychoneural project for all mental phenomena. Limitations of the brain sciences of the day led him to adopt instead a model that relied on a concept of mental function borrowed from physics. The notion that depressed affect is derived from retroflexion of aggressive impulses directed against an ambivalently loved internalized object was actually formulated by his Berlin disciple Karl Abraham and later elaborated by Freud. Abraham and Freud hypothesized that turned-inward anger was intended as punishment for the love object that had thwarted the depressed patient’s need for dependency and love. Because, in an attempt to prevent the traumatic loss, the object had already been internalized, the patient then became the target of his or her own thanatotic impulses. A central element in those psychic operations was the depressed patient’s ambivalence toward the object, which was perceived as a frustrating parent. Aggression directed at a loved object (parent) was therefore attended by considerable guilt. In the extreme, such ambivalence, guilt, and retroflexed anger could lead to suicidal behavior.

According to this model, depression is an epiphenomenon of the transduction of thanatotic energy, a reaction that takes place in the closed hydraulic space of the mind. Freud’s earlier writings had similarly portrayed anxiety as being derived from the transformation of dammed-up sexual libido. Although Freud envisioned that psychoanalytic constructs would one day be localized neuroanatomically, the hydraulic mind is a metaphor that does not refer to actual physiochemical space in the brain.

The concept of emotional behavior as an arena of incompatible forces confined to a psyche that is relatively impervious to current influences outside of the organism is the major liability of the aggression-turned-inward model and, perhaps, of orthodox psychoanalysis itself. Although the sexual-energy-transduction hypothesis of anxiety has been discarded in modern psychoanalytic thought, in modified versions, the aggression-turned-inward model continues to be used in clinical conceptualization. The lingering popularity of the model may be due, in part, to its compatibility with the clinical observation that many depressed patients suffer from lack of assertion and outwardly directed aggressiveness. However, a substantial number of hostile, depressed patients are also encountered in clinical practice (indeed, “depression with anger attacks” has been recently described), and clinical improvement in most patients typically leads to decreased, not increased, hostility. Such observations shed doubt on the aggression-turned-inward mechanism as a universal explanation for depressive behavior. Finally, little evidence exists to support the contention that outward expression of anger has therapeutic value in clinical depression.

Outwardly directed hostility in depression is not a new clinical observation; in fact, ancient Greek and Roman physicians had noted it. Hostility is best considered a manifestation rather than a cause of depressive disorder, especially when the disorder is attended by mixed bipolar features. The hostility of the depressed patient can also be understood as an exaggerated reaction to frustrating love objects, as secondary to self-referential attribution, or simply as nonspecific irritability of an ego in affective turmoil; this could, in part, be a function of a concurrent personality disorder from the erratic cluster. Such commonsense explanations that do not invoke unobservable hydraulic transmutations have greater appeal from heuristic and clinical perspectives.
Object Loss and Depression

Object loss refers to traumatic separation from significant objects of attachment. Ego-psychological reformulations of the Abraham–Freud conceptualization of depression have paid greater attention to the effect of such losses on the ego, de-emphasizing the id-libidinal and related hydraulic aspects. The depressant effect of separation events often resides in their symbolic meaning for a person rather than in any arbitrary objective weight that the event may have for clinical raters. However, love loss, bereavement, and other exits from the social scene, as defined by the London psychiatrist Eugene Paykel, are presently the concepts most commonly used in practice and research.

Although love melancholy had been described since antiquity, the two affective states were systematically compared for the first time in Freud’s 1917 paper on mourning and melancholia. According to current data, the transition from grief to pathological depression occurs in no more than 10 percent of adults and 20 percent of children. These figures suggest that such transition occurs largely in persons predisposed to mood disorders.

John Bowlby of the Tavistock Clinic, London, did a comprehensive clinical investigation of the attachment that the child establishes with the mother or mother substitutes during development, a bond considered the prototype for all subsequent bonds with other objects. Like many psychoanalytic explanations of adult symptom formation, the object loss model is formulated as a two-step hypothesis, consisting of early breaks in affectional bonds, which provide the behavioral predisposition to depression, and adult losses, which are said to revive the traumatic childhood loss and so precipitate depressive episodes. However, the role of proximate separations in provoking depressive reactions rests on more solid clinical evidence than the hypothesized sensitization resulting from developmental object loss. That realization led Bowlby to regard childhood sensitization resulting from early deprivation as a generic characterological vulnerability to a host of adult psychopathological conditions.

Compared with aggression turned inward, object loss is more directly relevant to clinical depression, yet it is still pertinent to question whether it is an etiological factor. Studies at the Wisconsin Primate Center indicated that optimal homeostasis with the environment is most readily achieved when the individual is securely attached to significant others, and the dissolution of such ties appears to be relevant to the emergence of a broad range of psychopathological disturbances rather than depression per se. A related methodological question is whether object loss operates independently of other etiological factors. For instance, a history of early breaks in attachment may reflect the fact that one or both of the patient’s parents had mood disorder, with resultant separation, divorce, suicide, and so forth.

On balance, the ego-psychological object loss model is conceptually superior to its id-psychological counterpart. In postulating an open system of exchange between a person and the environment, the model permits consideration of etiological factors other than separation, such as heredity, character structure, and adequacy of social support—all of which might modulate the depressant effect of adult separation events. Conceptualizing the origin of depression along those lines is in the mainstream of current ideas of adaptation, homeostasis, and disease. An important treatment implication is the value of social support in preventing relapse and mitigating chronicity of depression. That is, indeed, an ingredient in the interpersonal psychotherapy of depression, which can be conceptualized as a form of brief, focused, and practical psychodynamic therapy.
Loss of Self-Esteem and Depression

Reformulation of the dynamics of depression in terms of the ego suffering a collapse of self-esteem represents a further conceptual break with the original id-psychological formulation; depression is said to originate from the ego’s inability to give up unattainable goals and ideals. The model further posits that the narcissistic injury that crushes the depressed patient’s self-esteem is imposed by the internalized values of the ego rather than the hydraulic pressure of retroflected thanatotic energy deriving from the id. Because the construct of the ego is rooted in social and cultural reality, loss of self-esteem may result from symbolic losses involving power, status, roles, identity, values, and purpose for existence. Thus, the existential and sociocultural implications of depression conceived as a derivative ego state provide the clinician with a far more flexible and pragmatic tool for understanding depressed persons than the archaic hydraulic metaphors related to libidinal vicissitudes. That model represents one of the first attempts to formulate depression in terms that subsequent psychological theory and research could operationalize in more testable form.

Self-esteem is part of the habitual core of the individual and, hence, is integral to the personality structure. Indeed, low self-esteem conceived as a trait is a major defining attribute of the depressive (melancholic) personality. Although it is understandable that such individuals can easily sink into melancholia in the face of environmental adversity, it is not obvious why persons with apparently high self-esteem (e.g., those with hypomanic and narcissistic personalities) also succumb to melancholy with relative ease. To explain such cases, one must invoke an underlying instability in the system of self-esteem that renders it vulnerable to depression. The opposite is also known to occur; that is, manic episodes may develop from a baseline of low self-esteem, as in the case of bipolar disorder patients with antecedent traits of shyness, insecurity, and dysthymia.

The foregoing considerations suggest that the vicissitudes of self-esteem deemed central to the model of depression as loss of self-esteem are manifestations of a more fundamental mood dysregulation. In classic psychoanalysis, such dysregulation is considered to be of constitutional origin. In general, attempts by psychoanalytic writers to account for bipolar oscillations have not progressed beyond metapsychological jargon, with the notable exception of denial of painful affects as a mechanism in the phenomenology of mania.

Cognitive Model

The cognitive model, developed by Aaron Beck at the University of Pennsylvania, hypothesizes that thinking along negative lines (e.g., thinking that one is helpless, unworthy, or useless) is the hallmark of clinical depression. In effect, depression is redefined in terms of a cognitive triad, according to which patients think of themselves as helpless, interpret most events unfavorably vis-à-vis the self, and believe the future to be hopeless. In more recent formulations in academic psychology, these cognitions are said to be characterized by a negative attributional style that is global, internal, and stable and that exists in the form of latent mental schemata that generate biased interpretations of life events.

Because the cognitive model is based on retrospective observations of already depressed persons, it is virtually impossible to prove that causal attributions such as negative mental schemata precede and, therefore, predispose to clinical depression; they can just as readily be regarded as subclinical manifestations of depression. The theoretical importance of the cognitive model lies in the conceptual bridge it provides between ego-psychological and
behavioral models of depression. It has also led to a new and widely accepted system of psychotherapy that attempts to alter the negative attributional style, to alleviate the depressive state, and, ultimately, to fortify the patient against future lapses into negative thinking, despair, and depression.

The cognitive model, therefore, has the cardinal virtue of focusing on key reversible clinical dimensions of depressive illness, such as helplessness, hopelessness, and suicidal ideation, while providing a testable and practical psychotherapeutic approach. That approach, however, is less likely to succeed in patients with the full-blown melancholic manifestations of a depressive disorder. It is doubtful that negative cognitions alone could account for the profound disturbances in sleep, appetite, and autonomic and psychomotor functions encountered in melancholic depressions. Furthermore, conceptualizing a multifaceted malady such as depression largely or solely as a function of distorted cognitive processes is reminiscent of pre-Esquirolian notions that emphasized impaired reasoning in the development of depression. Finally, recent extensions or modifications, or both, of cognitive therapy in association with behavioral therapy (cognitive–behavioral therapy) for all emotional disorders (and even for schizophrenia) are reminiscent of earlier global claims of the psychodynamic perspective.

**Learned Helplessness Model**

The learned helplessness model is, in some ways, an experimental analogue of the cognitive model. The model proposes that the depressive posture is learned from past situations in which the person was unable to terminate undesirable contingencies. The model is based on experiments in dogs that were prevented from taking adaptive action to avoid unpleasant electrical shock and subsequently showed no motivation to escape such aversive stimuli, even when escape avenues were readily available. Armed with evidence from many such experiments, University of Pennsylvania psychologist Martin Seligman postulated a trait of learned helplessness (a belief that it is futile to initiate personal action to reverse aversive circumstances) formed from the accumulation of past episodes of uncontrollable helplessness.

The learned helplessness paradigm is a general one and refers to a broader mental disposition than depression. Thus, it is potentially useful in understanding such diverse conditions as social powerlessness, defeat in sporting events, and posttraumatic stress disorder (PTSD). In addition, past events might shape a characterological cluster—consisting of passivity, lack of hostility, and self-blame—relevant to certain depressive phenomena. The low hostility observed in some patients during clinical depression could, for instance, be ascribed to the operation of such factors. Learned helplessness could thereby provide plausible links between aspects of personal biography and clinical phenomenology in depressive disorders. Therapeutic predictions for alleviating depression and related psychopathological states capitalize on new cognitive strategies geared to modifying expectations of uncontrollability and the negative attributional style. This illustrates how insights gained from experimental paradigms can be combined fruitfully to address clinical disorders.

Nonetheless, the clinician should be wary of unwarranted clinical extrapolations. For example, some therapists have argued that the depressed patient’s passivity is “manipulative,” serving to obtain interpersonal rewards. It has also been suggested that such factors have a formative influence on the development of the depressive character. That interpretation appears more relevant to selected aspects of depression than to the totality of
the disorder. Depressive behavior and verbalizations clearly have a powerful interpersonal impact, but casting depression as merely a masochistic lifestyle developed to secure interpersonal advantages represents a mechanistic circular argument that could be viewed as disrespectful of the clinical agony of patients with mood disorders. Finally, although most formulations focusing on helplessness have emphasized acquisition through learning, recent experimental research in animals tends to implicate genetic factors in the vulnerability of learning to behave helplessly. The value of the helplessness paradigm may reside in its utility in predicting a variety of subthreshold affective disturbances generic to civilian reactions to adversity and trauma.

**Depression and Reinforcement**

Other behavioral investigators, including, notably, psychologist Peter Lewinsohn, have developed clinical formulations of depression that hinge on certain deficits in reinforcement mechanisms. According to the reinforcement model, depressive behavior is associated with lack of appropriate rewards and, more specifically, with receipt of noncontingent rewards. The model identifies several contributory mechanisms. Some environments may consistently deprive persons of rewarding opportunities, thereby placing them in a chronic state of boredom, pleasurelessness, and, ultimately, despair. That reasoning, however, may offer more insight into social misery than clinical depression. A more plausible postulated mechanism is the provision of rewards that are not in response to the recipient’s actions; in other words, the gratis provision of what a person considers undeserved rewards may lead to lowering of self-esteem. Predisposition to depression is formulated in terms of inadequate social skills, which are hypothesized to decrease a person’s chances of responding to potentially rewarding contingencies in the environment. Indeed, recent research on the relationship between personality and depression suggests that such deficits might underlie certain depressive states. Therefore, psychotherapeutic approaches designed to enlarge a patient’s repertoire of social skills may prove valuable in preventing some types of depression.

The concepts of depression that have been derived from behavioral methodology and developed in the last several decades are scientifically articulate and, therefore, testable approaches to clinical depression. However, the important distinction between depression on self-report inventories and clinical depression tends to be overlooked in investigations testing the reinforcement paradigm. Furthermore, the behavioral model does not address the distinct possibility that reinforcement deficits may, in part, represent the psychomotor deficits of depressive illness. Nevertheless, by focusing on reward mechanisms, the behavioral model provides a conceptual bridge between purely psychological and emerging biological conceptualizations of depression.

**Biogenic Amine Imbalance**

The formulation of sophisticated biological explanations of mood disorders had to await the development of neurobiological techniques that could probe the parts of the brain involved in emotions. Although the complex physiology of the limbic-diencephalic centers of emotional behavior generally cannot be directly observed in humans, much has been learned from animal work. The limbic cortex is linked with both the neocortex, which subserves higher symbolic functions, and the midbrain and lower brain centers, which are involved in autonomic control, hormonal production, and sleep and wakefulness. Norepinephrine-containing neurons are involved in many functions that are profoundly disturbed in
melancholia, including mood, arousal, appetite, reward, and drives. Other biogenic amine neurotransmitters that mediate such functions are the catecholamine dopamine—especially important for drive, pleasure, sex, and psychomotor activity—and the indoleamine serotonin, which is involved in the regulatory control of affects, aggression, sleep, and appetite. Cholinergic neurons, secreting acetylcholine at their dendritic terminals, are generally antagonistic in function to catecholaminergic neurons.

Although the opioid system might, on experimental and theoretical grounds, also serve as one of the neurochemical substrates for mood regulation, no cogent model of mood disorders involving that system has appeared. Likewise, biochemical formulations of mood disorders have paid relatively little attention to the major excitatory brain neurotransmitter glutamate and the inhibitory neurotransmitter γ-aminobutyric acid (GABA).

**Biogenic Amine Hypotheses.** Joseph Schildkraut at Harvard University and William Bunney and John Davis at NIMH published the first formal hypothesis connecting depletions or imbalances of biogenic amines (specifically norepinephrine) and clinical depression. The serotonin counterpart of the model was emphasized in the models proposed by Alec Coppen in England and I. P. Lapin and G. F. Oxenkrug in Russia. Both catecholamine and indoleamine hypotheses were essentially based on two sets of pharmacological observations. First, reserpine (Serpasil), which decreases blood pressure by depleting biogenic amine stores, precipitates clinical depression in some patients. Second, antidepressant medications, which alleviate clinical depression, raise the functional capacity of the biogenic amines in the brain. This style of thinking is known as the *pharmacological bridge*, extrapolating from evidence on the mechanism of drug action to the neurotransmitter pathologies presumed to underlie a given psychiatric disorder. Such pharmacological strategies have been of heuristic value in developing research methods for the investigation of mood disorders and schizophrenia. Indeed, the research methodology developed by the relatively few investigators working in this area during the last half century is among the most elegant in the history of psychiatry.

Variations of the biogenic amine model assign somewhat different relative weights to the biogenic amines norepinephrine and serotonin in the development of pathological mood states. Arthur Prange and colleagues at the University of North Carolina formulated a permissive biogenic amine hypothesis in which serotonin deficits permit the expression of catecholamine-mediated depressive or manic states. That hypothesis was supported by subsequent animal research showing that an intact serotonin system is necessary for optimal functioning of noradrenergic neurons. Omission of tryptophan from the diet of antidepressant-responsive depressed patients may annul the efficacy of the antidepressant; among healthy volunteers, that special diet also induces sleep electroencephalographic characteristics of clinical depression. Although such findings are provocative, the precursor-loading strategy to increase the brain stores of serotonin (e.g., with l-tryptophan) has not been unequivocally successful in reversing clinical depression. Dietary loading with catecholamine precursors has fared even worse than serotonin-precursor loading in the treatment of depression.

The cholinergic–noradrenergic imbalance hypothesis proposed by David Janowsky and colleagues represents yet another attempt to elucidate the roles of biogenic amines. This hypothesis, along with the related cholinergic supersensitivity hypothesis developed by J. Christian Gillin, has been tested extensively at the University of California at San Diego. Subsequent formulations by Larry Siever and Kenneth Davis at the Mount Sinai Hospital in
New York have refocused on noradrenergic dysregulation. The model assumes oscillation from one output mode to the other at different phases of depressive illness. In a provocative extrapolation from that model, bipolar depression would have low noradrenergic output, but many instances of major depressive disorder as with some anxiety disorders, could be biochemically conceptualized as high-output conditions.

Despite more than four decades of extensive research and indirect evidence, however, no deficiency or excess of biogenic amines in specific brain structures has been shown to be necessary or sufficient for the occurrence of mood disorders. It has not been possible either to confirm the putative role of central norepinephrine in depression or to discard it altogether. The role of dopamine as formulated, among others, by the Italian pharmacologist Gian Luigi Cessa, although studied less extensively than that of norepinephrine, deserves greater recognition, in that it might have relevance to atypical and bipolar depression, as well as to mania.

Preliminary data from a small brain imaging study has shown blunted serotonin responsivity in prefrontal and temporoparietal areas in unmedicated patients with major depressive disorder. Such data, considered in the context of the overall serotonin literature in depression, are provocative but not conclusive and serves to illustrate the fact that the case for serotonergic disturbance in depression continues to be based on indirect evidence. Moreover, the putative permissive role of serotonin is better documented for aggressive suicide attempts. Serotonergic dysfunction might subserve other conditions characterized by lack of inhibitory control, among them obsessive-compulsive disorder (OCD), panic disorders, bulimia nervosa, certain forms of insomnia, alcoholism (alcohol abuse or dependence), and a host of impulse-ridden personality disorders. Such considerations have led Dutch psychiatrist Herman van Praag and colleagues to postulate a dimensional neurochemical disturbance generic to a large group of disorders within the traditional nosology. This hypothesis might be variously regarded as a challenge to psychiatric nosology or as a statement of the need to supplement clinical classification with biochemical parameters. Both interpretations are in line with clinical observations during the last two decades testifying to the high prevalence of comorbidity in depressive, other emotional disorders, and certain impulse-control disorders.

It is implied that the foregoing postulated biochemical faults are genetically determined. Although biogenic amine models of mood disorders were developed retrospectively from the pharmacological action of antidepressant and thymoleptic agents, they have stimulated the development of new classes of antidepressants with more selective action on specific neurotransmitter receptors. Their introduction has virtually revolutionized the treatment of depression. Yet the fundamental biochemistry of mood disorders is still far from being understood. Curiously, although selective in action, the new compounds working on the serotonin system have broad effectiveness in a variety of mood-related conditions, such as dysthymic disorder, PTSD, OCD, panic disorder, social phobia, bulimia nervosa, and borderline personality disorder. Such data indirectly favor the hypothesis of an underlying biological commonality to several of these disorders. The foregoing considerations have, in turn, led to a provocative formulation of an increasingly prevalent “social syndrome” in populations experiencing social disruption, immigration, and abuse and characterized by anxiety, depression, violence-proneness, impulsivity, and suicidality—reflecting a perturbed serotonin system, the oldest, most basic brain structure involved in human socialization and territoriality, coping with stress, danger, and survival.
New antidepressants with dual action on both serotonergic and noradrenergic receptors and emerging data on their possible greater efficacy in melancholic depressions suggest that the biochemistry of mood disorders involves more complex dysregulation than is implied in single-neurotransmitter hypotheses. The work of George Henninger and colleagues at Yale University further suggests that monoamines better explain how antidepressants facilitate recovery from depression than their being the fundamental causes of depression. Moreover, emerging biochemical paradigms are moving away from distal biochemical lesions to focus on molecular perturbations closest to the putative genetic underpinnings of mood disorders. Originally tied to the mechanism of action of mood stabilizers in bipolar disorder, such work is exploring second messenger systems, phosphorylation G proteins, signal transduction, DNA transcription, and messenger RNA translation. Again, such search for molecular mechanisms represents “backward logic” from the putative mechanism of action of selected thymoleptic agents. The same can be said about Frederick Petty’s GABAergic and Shih-Jen Tsai’s brain-derived neurotrophic factor (BDNF) hypothesis on the origin of bipolar disorder.

**Neuroendocrine Links.** Functionally inadequate mobilization of neurotransmitters in the face of continued or repeated stress, as indirectly reflected in pathological modification of noradrenergic and serotonergic receptor function, could represent neurochemical final common pathways of homeostatic failure. Such mechanisms could also provide links with psychoendocrine dysfunction; the hypothesized neurotransmitter deficits may underlie the disinhibition of the hypothalamic–pituitary–adrenal axis, characterized by steroidal overproduction, the most widely studied endocrine disturbance in depressive illness. When challenged with dexamethasone (Decadron), the altered axis resists suppression, which offered Bernard Carroll’s team (then at the University of Michigan) the possibility of developing the dexamethasone-suppression “test” (DST) for melancholia. This procedure is of uncertain specificity for depressive illness and, thus, is unsuitable to serve as a diagnostic test. However, that line of research has been useful in pathogenetic understanding. For instance, it led to the demonstration by Emory University’s Charles Nemeroff of increased concentrations of corticotropin-releasing factor (CRF) in the cerebrospinal fluid (CSF) of patients with major depressive disorder. CRF also appears relevant to the pathophysiology of anxiety disorders, such as panic disorder, and PTSD. The research of Florian Holsboer’s group at Munich’s Max Planck Institute has shown impaired glucocorticoid and mineralocorticoid receptor function in these disorders, with relevant pathophysiological and therapeutic implications.

Another neuroendocrine index of noradrenergic dysregulation, blunted growth hormone response to the α2-adrenergic receptor agonist clonidine (Catapres), likewise points to limbic-diencephalic disturbance. However, studies performed in the United States suggest that it is positive in both endogenous depression and severe anxiety disorder (panic disorder). Thyroid-stimulating hormone (TSH) blunting on thyrotropin stimulation, another common neuroendocrine disturbance in depression, also shows limited specificity.

What is remarkable, however, is that the DST, clonidine, and thyrotropin challenge data, in aggregate, identify most persons with clinical depression. Such evidence of midbrain disturbance argues for considering clinical depression to be a legitimate disease. The disease concept of depression is further buttressed by computed tomography (CT) scans showing enlarged pituitary and adrenal glands, a state marker of depressive illness.

**Stress and Depression.** The concept of a pharmacological bridge implies two-way traffic. The hypothesized chemical aberrations may be primary or genetically based. Provision
should also be made, however, for the likelihood that psychological events that precipitate clinical depression might initiate or exacerbate neurochemical imbalance in vulnerable subjects. That suggestion is supported by studies in animals in which early separation from peers and inescapable frustration effect profound alterations in the turnover of biogenic amines and in postsynaptic receptor sensitivity. Thus, in genetically predisposed persons, environmental stressors might more easily lead to perturbations of limbic-diencephalic neurotransmitter balance. Finally, in vulnerable individuals, especially during the formative years of childhood, psychological mechanisms might more easily perturb midbrain neurochemistry. Traumatic experiences appear particularly potent in this regard. The hippocampus has been the subject of intense recent research as the possible neuroanatomical substrate linking such loss and trauma to adult depression. Ongoing ingenious experimental paradigms in primates and rodents continue to explore the role of early experience and stress in subsequent depressive-like behaviors in these animals. In humans, a new provocative finding indicates that a polymorphism of the serotonin transporter gene would identify who among traumatized children would develop adult depression. Likewise, a polymorphism of the monoamine oxidase (MAO), a gene plays a significant role in determining who among battered children will grow into an adult sociopath. Animal models of mania are sparse and problematic.

**Neurophysiological Approaches**

**Neuronal Hyperexcitability.** Lithium is known to replace intracellular sodium and hyperpolarize the neuronal membrane, thereby decreasing neuronal excitability. Abnormalities in neuronal electrolyte balance (an excess of residual sodium, defined by radioisotope techniques) and hypothesized secondary neurophysiological disturbances were the focus of British investigations by Alec Coppen and colleagues in the early 1960s. The data appear compatible with the hypothesized movement of excess sodium into the neuron during an episode of mood disorder and redistribution toward the preillness electrolyte balance across the neuronal membrane during recovery. Intraneuronal sodium leakage is postulated in both depressive and manic disorders but is deemed more extreme in the latter. Because the harmonious activity of the neuronal cell and, by implication, that of a group of neurons depends on the electrical gradient maintained across its membrane by differential distribution of sodium, abnormalities in sodium concentrations and transport are hypothetically relevant to the production of an unstable state of neurophysiological hyperexcitability. In formulating their thesis of neurophysiological arousal in melancholic states, Joseph Mendels and Peter Whybrow (both of whom have worked at the University of Pennsylvania) have capitalized on the foregoing electrolyte disturbances. The view that mania represents a more extreme electrophysiological dysfunction in the same direction as depression violates the commonsense notion of symptomatological “opposition” between the two kinds of disorder, yet it may, in part, account for the existence of mixed states in which symptoms of depression and mania coexist. The NIMH team led by Frederick Goodwin first showed that a substantial minority of depressed patients with a bipolar substrate respond to lithium salts, which further supports the concept of a neurophysiological common denominator to mania and depression. Perturbations of calcium metabolism also appear relevant to bipolar patients. Therapeutic implications of this observation (e.g., the use of calcium channel inhibitors in bipolar I disorder) have not yielded consistent results. Finally, rubidium, another alkali metal, has been explored in the depressive phase of bipolar disorders, again with inconclusive results.
**Rhythmopathy.** European studies have shown that depressed patients are phase advanced in many biological rhythms, including the latency to the first rapid eye movement (REM) in sleep. Shortened REM latency, which has been extensively studied by David Kupfer and colleagues at the University of Pittsburgh, has been proposed as another laboratory “test” for depressive disorder. Shortened REM latency may serve as a trait marker for depression because it has been found in dysthymia and so-called borderline personality, as well as among the clinically “well” offspring of adults with major depression.

Formulations of circadian rhythms by Thomas Wehr and Norman Rosenthal, working at NIMH, have focused on abnormalities on brain regulation of temperature, activity, and sleep cycles. Others have investigated the role of the pineal hormone melatonin in mood disorders, without achieving consistent results. The application of circadian rhythm research concepts to women with mood disorders has also led to imaginative methods, but, again, without definitive characterization of the neurophysiologic faults.

At a basic level, instrumental REM sleep deprivation in neonates has been recently shown to lead to adult “depression-like” behaviors in rats. In human studies, sleep deprivation and exposure to bright white light has been shown to correct phase disturbances and thereby terminate depressive episodes, especially in subjects with periodic and seasonal depressions. It has even been shown that the average person is light deprived, and that phototherapy can benefit even those without clear-cut seasonal patterns. Unfortunately, except for their use in mild seasonal depressions and suppression of sleep deprivation to prevent hypomania in bipolar disorder, the foregoing circadian studies have not had a palpable impact on practice. Their application in the large segment of mood-disordered patients remains cumbersome, if not elusive. Their effect can be better assessed at the level of theory. Although the specificity and efficacy of these neurophysiological indices and manipulations for clinical depression and bipolar disorder require more extensive research, cumulatively, they point to midbrain dysregulation as the likely common neurophysiological substrate of affective disorders. The foregoing considerations further suggest that the ancient Greeks, who ascribed melancholia to malignant geophysical influences, did not indulge in mere poetic metaphor. The ancients had observed the disturbed circadian patterns and advocated their readjustment to restore euthymia.

**Affective Dysregulation.** A major challenge for research in mood disorders is to characterize the basic molecular mechanisms that underlie the neurophysiological rhythmopathies, which, in turn, might account for the recurrent nature of the affective pathology as envisioned by Kraepelin. This means that in the most typical recurrent forms of the disorders, the constitutional foundations (manifested as cyclothymic and dysthymic traits and/or a broad range of emotional disequilibrium covered by the rubric of “neuroticism”) are so unstable that the illness may run its entire course more or less autonomously, with the environment largely serving to turn on and off the more florid phases (episodes). Parisian psychiatrist Jean Delay, a pioneer in psychopharmacology in the 1950s, also emphasized affective dysregulation as the fundamental pathology in the spectrum of mood disorders. Robert Post, at NIMH, hypothesized that the electrophysiological substrates could be so kindled that an oligoepisodic disorder initially triggered by environmental stressors could assume an autonomous and polyepisodic course. He hypothesized that this phenomenon might occur because neuronal perturbations brought about by stressors in the early course of mood disorders get incorporated into the DNA. This fascinating kindling hypothesis, however, does not seem to pertain to garden-variety mood disorders but to those with extreme cyclicity. The
monograph on manic-depressive illness by Fred Goodwin and Kay Jamison presents in-depth arguments for this cyclical paradigm of thymopathy.

The amygdala, through its connection with the serotonin transporter, appears to play a crucial role in the dysregulation of the emotional life of affectively ill patients. Data indicate that the dysregulation is both in function and anatomic structure.

THEORETICAL SYNTHESIS

Pathophysiological Understanding

Modern psychobiology attempts to link experience and behavior to the central nervous system (CNS). Building conceptual bridges between the psychological and biological approaches to mood disorders requires sophisticated strategies that go beyond the Cartesian notion of limited mind–body interactions through the pineal gland and the generalizations of the Meyerian school.

William McKinney and Hagop Akiskal in 1973 developed a conceptual framework that considers the affective syndromes as the final common pathway of various psychological and biological processes. The overarching hypothesis is that psychological and biological etiological factors converge in reversible deficits in the diencephalic substrates of pleasure and reward. Those areas of the brain subserve the functions that are disturbed in melancholia and mania. The integrative model links the central chemistry and physiology of reward mechanisms with the object loss and behavioral models of depression, both of which give singular importance to the depressant role of loss of rewarding interpersonal bonds. A key element of the model is the circadian disturbances observed since ancient times in both depressive and manic syndromes. Both syndromes are conceptualized as clinical manifestations of a disordered limbic system with its subcortical and prefrontal extensions. Brain imaging studies in melancholic patients by Wayne Drevets, originally at Washington University, have visualized limbic disturbances extending into subcortical structures and occurring primarily in patients with a familial diathesis for depression; the amygdala appears to be the focal limbic structure in the latter studies. Clinical experience and research data suggest that multiple factors described in the following subsections converge to produce or exacerbate dysregulation in these brain regions, leading to the final common pathway of clinical depression. The data on mania are more tentative and are mentioned when relevant.

Heredity. Evidence indicates a significant genetic role in the causation of bipolar and recurrent major depressive disorders. Although it is not known exactly what is inherited and biological endophenotypes have not been delineated, temperamental dysregulation might be hypothesized to fulfill the role of a behavioral endophenotype. The depressive inheritance might translate into impaired coping under stress (neuroticism), and bipolar inheritance might translate into affective dysregulation (cyclothymia), involving over- and underreactivity to life situations, circadian events, and biological stressors. Whatever the precise nature of the inherited fault or excess, current research suggests that heritability involves a broad spectrum of disorders, including milder affective states, as well as temperamental inclinations. Recent findings, from both clinical and genetic investigations, have emphasized the importance of broad affective phenotypes that incorporate panic and anxiety reactivity within both traditional unipolar and bipolar disorders. For instance, the affective dysregulation underlying bipolar disorder can manifest in euphoria, irritability, depression, panic attacks, and social anxiety. Such tendencies are observed among patients and their first-degree relatives. Genetic
heterogeneity is likely and may involve inheritance of a single dominant gene with variable penetrance in some families or specific subtypes, or oligogenic inheritance in the majority of cases. Different genetic mechanisms will, in all likelihood, involve more than one disorder (e.g., depression and generalized anxiety; bipolar I disorder, psychosis, stimulant abuse, and dopsomania; bipolar II disorder, panic disorder, and bulimia nervosa). Another distinct possibility is that some forms of schizophrenia, bipolar I and II disorders, and recurrent depressions lie on an oligogenic BPS. A polymorphism involving the short alleles of the serotonin transporter gene appears relevant to depressive dispositions. The genetic mechanism involving mood reactivity and panic appears to be subserved by chromosome 18q. The partial overlap of manic and schizophrenic phenomenology might be related to a polymorphism related to a variety of genes.

It is relevant to point out at this juncture that at least five genetic loci have been identified with shared liability for both bipolar and schizophrenic disorders. These are the loci for BDNF, catechol-O-methyl transferase (COMT), neuroregulin (NRGI), d-amino acid oxidate activator (DAOA; also known as G72), and Disrupted in Schizophrenia 1 (DISC1). It is unlikely that these findings coming from laboratories worldwide represent systematic diagnostic error. One heuristic favored theoretical interpretation of these data is that bipolar and schizophrenic disorders represent oligogenic inheritance, requiring multiple additive genes. A competing hypothesis is that there exist distinct mood disorder phenotypic spectra, each with their own genotypes, only some of which cross the border into psychosis; others cross the border with anxiety and panic; still others may involve “comorbidity” with migraine.

**Developmental Predisposition.** Parents with mood disorders are often in conflict, which may lead to separation, divorce, and suicide. It can be said that heredity often determines the type of environment into which the child predisposed to mood disorder is born. Developmental object loss, although not specifically involved in causing mood disorder, might modify the expression of the illness, possibly by leading to earlier onset, more severe episodes, and an increased likelihood of personality disorder and suicide attempts. The serotonin transporter polymorphism mentioned earlier appears to mediate the relationship between early trauma and depression. Likewise, this polymorphism appears relevant to neuroticism and suicide attempts.

**Temperament.** Since ancient times, persons prone to mania and melancholia have been described as possessing certain temperamental attributes, representing variations on the theme of what today is subsumed under cyclothymic, dysthymic, and anxious-inhibited temperaments, as well as the traits of high neuroticism describing emotionality. Many monozygotic twins discordant for full-blown mood disorders, studied by Aksel Bertelsen’s Danish research team, exhibited affective instability with temperamental moodiness, which strongly suggests that such attributes are genetically determined. Research conducted by Kendler’s team at the Medical College of Virginia further suggests that several of the temperamental attributes might be transmitted as part of the genetic liability to mood disorders. Research has also identified such temperaments in the prepubertal offspring of parents with bipolar I disorders, suggesting that they precede by years to decades the overt onset of major mood disorder episodes. The atmosphere of high expressed emotion and the negative critical remarks by relatives and affectively unstable patients documented in the recent psychological literature on mood disorders often reflect the interpersonal clashes between patients and their temperamentally intense relatives. Thus, temperaments appear to be intimately involved in generating much interpersonal friction, emotional arousal, and sleep
loss (just to cite common perturbations), thereby eliciting many of the life stressors that precipitate affective episodes. The use of stimulant drugs either to self-treat lethargy or to enhance hypomanic traits could further contribute to episode precipitation. As for the depressive disposition, the work of Maria Kovacs at the University of Pittsburgh has shown that dysthymia in children evolves into major depressive episodes postpubertally, of which a proportion switch to bipolar states. These data cohere with the work conducted at the University of Tennessee, Memphis, showing shortened REM latency in early-onset dysthymic subjects. The familial bipolar diathesis revealed in the Tennessee work, along with its tendency to switch to hypomania, suggests commonalities between depressive and bipolar II disorders.

**Life Events.** Most individuals do not develop clinical depression when exposed to environmental adversity. Such adversity seems to play a pathogenic role primarily in those with an affective diathesis. In fact, the work of Kendler at the Medical College of Virginia indicates that genetic factors might underlie the depressive disorder patients’ susceptibility to life events. Furthermore, current data suggest that social stressors in the onset of depression are more relevant to the first few episodes of the illness. The evidence linking such events to mania is less convincing. At any rate, stressful events often appear to be triggered by the temperamental instability that precedes clinical episodes. Interpersonal losses are common events in the lives of individuals with intense temperaments. The arousal and sleep loss associated with such events can precipitate both depressive and manic states.

A recent study by Peter McGuffin’s team at the Institute of Psychiatry, London, raised the possibility that one mechanism by which heredity produces depression is the creation of environmental adversities in the lives of individuals predisposed to this illness. This work has been replicated by independent groups of investigators. Whatever the origin of environmental adversity, it is common clinical experience that loss represents an important, perhaps even central, theme in clinical depression. Variables that seem to modulate the effect of adult losses include concurrent life events, resultant changes in lifestyle, lack of interpersonal support, deficient social skills, and the symbolic meaning of the putative loss. The research program of George Brown and his followers in London capitalizes on the foregoing considerations, particularly the importance of early and proximate losses in socioeconomically disadvantaged women who lack supportive relationships. However, that conceptualization downplays the degree to which the social context of the depression reflects the dysthymic temperamental liabilities of those depressed women. Recent research indicates that even social support is determined to a considerable degree by the genetic mechanisms that underlie mood disorders. Indeed, the short alleles of the serotonin transporter gene are now implicated in mediating between adverse events and clinical depression.

**Biological Stressors.** Many physical diseases and pharmacological agents are known to precede the onset of both depressive and manic episodes. Like psychosocial stressors, however, they do not generally seem to cause de novo episodes, but mobilize them in persons with a personal and family history of mood disorders. Thyroid disturbances have a role in practice because they are associated with rapid cycling in bipolar patients, especially women; lithium is often contributory to such disturbances occurring in the depressions in which bipolar women are not uncommonly “stuck.”

**Sex.** Clinical and epidemiological studies concur in suggesting that women are at higher risk for mood disorders, with the risk highest for depression. This now appears to be, in part, a function of anxious-depressive traits represented by neuroticism. These traits have strong
genetic determinants. Women have higher concentrations of MOA (the enzyme that breaks down monoamine transmitters) in the brain and more precarious thyroid status. In addition, low estrogen and high progesterone concentrations have been postulated as possible mediating factors in postpartum depressions, premenstrual accentuation of affective instability, and women’s vulnerability to the depressant effect of steroidal contraceptives. Finally, recent data point to the role of estradiol in depressions occurring during the transition to menopause. Personality factors might also be relevant to the sex differences in depression. In recent collaborative work with University of Pisa psychiatrist Giulio Perugi, Akiskal proposed the hypothesis that female sex might favor greater expression of dysthymic attributes, whereas hyperthymic traits appear to be favored by male sex. Those considerations tend to parallel, respectively, the ruminative and active cognitive response styles reported by Susan Nolen-Hoeksema, originally at Stanford University, to distinguish the sexes. What specific sex-related biographical factors might interact with sex-related biological factors to produce such trait differences is largely unknown. An intriguing possibility is that women, because of temperamental inclination to depressive cognitions, might react more intensely to childhood adversities, as well as be more specifically vulnerable to adult stressors related to bonding with men and child rearing. Research by Mark George and colleagues has raised the provocative possibility that women overrespond to sad circumstances over a lifetime, thereby permanently altering anterior limbic and prefrontal brain function in a “depressive” direction. The high prevalence of anxious-depressive conditions in women—most pronounced at the clinical level—might be linked, hypothetically, to an evolutionary adaptive advantage conferred by traits of fear, inhibition, and avoidance to women who bear the responsibility of pregnancy and child rearing. The higher prevalence of minor depressions in women, rediscovered in a recent Danish study, is in line with the foregoing hypothesis.

The integrative model presented here (Fig. 13.1-3) goes beyond the general provisions of the unified approach developed three decades ago. It is submitted that, at least in the highly recurrent forms of the malady, affective temperaments represent the intermediary stage between remote (hereditary) and proximate (stressful) factors and that limbic-diencephalic dysfunction is best characterized as the biological concomitant of the clinical manifestations of the affective syndromes. Like the temperamental dysregulations, these biological disturbances represent a putative stage in the pathogenetic chain. They emerge as temperamental instabilities that react to, provoke, or invite life events, substance use, and alterations in circadian rhythms—which, in turn, appear to usher in the behavioral, emotional, and cognitive manifestations of the illness. It is finally relevant to point out that biological stressors such as hormonal disturbances and traumatic brain injury appear to compromise limbic-diencephalic function as their depressant mechanism.
Therapeutic Perspectives

The foregoing integrative model mandates the joint use of somatic-pharmacological and psychosocial interventions. Although the milder forms of mood disorders can be managed with psychotherapy, somatic treatments are usually required to reverse the biological disturbances in melancholia before the patient can respond to interpersonal feedback. Depressive disorders with psychotic features often necessitate more definitive somatic interventions, such as electroconvulsive therapy (ECT). Continued psychopharmacological treatment is also effective in decreasing rates of relapse and future recurrence in most. Bipolar disorder and most forms of depression are considered lifelong illnesses needing indefinite maintenance pharmacotherapy.

Psychosocial therapy by skilled clinicians can provide support, combat demoralization, change maladaptive self-attributions, and improve conjugal and vocational functioning. Recent fascinating data support the notion that psychosocial interventions such as cognitive–behavioral therapy modulate cortical-limbic function described earlier as the final common pathway of depressive illness. Whether such therapy can also modify personality traits to fortify the patient against new episodes is a future research challenge. It might prove more profitable to attempt to help patients to explore professional and object choices that match their temperamental proclivities and assets, which, in turn, might provide them greater harmony and adaptation in life. Although much needs to be learned about the indications for medication and psychotherapy in different subtypes of mood disorders, research not only does not support a negative interaction between the two forms of treatment, but, on selected parameters, suggests additive and even synergistic interaction. There is a great need for
patients, their families, and clinicians to understand how a biologically driven illness like depression should be approached from a pragmatic psychotherapeutic perspective.

The challenge for psychiatric research in the decade ahead is to elucidate the basic mechanisms by which the predisposing, precipitating, and mediating variables reviewed here and others yet to be identified interact to produce the final common path of decompensation in melancholia. Because of the heterogeneity of depressive conditions presenting as a psychobiological final common clinical syndrome and because antidepressant agents, irrespective of specificity to one or another biogenic amine, are approximately equally effective in two-thirds of those with depressive disorders, the antidepressant agents may be acting not on the primary lesions of these disorders but on a neurochemical substrate distal to the underlying biological faults. Choice of antidepressants is still highly determined by the side effect profile least objectionable to a given patient’s physical status, temperament, and lifestyle. That so many different classes of antidepressants—with different mechanisms of action—have been marketed since the 1990s represent indirect evidence for heterogeneity of putative biochemical lesions. The investigation of central neurotransmitter receptor function continues to occupy much current effort to delineate the mechanism of antidepressant action and side effects of classic agents, as well as the new compounds that have made the treatment of depression “clinician and patient friendly.” Whether study of specific receptors will unravel the molecular mystery of depression remains to be seen. Since the 1990s, studies have begun on antidepressant and mood-stabilizing effects on molecular mechanisms believed to be closer to the “genetic underpinnings” of mood disorders. Herein is the promise of the future—a new generation of psychiatrists conversant with both clinical phenomenology and molecular biology. Data suggest that the biological specificity of genetic factors in mood disorders might be translated into distinct temperamental dysregulations, which, in turn, might predispose to different affective subtypes.

Returning to the therapeutic arena, mounting clinical evidence indicates that, in a special subgroup of depressed patients with bipolar disorder, antidepressants might provoke mixed episodes, hypomanic episodes, or both, and possibly increase later cycling. The kindling-sensitization model suggests the utility of anticonvulsant medication on episode escalation and might represent yet another example of pathophysiological intervention. Whatever the merit of this model, the 1990s witnessed intense clinical and research interest and U.S. Food and Drug Administration (FDA) approval of the clinical introduction of divalproex (Depakote) and lamotrigine (Lamictal) for bipolar disorder, and many other promising anticonvulsants are being developed for that disorder. Anticonvulsant mood stabilizers appear to possess a broad spectrum of activity on bipolar disorders, including mixed dysphoric and rapid-cycling forms. Lithium, by contrast, seems more specific to euphoric or “classic” mania. On the other hand, the introduction of atypical antipsychotics—olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel), and aripiprazole (Abilify)—for mania raises intriguing questions about a common neural substrate for schizophrenic and manic disorders. Psychoeducational interventions geared to disturbed rhythms of the disorder represent another example of rational therapeutics. Mood clinics should help patients and their significant others to dampen stimulation so that it is kept at an optimal level for depressed patients with cyclothymic traits. All offending drugs (e.g., cocaine, caffeine, and sedative-hypnotic agents) should be gradually eliminated and circadian disruptions and sleep loss minimized. The greater challenge is to learn how to curb the ill-advised actions of patients with cyclical depressions. Unfortunately, current data indicate neurocognitive deficits, particularly in executive function, that underlie and/or complicate these disorders. Psychoeducation and psychotherapy have the task of ameliorating the resulting social
problems, and despite much progress in this realm, these deficits remain stable over time. Compliance with mood-stabilizer regimens that, for many, would attenuate episodes and prevent such sequelae is difficult to achieve. Further research on treatment or medication-adherence techniques is needed for promoting more efficient use of mood stabilizers.

It is tempting to suggest that biogenic amines, the “humors” of modern psychobiology, play the same heuristic role as the ancient humors did for many centuries. The black humor, appropriately evoked in the construct of melancholia in DSM-5, may not have the same claim for etiological relevance to depressive disorders as norepinephrine and serotonin, but at least it has a classic heritage. Dopamine, by contrast, may represent the sanguine humor that drives hypomanic temperaments and manic behavior. When genetic factors contributing to clinical depression and mania are discovered, in all likelihood, they will be more linked to temperamental dispositions than to full-blown affective disease phenotypes. The clinician will still need to interpret the myriad influences that effect such inclinations to produce disease in an individual patient—that is, fundamental scientific advances in mood disorders, rather than diminishing the role of practitioners, will actually increase it. It is to be regretted that, despite destigmatization efforts and a rich armamentarium of therapeutic developments, the clinical care of affectively ill patients at the severe end of the spectrum continues to be grossly inadequate. More research will not improve this dismal situation unless the human and social dimensions of severe mood disorders are addressed with the requisite clinical and public health policies. Caring for patients with mental illness is a dimension distinct from evidence-based treatments along psychopharmacological and psychotherapeutic lines: It requires the allocation of human resources and integrated mental health structures geared to the total patient.

In any discipline, scientific truth is a function of its technology, but understanding the phenomena under consideration is a matter of philosophical temperament that seeks integration and the hope for a unified vision. Research into the causes and treatment of mood disorders has generated abundant recent data suitable for integration into theory and practice, and conceptualizing the origin and treatment of mood disorders can no longer be justified on the grounds of ideological preference alone.

REFERENCES


Application of the tools of epidemiology to psychiatry over the past several decades have led to numerous advances in the understanding of the magnitude, correlates, patterns of comorbidity, course, impact, and service patterns of mood disorders. Advances in epidemiology were comprised of methodologic developments including the introduction of structured and semistructured diagnostic interviews, statistical methods for estimating prevalence and correlates of mental disorders, and the shift from clinical to population-based samples to obtain estimates of the magnitude and correlates of mental disorders unbiased by treatment seeking. The results of recent epidemiological studies that have shown the high prevalence of subthreshold conditions and pervasive comorbidity between disorders have illustrated the need for further development of the psychiatric diagnostic system. There is now widespread agreement regarding the need to expand the current categorical diagnostic system because of the arbitrary thresholds that distinguish disorders, and the lack of distinct boundaries between different classes of disorders.

During the past decade the descriptive epidemiology of mood disorders has come to maturity. In recent years there has been a proliferation of epidemiologic research, both in the United States and abroad, that has strengthened the evidence based on the magnitude, correlates and consequences of mood disorders including bipolar disorder and major depressive disorder. This work has highlighted the dramatic personal and societal impact of bipolar disorders.

This section will provide an update on recent large scale studies of the prevalence of mood disorder subtypes in adults and children, and summarize the correlates, patterns of comorbidity, impact, and service patterns for mood disorders from population-based studies. Findings show substantial concordance with those reported in earlier volumes of this textbook, and highlight the need to shift from cross-sectional descriptive epidemiology to

▲ 13.2 Mood Disorders: Epidemiology

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DESCRIPTIVE EPIDEMIOLOGY

Bipolar Disorder

The largest series of international studies that provide prevalence rates of mood disorders is the World Health Organization (WHO) World Mental Health (WMH) surveys. Data on bipolar disorder collected in a subset of 11 population-based surveys were carried out in the Americas (São Paulo metropolitan area, Brazil; Colombia; Mexico; and United States), Europe (Bulgaria and Romania), Asia (Shenzhen, People’s Republic of China; Pondicherry region, India; and 9 metropolitan areas in Japan), Lebanon, and New Zealand. With the exception of Japan (unclustered 2-stage probability sample), all surveys were based on stratified multistage clustered area probability samples. In the past few decades, the lifetime prevalence of Bipolar I (BPI) disorder has generally estimated at about 1 percent. The most recent estimates from the largest population-based survey, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) have reported substantially greater lifetime prevalence estimates of bipolar I disorder of 3.3, Bipolar II (BPII) of 1.1 with corresponding 12 month rates of 2.0 and 0.8, respectively. Recent studies have begun to include estimates for bipolar II disorder and BPS disorders as well as bipolar I disorder. As would be expected, prevalence tends to increase with successively more inclusive disorder definitions. For example, in the WMH Surveys, the cross-national lifetime prevalence of BPS disorders was 2.4 percent; of which 0.6 percent met criteria for bipolar I disorder, 0.4 percent for BPII, and 1.4 percent for subthreshold bipolar disorder. In many (but not all) studies assessing bipolar II disorder, its prevalence is actually lower than that of bipolar I disorder; this may indicate that the majority of people who experience hypomanic episodes also experience manic episodes, or may be explained by the major depressive episode requirement for diagnosis of bipolar II disorder.

An increasing number of studies have also begun to estimate the occurrence of bipolar disorder in youth. Lifetime prevalence rates of bipolar disorder in youth range from 0.2 percent in the Great Smoky Mountains Study to 2.9 percent for bipolar I disorder or bipolar II disorder in the National Comorbidity Survey-Adolescent supplement (NCS-A). Young adults aged 19 to 24 in the Canadian Community Health Survey had a lifetime prevalence of 3.8 percent. A few studies have also estimated 12-month prevalence rates of bipolar disorder ranging from 1.3 to 2.5 percent. Prevalence rates of mania range from 0.4 (12-month) to 2.0 percent (12-month); and rates of hypomania range from 0.1 (lifetime) to 0.9 percent (6-month). The results of longitudinal studies converge in estimating the prevalence of bipolar disorder at between 1.4 and 2.1 percent, which approximates cross-sectional prevalence rates in adult samples. This was confirmed by a recent meta-analysis of epidemiologic studies of bipolar disorder in children and adolescents, which reported a mean prevalence of 1.8 percent.

Major Depression

The WMH surveys also provided the largest aggregate data on the prevalence of major depressive disorder. As shown in Figure 13.2-1, lifetime and 12-month prevalence rates were estimated in 18 countries, divided according to high and low-middle income. The lifetime prevalence estimates average 11.1 (range 8.0 to 18.4) in low and 14.6 (range 6.6 to 21.0) in
high-income countries, whereas the 12-month prevalence rates average 5.5 in high (range 2.2 to 8.3) and 5.9 (range 3.8 to 10.4) in low-income countries. More recent prevalence estimates from the NESARC study were 13.2 for lifetime and 5.3 for 12-month major depressive disorder. These aggregate findings suggest that the descriptive epidemiology of mood disorders has come to maturity. Although there is a wide range of estimates, the average rates of both lifetime and 12-month depression are fairly consistent across studies that employ comparable methodology.

Several cross-sectional and prospective studies have also reported rates of major depressive disorder in youth. The lifetime rates of major depressive disorder in childhood range from about 0.6 to 4.8 percent with a median of 2.2 percent. Results of the NCS-A study of adolescents in the United States yielded lifetime and 12-month prevalence of major depressive disorder of 11.0 and 7.5 percent, respectively. Both the TRacking Adolescents’ Individual Lives Survey (TRAILS) study in the Netherlands also characterized major depressive disorder with severity based on impairment. As expected the lifetime rates in these studies were substantially lower than those of nonsevere major depressive disorder with lifetime and 12-month rates of 3.0 and 2.3 percent, respectively. In the NCS-A, the prevalence of major depressive disorder increased significantly across adolescence, with markedly greater increases among females than among males. Most cases of major depressive disorder were associated with psychiatric comorbidity and severe role impairment, and a substantial minority reported suicidality. Treatment in any form was received by the majority of adolescents with 12-month DSM-IV major depressive disorder (60.4 percent), but only a minority received treatment that was disorder-specific or from the mental health sector.

Numerous studies have begun to expand the diagnostic criteria for mental disorders to collect information on the spectra of expression of particular conditions. With respect to mood disorders, the spectrum concept of bipolar disorder long advocated by clinicians has now been validated in community samples of adults and children. Application of the spectrum concept of bipolar disorder has yielded rates of bipolarity of up to 5 percent and depression of up to 20 percent. Likewise, many individuals in the community may show some (a few or more) depressive symptoms that do not reach the severity or duration threshold for specific mood disorders in the DSM-5 system but, nevertheless, also have substantial morbidity and dysfunction. Although these subthreshold disorders may be less severe forms of major depressive or bipolar disorders, they may also cause substantial suffering as well as disability. Subtypes of subthreshold depression identified in the Zurich Cohort Study and replicated in

FIGURE 13.2–1. Lifetime prevalence of major depression in the world mental health.
numerous subsequent studies include recurrent brief depressive disorder and minor depressive disorder (as well as recurrent brief hypomania).

**CORRELATES OF MOOD DISORDERS**

**Gender**

The most consistent finding across all of the studies on the prevalence and incidence of unipolar major depression is that it is approximately twofold more common among women than men. This gender difference begins in early adulthood, is most pronounced in people between the ages of 30 and 45, and also persists in the elderly. Because there are no data (aside from biological–hormonal differences) that show that female gender per se means increased vulnerability for depression, increased stress sensitivity, maladaptive coping strategies, and multiple social roles (all of which are frequently seen in women) and substance use disorders that can mask depressive symptoms (more frequently seen in men) have been suggested for the explanation of the gender difference. In addition to these psychosocial theories, recent studies show that because prior anxiety disorders are more common in women, preceding anxiety disorder may also be a significant factor contributing to the higher depressive morbidity in women. Thus, gender difference in unipolar major depression seems to result from the complex interaction of the mentioned biological and psychosocial variables. Minor depressive disorder and recurrent brief depressive disorder are also more common among women, but the difference is not so marked as that in major depression.

In contrast to unipolar depression, the gender ratio in bipolar disorders (all subtypes combined) is approximately 1:1. However, among bipolar II disorder patients and in special subpopulations (mixed/dysphoric mania, mixed depressive episode, winter depression, bipolar depression with atypical clinical features, rapid cycling bipolar disorder), women are overrepresented. Looking at the depression–mania continuum as a whole spectrum, there is a clear trend: the higher the depressive component, the higher the proportion of women. Consequently, in the rare cases of unipolar mania (manic episode without any major or minor depression), men are markedly overrepresented. The gender differences in lifetime prevalence rates are more marked than in 1-year and current prevalence rates, which may be attributable—at least in part—to the stronger male tendency to forget previous episodes and deny emotionally negative events. Recent population-based epidemiological surveys showed that the lifetime prevalence and 1-year prevalence of major depression, dysthymia, and bipolar (I + II) disorders were much higher among people with same-sex sexual behavior, (including bisexuality) particularly in the case of men.

**Age**

Depressive disorders show much higher lifetime prevalence among people younger than 45 years, but the age of onset differs between unipolar and bipolar and familial and nonfamilial cases. The average age of onset of recurrent unipolar major depressive episode falls between the ages of 30 and 35 years, whereas single-episode major depression that often lacks family history of mood disorders usually begins some years later. The genetic predisposition for depression decreases with age. However, social stressors appear to place younger individuals at a greater risk for depression than elderly ones. On the other hand, isolation, loss of interpersonal contacts, medical disorders, and disability play a more important role in the development of depression in later life. Early-onset depression is associated with a higher
female to male ratio than late-onset depression. Because major depressive disorder is a frequent and highly recurrent illness, the probability of recurrence does not decrease with age. The incidence of major depressive disorder in old age is lower in both sexes, but first incidence and prevalence of minor depressive disorder show the opposite trend. The incidence of unipolar major depressive disorder in the postpartum period is just slightly increased, but this is not the case in the postmenopausal years. Pure (primary) dysthymic disorder typically starts in late adolescence or early adulthood, but, in the absence of appropriate treatment, almost all cases develop later into major depression. The first incidence of dysthymia is also common in old age, but this is typically the consequence of the adverse psychosocial and biological conditions frequently seen among the elderly.

The age of onset of bipolar disorder most commonly around 20 years of age, is substantially (about 10 years) lower than that of unipolar depression. Bipolar men appear to have 4 to 5 years earlier onset than bipolar women. In more than half of the cases, onset is before the age of 20, frequently in late adolescence. In contrast to this, first-onset mania is very rare among elderly people. The ages of onset of bipolar I disorder and bipolar II disorders are similar, but there is a slight tendency for higher age of onset in bipolar II disorder patients. The incidence of the depressive phase of bipolar disorder after childbirth is relatively high, and the majority of patients with “postpartum depression” have bipolar disorder. Like unipolar depression, bipolar patients with positive family history of mood disorders are significantly younger at the beginning of the illness and need less stressors to precipitate the illness than those lacking such history.

Race and Ethnicity

It is well known that cultural differences may influence the clinical presentation of depression and mania, leading to unreliable figures in prevalence studies performed by standard methodology. However, there is now consistent evidence that rates of mood disorders are lower in blacks and Hispanic than in whites. Because of their increased exposure to psychosocial stress and other risk factors for mood disorders, the lower rates in these ethnic subgroups is paradoxical.

SOCIAL CORRELATES

Marital Status

The relationship between marital status and mood disorders is quite complex. For example, being single, divorced, or separated can be either a risk factor for depression or the result of the adverse life events generated by depressive or manic psychopathology, or both. Major depressive disorder and bipolar illness are most frequent among divorced, separated, or widowed individuals. Single women have lower rates of depression than married women do, but the opposite is true for men. However, being single as a result of having never married, as a result of the dissolution of a difficult marriage, and as a result of widowhood represent three very different conditions. The risk of an major depressive episode is very high among recently widowed individuals of all ages, but is particularly high in the elderly. Patients with mood disorder are overrepresented among the divorced, and the rate of family breakdown (separation, divorce) is elevated slightly in dysthymic patients, substantially in major depressive patients, and markedly in bipolar I disorder and bipolar II disorder patients. The presence of mania, hypomania, or major depression is a strong predictor for future separation or divorce, which can cause serious distress for the patients and for their spouses and may
generate negative life events for their children. These early negative life events (e.g., parental loss before adolescence) are well-known predisposing factors for adult mood disorders, particularly in the case of family loading (case of subjects with positive family history of mood disorders).

**Socioeconomic Factors**

Although the relationship between depressive symptoms and low social class is well documented, most studies found only a weak (but consistent) correlation between major depressive disorder or bipolar I disorder and lower socioeconomic status. Individuals with lower socioeconomic status have a lower level of educational, lower income, and poorer living conditions, as well as a higher rate of unemployment and, ultimately, homelessness. As has been demonstrated in the NCS, the proportion of major depressive episode was approximately three times higher among individuals without a workplace than among those with one. However, as in the case of marital status and mood disorder, cause and effect may be reversed here, too. Mood disorder can easily lead to unemployment, divorce, or low income, resulting in regression on the social hierarchy scale. Because hypomania is not as disruptive as mania, in terms of academic and social carrier, the educational level of bipolar II disorder patients is above the average and, in contrast to unipolar major depression and bipolar I disorder, bipolar II disorder patients tend to belong to higher social classes and are relatively overrepresented among socially active, creative people.

**Residence**

As urban communities are more stressful than rural ones, it is not surprising that most studies performed in Western societies concluded that major depression was more frequent in urban residents than in their rural counterparts. In the ECA study, this rural–urban difference also persisted after controlling for marital status, race, and socioeconomic status. The results of the NCS show that respondents living in rural areas had approximately 40 percent lower odds of 1-year comorbidity of three or more mental disorders than did those living in urban areas. The urban–rural distinction provides little information about the real living and social conditions in general, but it can be a good marker for the density of the population and for other important sociological variables.

**Seasonal Factors**

Despite the fact that more than two-thirds of patients with recurrent major mood disorders show irregular seasonal patterns individually, statistically, spring and fall are the peak times for depression, just as summer is for mania. Because seasonal affective disorders (fall–winter depression and spring–summer depression) occur in approximately 20 to 25 percent of the patients with recurrent major mood disorders, it is possible that the seasonal pattern observed in unipolar depression and bipolar disorder in general is the consequence—at least in part—of the characteristic annual rhythms of these specific seasonal subtypes. The seasonal profiles of committed and attempted suicides, the prescription of antidepressants and ECT, and the availability of L-tryptophan (the main precursor of serotonin) are very similar to the seasonal onset of major depression. However, acute and long-term pharmacotherapy of mood disorders (more precisely, its cessation) can change the seasonal pattern of depression and mania, which should be taken into account either in planning studies or in the interpretation of the results. On the other hand, the decreasing seasonal variation in suicides that has been
observed in many countries in the last two decades may reflect, among others, the reduced rate of depression-related suicides in the given population.

**Geographic Trends**

There is a general, but weak, trend for lower prevalence of depression and higher rate of mania in regions located closer to the Equator. Consistently, at least in the Northern Hemisphere, winter depression (which affects between 1 and 6 percent of the community) seems to be more frequent in countries situated farther from it. A significant positive correlation was found between prevalence of winter depression and latitude in North America (where its prevalence is twice as high as in Europe), whereas a similar, but only slight, tendency was observed in Europe. On the other hand, the distribution of summer depression across the latitudes shows the opposite tendency. However, the relationship between these two forms of seasonal affective disorder and latitude (e.g., the length of daily photoperiod) is weak. Other climatic and genetic influences, as well as social and cultural factors—which can also be interrelated with the daily photoperiod—may play a role, too. In the NCS-R, major depressive disorder (seasonal and nonseasonal forms combined) was largely unrelated to geography. Regarding the West–East dimension, the lower prevalence rates of major depressive and bipolar I disorders reported from Far Eastern countries may be related primarily to cultural differences and methodological shortcomings, but there is some recent evidence indicating that the prevalence of major mood disorders in these countries may, in fact, be lower.

**PSYCHOSOCIAL FACTORS**

**Social Stressors**

Social stressors, in general, have been well recognized as risk factors for mood disorders. However, different kinds of social stressors (i.e., childhood vs. adulthood events, acute vs. chronic stressors, positive vs. negative life events) can play different roles in the predisposition and precipitation of depressive or manic disorders. In the case of major depression and bipolar disorder, the association of acute stressors and the onset of illness become progressively weaker with the increasing number of previous episodes, and patients at high genetic risk for mood disorders commonly experience depressive or manic episodes without any negative life event. In the development of major mood disorders, chronic stressors (e.g., unemployment, difficult marriage) play a more important role than specific, acute stressors. However, accumulation of stressful negative life events is the strongest predisposing factor. The higher level and, probably, the different nature of social stressors in individuals living in urban communities may be among the main sources accounting for their higher psychiatric morbidity. The fact that subjective perception of life events is more important than the event itself makes the estimation of the causative role of life events more difficult. On the other hand, it has also been demonstrated that acute, positive life events (that are quite rare in Western communities) can also precipitate either major depression or mania in vulnerable individuals. Negative life events should not be considered as only predisposing or precipitating factors, as they are frequently the result of the behavior of patients with major depressive disorder and, particularly, patients with bipolar disorder.
Social Support

Social support can improve coping and modify (e.g., reduce or eliminate) the occurrence of psychosocial stressors or the adverse consequences of them. The consistent finding in the literature that living alone, having low socioeconomic status, and being unemployed are significant risk factors for mood disorders. In other words, it means that weak or lacking social support (including social network, social interaction, and instrumental support) can also be considered a major risk factor. However, regarding social interactions, the frequency of the interactions is more important than the amount. Poor social support is related to onset, relapse, and recurrence of depression, but there is no evidence for the excess of depression among women caused by reduced social support.

COMORBIDITY

Individuals with major mood disorders are at an increased risk of having one or more additional comorbid Axis I disorders. The most frequent disorders are alcohol abuse or dependence, panic disorder, OCD, and social anxiety disorder. Conversely, individuals with substance use disorders and anxiety disorders also have an elevated risk of lifetime or current comorbid mood disorder. In both unipolar and bipolar disorder, men more frequently present with substance use disorders, whereas women more frequently present with comorbid anxiety and eating disorders. In general, bipolar patients more frequently show comorbidity of substance use and anxiety disorders than do patients with unipolar major depression. Recent clinical and epidemiological studies show that, if bipolar II disorder is also considered, comorbidity of substance use disorders and anxiety disorders is the highest in the bipolar II disorder subgroup. Because comorbid substance use disorders and anxiety disorders worsen the prognosis of the illness and markedly increase the risk of suicide among unipolar major depressive and bipolar patients, the data presented above are consistent with previous findings showing that bipolar patients (particularly bipolar II disorder patients) are at the highest risk of suicide. These findings also indicate that Axis I comorbidity might be among the most important contributing factor to that risk. However, there is a substantial overlap between mood and substance use disorders. Data from the NESARC study revealed that, 41 percent of those with alcohol use disorders met criteria for primary depression, 17 percent for concurrent depression, and 42 percent for secondary depression. This finding supports and extends the results of previous studies conducted among alcoholics in treatment and has strong diagnostic and treatment implications.

Untreated major mood disorders (and particularly bipolar disorder) carry extremely high risk of both completed and attempted suicide. This is partly due to the fact that they use more violent/more lethal methods. If patients with major mood disorders attempt or commit suicide, they do it mostly during their severe major (mostly mixed) depressive episode and less frequently in dysphoric mania but very rarely during euphoric mania and euthymia suggesting that suicidal behavior in patients with major mood disorder is a “state-dependent” and severity-dependent. Consequently, the early recognition and appropriate acute and long-term treatment of mood disorders is crucial for suicide prevention. The careful and systematic exploration of clinically detectable suicide risk factors helps clinicians to identify suicidal patients, but unfortunately, at the stage of present knowledge, all suicides cannot be predicted and prevented.
SERVICE PATTERNS

Adults

Despite the great progress in the diagnosis and treatment of depressions in the last two decades, they still remain underdiagnosed and undertreated. North American and European surveys show that approximately half of those who develop mood disorders seek treatment for them, but only a small fraction (about one-third) of recognized depressives receive appropriate treatment. The results of the NESARC study revealed that only 36.8 percent of those with a current mood disorder had sought disorder-specific treatment for a mood disorder. Interestingly, people with manic episodes were less likely than those with major depressive episodes to seek disorder-specific treatment. An increasing rate of health service utilization is related to increasing severity of depression and to comorbid psychiatric and medical disorders.

Despite the fact that many patients with depressive disorders seek help in primary care, general practitioners still have difficulties recognizing and treating depression. The current prevalence of major depression in primary care is approximately 10 to 15 percent and that of dysthymic disorder is approximately 6 to 8 percent. Paradoxically, because severe major depression is much more common among those with comorbid chronic medical disorders, depressions with significant somatic comorbidity, in particular, remain unrecognized in primary care. Population-based studies also show that in individuals with two or more chronic physical illnesses, the 1-year prevalence of severe major depression is fourfold higher than that of individuals without such conditions. Women more often seek treatment for their depression and are more compliant with the treatment than are men, but, unfortunately, “male depression” is less frequently recognized. Because there is no gender difference in the response to antidepressant pharmacotherapy, these facts can help to explain the so-called suicide paradox—that is, despite the fact that major depression is much more common in women, it is men who are markedly overrepresented among suicide victims. Besides general practitioners, other professionals (i.e., internists, cardiologists, neurologists) also frequently see depressed patients. The point prevalence of major depressive disorder in acute (medical–surgical hospital) care is also higher than 10 percent, a figure well in excess of the point prevalence rate for the general population. Concomitant depression increases the morbidity and mortality from concurrent medical illness, and patients with simultaneous medical disorder and depression are less compliant with treatment and take longer to recover than nondepressed medical patients.

Depressed patients, particularly those who go unrecognized, frequently seek general health care, but depression, if correctly identified, can be effectively treated even in primary care. On the other hand, despite the fact that more than half of suicide victims contact different levels of health care 4 weeks before committing suicide, the rate of adequate (antidepressive) pharmacotherapy among depressed suicide victims is disturbingly low. However, epidemiological and clinical studies, as well as the steadily increasing use of antidepressants (the latter is accompanied by a constant decline in national suicide rates in most well-developed countries, particularly in those with traditionally high suicide rates) indicate that, in the last 25 to 30 years, the referral, recognition, and successful treatment of depression increased, suggesting that the prognosis for depressive illness, in general, is improving. Given the high prevalence of depressive disorders in the population, and particularly in most clinical settings, as well as the strong relationship between untreated depression and suicidal behavior indicates that better and more widespread treatment of depression is an important part of
suicide prevention. The repeated postgraduate education of GPs and other healthcare workers in combination with gatekeeper training and public education is particularly useful.

**Youth**

Despite the magnitude and serious consequences of depression in youth, only about one-quarter to less than half of those with mental disorders receive mental health services. Factors associated with service utilization include ethnicity, high global impairment, comorbidity, prior history of depression, suicide attempt, and impact of the child’s problem on the family. School services are the most common point of entry for children seeking services, although those who enter through the education sector are least likely to transition to specialty mental health services. The actual diagnostic process and services provided differ dramatically by the context of entry to service.

There has been accumulating controlled research on the effects of antidepressants in youth, but few studies of either the comparative efficacy of various agents that are commonly used in clinical practice or of individual and family therapies either in conjunction with or independent from drug treatments. One study that demonstrated the efficacy of combined pharmacologic and psychotherapeutic treatment has provided a model for future studies that can guide policy in health services for adolescents.

**IMPACT OF MOOD DISORDERS**

The importance of role disability has become increasingly recognized as a major source of indirect costs of illness because of its high economic impact on ill workers, their employers, and society. The introduction of the concept of Disability Adjusted Life Years (DALYs), which estimate the disease-specific reduction in life expectancy attributable to disability and increased mortality has highlighted the dramatic public health impact of mental disorders. By the year 2020, it is estimated that psychiatric and neurologic disorders will account for 15 percent of the total burden of all diseases Major depression is the leading cause of disability among those age 5 and over, and the second leading source of disease burden surpassing cardiovascular diseases, dementia, lung cancer, and diabetes.

In the most recent estimates of the impact of chronic diseases by the WHO, 2.5 percent of the total proportion of DALYs was attributable to major depressive disorder and 0.5 percent to bipolar disorder. In terms of DALYs for Mental, Neurological, and Substance Use Disorders, 24.5 percent was attributable to major depressive disorder and 5 percent to bipolar disorder. Comparative studies of role disability reveal that the effects of mood disorder outweigh those of most other mental and neurological disorders with a few exceptions. The dramatic impact of mood disorders on lifetime disability highlights the importance of epidemiology in surveillance, understanding and control of the major mental disorders.

The global burden of mental disorders in children and adolescents up to 24 years of age has also been examined. Similar to studies within the United States, there is a broad range to estimates of the rates of mental disorders. A recent review reported estimates that ranged from 8 (in the Netherlands) to 57 percent (for young people receiving services in five sectors of care in San Diego, California, USA). Results from The Australian National Survey of Mental Health and Well Being showed that at least 14 percent of adolescents younger than 18 years had a diagnosable mental or substance use disorder within the previous 12 months, and this figure rose to 27 percent in the 18- to 24-year age. Meta-analysis of the childhood and
adolescent data has shown that at least one out of every four to five young people in the general population will suffer from at least one mental disorder in any given year. However, there is much less information on the burden of mental disorders in developing countries and substantial cross-cultural variations are likely.

**Mortality and Mood Disorders**

There are now several prospective studies that have investigated mortality among those with a range of mental disorders. The increased mortality associated with mood disorders has been well-documented. Data from large population registries in Sweden and Denmark have shown that bipolar disorder is associated with substantial elevation in risk of both mortality in general, particularly death by suicide. The mortality risk associated with mood disorders tends to decrease with age; that is, the high risk of death by suicide associated with affective disorders in the Danish Registry was much greater during the first 12 months following the initial admission compared to later years. No differences in excess mortality have been shown for different subgroups of mood disorders in either of these registries.

**HISTORICAL TRENDS**

Whereas early community surveys suggested a strong cohort effect for mood disorders, both retrospective and prospective studies show that there has been no direct evidence for a marked increase in the incidence and prevalence of depression over the past decades. The observed changes are mainly due, in particular, to artifacts of memory and, to a lesser degree, to higher subjective awareness, better definitions and methods of case identification, redistribution by age and sex (with higher rates among younger women being of recent origin), and increase in childhood-onset mood disorders. Similar findings have emerged for depression in youth with comprehensive meta-analyses showing that there has been no increase in rates of depression across the last three decades.

**REFERENCES**


13.3 Mood Disorders: Genetics

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INTRODUCTION

The substantial role of genes in the susceptibility to mood disorders has long been supported by family, twin and adoption studies. That mood disorders run in families is a common observation of patients and clinicians. However, genes clearly only contribute a predisposition that must interact with environmental factors in order to cause disease. Studies of the inheritance of different forms of mood disorder and other psychiatric disorders suggest complex genetic relationships. Different forms of illness such as bipolar II may share some, but not all, genes with bipolar I. Studies of a variety of phenotypes related to mood disorder suggest a similar pattern of partial genetic overlap. Alternatively, some aspects of mood disorder seem more quantitative in nature. Early attempts to identify the specific genes involved through linkage analysis of large families and association analyses of specific candidate genes were met with mixed success and few reproducible results. Very high throughput microarray-based methods more recently made possible large-scale genome-wide association studies (GWAS) that promised to identify additional genes. However, these studies also suffered initially from poor replicability, which has been improved through the use of increasingly larger samples. Yet, the identified risk genes presently explain only a small portion of the genetic variance in mood disorders. The identification of specific genes has a number of important clinical ramifications. Most importantly, a better understanding of basic pathophysiology may lead to novel treatments and drug targets. Better knowledge of pathophysiology may also inform future diagnostic systems based more on underlying biology, rather than symptom profiles. Additionally, pharmacogenetics, or the study of how genes influence medication response, is making progress and promises tools to aid physicians in drug selection.
GENETIC EPIDEMIOLOGY

Genetic epidemiological studies can provide a great deal of information about the familial and genetic nature of a disorder by examining the rates of illness among relatives. Such studies also address how different forms of mood disorder may differ in their genetic transmission and how they may relate to each other. However, these studies must be considered in the light of their various methodological limitations. First, many studies were conducted before the distinction between bipolar disorder and major depression; thus, the statistics from these studies pool both illnesses. Similarly, many studies preceded the introduction of operationalized diagnostic criteria, making comparisons across studies difficult. Additionally, if the results of a study are to be meaningfully generalized to the population, it is critical that the subjects to be studied are selected in a systematic fashion, free of ascertainment bias. For example, if probands (the first ill subject identified in a family) are selected based on their strong family history, then the results of a family study may inaccurately indicate a strong familial rate of illness in the population. Finally, for reasons of feasibility, many of these studies used the family history method, in which the rates of illness in family members are determined by questioning the proband about his or her family. Although there are several excellent standardized instruments available, this method is inherently less accurate than the direct interview method, in which each family member is interviewed to make a diagnosis.

Family studies address the question of whether a disorder is familial and compare the rates of illness among first-degree relatives of a proband with the disorder to either the rates in the general population or the rates in first-degree relatives of control subjects. Rates of illness are typically adjusted for age to indicate the morbid risk. Compared to a rate of 1 percent in the general population, family studies indicate a sevenfold higher morbid risk to first-degree relatives of bipolar probands, suggesting a strong familial risk. Similarly, family studies of probands with major depression reveal morbid risks for depression among first-degree relatives that are elevated two- to threefold over the general population. These data strongly support the familial nature of mood disorders. Furthermore, major depression is generally found at an elevated rate in the families of bipolar probands, although the rate of bipolar disorder is only slightly elevated in the families of probands with major depression. This familial overlap suggests some degree of common genetic underpinnings between these two forms of mood disorder.

Family studies clearly indicate that mood disorders are familial but are unable to distinguish whether it is genetic or environmental factors that mediate the familial transmission. Families might share a variety of different environmental factors that could transmit the illness, including shared exposure to infectious agents, toxins, and other brain insults. Twin studies provide the most powerful approach to separating genetic from environmental factors, or “nature” from “nurture.” The most common strategy is one in which both monozygotic (MZ) and same-sex dizygotic (DZ) twin pairs are identified with one twin having a mood disorder. The cotwins are then examined to determine the proportion of twin pairs in which both twins are affected. This is termed the concordance rate. As the twin pairs have been raised together and share the same environmental factors, a difference in concordance rate between MZ and DZ pairs reflects the role of heritable genetic factors. Twin studies generally find a two to fourfold increase in concordance rate for mood disorder in MZ twins compared to DZ twins, providing the most compelling data for the role of genetic factors in mood disorders. It is equally noteworthy that the concordance rate for MZ twins is only around 70 to 80 percent, not 100 percent. This is clear evidence that nonheritable environmental factors also play a
significant role in mood disorders. In studies that distinguish bipolar disorder from major depression, the MZ to DZ concordance ratio for bipolar–bipolar pairs is higher than that for depression–depression pairs, indicating a greater role for genetics in bipolar disorder than in depression. Furthermore, the rate of depression is elevated in the MZ cotwins of bipolar probands, and, to a lesser extent, the rate of bipolar disorder is elevated in the cotwins of probands with depression. This is consistent with the family data and argues for a genetic overlap between bipolar disorder and major depression.

A variety of limitations of twin studies have been raised, including the argument that parents treat MZ twins and DZ twins differently, so environment is not equally shared. Adoption studies provide an alternative approach to separating genetic and environmental factors in familial transmission. The most common experimental design is one in which probands are identified who have a mood disorder and were adopted at birth. The rates of psychiatric illness are then determined in both the biological and adoptive parents. Although only a limited number of such studies have been reported due to the difficulty in obtaining subjects, these results of such studies are supportive of the role of genetics and are generally consistent with the twin data.

In summary, family and twin data collectively suggest that genes explain approximately 75 percent of the etiology of bipolar disorder and 37 percent of major depression. More recently, methods have been developed to estimate heritability based on the genome-wide genotyping commonly done for GWAS as described in detail below. In this method, allele sharing is used as a measure of shared genetic vulnerability. The current understanding of the heritability of mood disorders has also been greatly enhanced by the recent availability of large population-based samples. For example, one study examined the extent of allele sharing among relatives in the Swedish national registry of more than nine million individuals from more than two million families. This study suggested that the heritability of bipolar disorder was 59 percent. Another study used population summary statistics to estimate heritability in a Danish sample of more than 2.6 million individuals. This study revealed heritability estimates of 62 and 32 percent for bipolar disorder and major depression, respectively. The heritability of bipolar disorder using population-based methods is quite a bit lower than that obtained from twin samples. This may be due to biases in how the twin samples were collected, as discussed above, which would inflate estimates of the genetic contribution. However, heritability estimates for major depression are reasonably consistent, whether derived from twin or population-based samples. Regardless of origin, all heritability estimates demonstrate that environment or other nonheritable factors must explain a substantial portion of risk for mood disorders, particularly major depression, since genes appear to contribute much less than 100 percent of the risk. Recent molecular methodologies, as discussed below, are helping to increase the current understanding of the nature of this heritability.

**GENETIC FEATURES OF MOOD DISORDERS**

For mood disorders, there is no 1-to-1 relationship between the genes (genotype) and the expressed trait (phenotype) that is transmitted in a simple and predictable fashion as observed for Mendelian traits. Therefore, mood disorders are said to be complex genetic disorders. What are the factors that contribute to this complexity?

Studies reporting heritability estimates of bipolar disorder that are less than 100 percent clearly demonstrate that it is a predisposition or susceptibility to disease that is inherited. The probability that someone will manifest a trait given that they have a certain genotype is
termed the penetrance of the gene. Mood disorders are said to have reduced penetrance (less than 100 percent). Furthermore, the penetrance of mood disorder genes increases with age, from a low risk for illness in childhood to a maximum in adulthood. Thus, in families of people with mood disorders, there are likely individuals who have the genes for mood disorder but do not develop the disease. These are termed nonpenetrant carriers. The converse of this situation is individuals who have mood disorder but do not have the genes. Such individuals with purely environmentally caused disease are termed phenocopies. These factors conspire to produce an indirect relationship between genes and disease.

Variable expressivity refers to the phenomenon of the same gene or group of genes resulting in a variety of different forms of illness. The twin data clearly demonstrate this for mood disorders. Identical twins with identical genomes are observed in which one twin has bipolar disorder and the other has depression. The sharing of genetic vulnerability between different forms of illness or disorders is also a manifestation of variable expressivity. Nonheritable factors must play a role in the specific manifestation of the predisposition to mood disorder. Variable expressivity may also result from modifier genes that influence the expression of the susceptibility gene. Such variability in expression is not unique to psychiatric disorders. For example, in neurofibromatosis, ill individuals range in manifestations and severity from those with only pigmented retinal lesions to others with multiple large tumors. Such a range in expression results from the same disease gene.

Another of the various factors complicating efforts to map genes for mood disorders is genetic heterogeneity. Heterogeneity refers to the likely role of multiple genes in the etiology of illness. The data for genetic heterogeneity in mood disorders at this point are compelling. There are several critical questions regarding the nature of heterogeneity in mood disorders: How many genes are involved? How large an effect does each gene have? In what ways do the genes interact to produce illness? These questions define a variety of models of heterogeneity, which are described below. Such models can be broadly grouped into those in which disease results from a few genes of major effect (major loci) and those in which disease derives from the combined action of many genes of small effect (polygenic). The answers to these questions are not currently known and are a topic of great debate currently framed as the portions of the missing heritability transmitted by common versus rare variants.

**MODE OF TRANSMISSION OF COMPLEX GENETIC DISORDERS**

Early attempts to understanding the mode of genetic transmission for mood disorders involved an examination of the pattern of transmission in families. This approach, termed segregation analysis, had relatively poor statistical power to distinguish forms of transmission but provided some support for autosomal dominant transmission. These studies also provided support for the polygenic multithreshold model described below.

Molecular tools and much larger sample sizes have led to a more powerful approach to these same questions. It is clear that mood disorders are complex traits, but in what ways might genes be transmitted so as to create the observed patterns of transmission and fit the complex nature of the phenotype? Current data suggest a mixture of genes of both large and small effect, which are transmitted in a variety of ways. The basics of genes and genetic transmission are covered elsewhere in this text. Here, different possible models of transmission will be reviewed in the context of their implications for mood disorders.
In single major locus transmission, one gene explains the majority of the genetic transmission in families. It results in the common Mendelian transmission patterns of autosomal dominant, autosomal recessive, and X-linked, as shown in the top pane of Figure 13.3-1. In autosomal dominant transmission, only one copy of the disease allele can cause illness, while in recessive transmission, two copies are necessary. X-linked describes the transmission of trait loci on the X chromosome. As described above, single major locus transmission of the same gene across many families seems highly unlikely, given existing data.

Alternatively, some phenotypes are better represented as numbers or quantitative traits, with blood pressure or height being classic examples. Such phenotypes are usually modeled as polygenic traits. Here, each gene contributes a small amount toward the overall genetic effect. The more polygenes an individual has, or the higher the genetic loading, the larger the value of the trait. In the simplest model, such traits are normally distributed in the population based on the distribution of individuals in the population with different numbers of polygenes. In Figure 13.3-1, this is illustrated in the middle pane. The question is whether such a model fits the observed data for mood disorders. Is the mood disorder phenotype best described as a continuous variable? One approach is to argue that the quantitative trait cannot be observed directly, but rather represents some latent trait that predisposes to mood disorder, like affective temperament. When an individual has a trait value above a certain threshold, they are more likely to develop the disease. These concepts are illustrated in Figure 13.3-2, according to a model in which affective temperaments mediate the underlying genetic disposition to bipolar disorder. This quantitative trait model is also consistent with the observation of milder forms of mood disorder spectrum traits in family members and the range in severity in the population. However, it is not clear exactly how to order different forms of illness as being “more” mood disordered. Is severe major depression less of a mood disorder than mild bipolar disorder? Though aspects of this model are attractive, the transmission of mood disorders is clearly more complex.
FIGURE 13.3-1. Models of genetic transmission. Many different models have been considered and tested to see if they explain the transmission of mood disorders. This is a selection of some of the more prominent models. In Mendelian or single major locus transmission (top pane), one gene transmits the illness. In a polygenic quantitative trait (QTL) model (middle pane), multiple genes add together to contribute to a quantitative trait. In this figure, the x-axis represents the number of polygenes that a given individual is carrying, as well as, the value of the resulting quantitative trait. The frequency of that trait value in the population is represented on the y-axis. In a QTL threshold model, illness results when an individual’s trait value, and therefore genetic loading, exceeds a critical threshold. In the bottom pane, some possible models of genetic heterogeneity are illustrated, including multiple single major loci, many loci of small additive effects, and gene interactions.
FIGURE 13.3–2. Affective temperament as a quantitative trait for bipolar disorder. This figure illustrates a polygenic, quantitative trait threshold model of bipolar disorder. If bipolar disorder is to some extent a polygenic trait, then it is likely that the risk variants occur and are transmitted primarily in mildly affected individuals who may have affective temperaments, but not illness. The affective temperaments would be normally distributed in the population, with more extreme temperaments conferring a greater risk for illness. This model is consistent with the observation of increased temperament traits in family members or bipolar patients, who are at a higher genetic liability for illness. At some critical threshold, the high genetic liability results in bipolar disorder.

The bottom pane in Figure 13.3-1 illustrates some models of genetic heterogeneity. Clearly, multiple genes are involved, but in what way do they combine or interact to produce illness? The first is a heterogeneity model involving multiple single major loci. In this model, multiple genes for mood disorder exist in the population, each able to alone cause mood disorder. As stated above, it is clear at this point that there are many genes for mood disorder. However, it remains very plausible that there could be many genes each operating as a single major locus in a subset of families. If the number of genes in the model is quite high, then mapping such genes could be very difficult. The second is an additive model, in which many genes may add together in order to produce a cumulative predisposition to illness. This is simply the polygenic quantitative trait model described above. A third model involves gene interactions. In this model, the probability of one gene manifesting the phenotype is modulated by the interacting effect of another gene. If an individual has one gene or the other, the risk for illness might be small, but if the individual has both disease alleles, then the risk increases. This is termed epistasis and is distinguished from an additive model in that the increase in risk from having two genes is greater than the sum of the risks of the individual genes. In a modifier model, the modifying gene has little or no effect on predisposition alone, but rather modifies the effect of another gene.

These three models of heterogeneity have very different implications for mapping genes for mood disorder. The heterogeneity model calls for possibly a large number of rare alleles, each of strong effect. In each individual and their family, the illness would result primarily from one gene, but that variant would be quite rare. In the polygenic model, each polygene contributes only a small amount to the overall genetic vulnerability. Under this model, each of the polygenes would be relatively common in the population, but the effect size of each
would be small, such that many polygenes would add together to produce the observed population prevalence of mood disorders. This implies that the alleles for mood disorder would primarily reside in individuals without mood disorder who have too few polygenes to develop the illness. Some of these individuals with a few risk alleles might instead have a spectrum trait, such as cyclothymic temperament. In the gene interaction model, each gene alone might have only a small effect. As it is particular combinations of genes that would convey larger genetic effects, the genes would best be identified by considering multiple genes simultaneously. These different models call for different approaches to mapping or identifying the disease genes.

GENETICS OF THE MOOD DISORDER SPECTRUM

The genetic relationship between the various forms of mood disorder is a topic of much recent interest. Among mood disorders, bipolar disorder and major depression are widely felt to have some sort of common genetic underpinning, although its exact nature is unclear. Twin and family data argue for major depression occurring in the twins or other relatives of bipolar probands at a greater rate than that expected by chance. However, it is less clear that bipolar disorder occurs in the relatives of probands with depression at an elevated rate. Twin studies indicate that “polarity” is usually consistent in MZ twins—in other words, bipolar–bipolar or depression–depression pairs are much more common than bipolar–depression pairs. Yet bipolar–depression pairs do occur. These data suggest that bipolar disorder and depression are neither completely identical nor completely distinct genetically. Rather, there is a partial genetic similarity.

A partial commonality of susceptibility genes would also predict that a portion of those with depression carry genes that may also predispose to bipolar disorder. Such patients have been said to have “bipolar III” disorder and have been the subject of much discussion and investigation. They are presumably identified by a family history of bipolar disorder or a history of developing hypomania or mania only in response to antidepressant treatment. Similarly, a hypomanic-like personality style termed hyperthymic temperament has been described. Patients with depression and a hyperthymic temperament are more likely to have a family history of bipolar disorder and to develop mania spontaneously. These patients with depression and a bipolar genetic diathesis may also be more likely to respond to lithium augmentation of antidepressant treatment. These data suggest that bipolar disorder and depression may be better understood as existing on a spectrum, consistent with a quantitative genetic trait.

Other forms of mood disorders have also been postulated to be, at least to some extent, genetically distinct. Although the risk for bipolar I is similar in the relatives of bipolar I or bipolar II probands, several studies have reported that the risk for bipolar II is greater than that for bipolar I in the relatives of bipolar II probands. This suggests that bipolar II, to some extent, breeds true and that a subset of the genes for bipolar disorder predisposes preferentially to bipolar II.
FIGURE 13.3–3. Familiality of clinical features in mood disorder. This figure illustrates how a family-based strategy can be used to evaluate different features of mood disorder that may be more or less genetically determined. In this sample of 589 bipolar families, relevant clinical features were evaluated for cluster within sibling groups. Familiality was measured as an odds ratio, which refers to the odds in favor of expressing the clinical feature. The strength of this association is indicated by a p value <0.05 (*) or <0.001 (**). Several clinical features displayed familiality under a narrow model that included only siblings with bipolar I disorder (BPI) and schizoaffective disorder bipolar type. These included features of bipolar disorder, such as psychosis, rapid cycling, and rapid mood switching, and comorbid conditions, such as alcoholism and panic disorder. These clinical features were more or less significant under a broad model that added bipolar II disorder (BPII) and major depression (MDD).

This family-based strategy has been used for a number of different features of mood disorder. Such evaluations have focused on clinical features that cluster within bipolar families and display familiality, as shown in Figure 13.3-3. Bipolar disorder with psychotic features is more commonly found in the families of probands with psychotic symptoms, suggesting that bipolar disorder with psychotic features may be a genetically distinct form of illness. Comorbid panic disorder also tends to co-occur in families and be associated with more rapid mood switching. The most strongly familial of bipolar disorder subforms is rapid cycling illness, which is twice as likely to occur in a relative if the proband has rapid cycling illness. Suicidality has also been shown to cluster in families in a way that suggests that it may represent a genetically distinct form of illness. This might result from a subset of mood disorder genes that are particularly virulent in terms of suicide or a modifier gene that influences suicidal risk in those vulnerable to depression. Early age at onset and comorbid alcoholism are other traits that have been reported to some extent to “breed true” in families with both bipolar disorder and depression.

Some traits have been associated with a higher heritability and hence a more pronounced role of genes. For example, major depression in general has a lower heritability than bipolar disorder. However, when families or twins are selected through a proband with an early age at onset and recurrency, a much higher heritability is observed. Furthermore, these traits of
early onset and recurrent illness run in the families. This suggests that these traits are associated with a stronger genetic effect and may result from a subset of the broader set of mood disorder genes. Such traits are important to identify, as they may enable the selection of a set of subjects with a more genetic form of illness that may be easier to map.

Several other kinds of traits have been hypothesized to share genes with mood disorders. It has been repeatedly observed that bipolar patients who respond well to lithium have a stronger family history of bipolar disorder. Lithium response has also been reported to cluster in families, suggesting that lithium responsive bipolar disorder is a genetically distinct form of illness. Some somatic illnesses have also been genetically associated with mood disorder. Migraine headache occurs at a higher frequency in the families of bipolar probands. Migraine in particular may be associated with bipolar II illness. Such somatic associations should not be surprising. At least half of genes expressed in brain are also expressed in other tissues. Therefore, mutations that predispose to mood disorder may also affect similar systems in different organs.

Aspects of temperament and personality may also be genetically related to mood disorders. Clinically, it is not unusual to observe relatives of mood disorder patients who have milder manifestations of mood disorder, such as dysthymia or cyclothymia. Family studies have supported this and shown that measures of cyclothymic, dysthymic, and anxious temperaments are elevated in relatives of bipolar patients. Similarly, measures of harm avoidance, reward dependence, novelty seeking, and self-directedness may be personality traits that are stable, genetically influenced, and associated with risk for depression. These observations raise the intriguing question of whether the alleles that contribute to risk for major mood disorders also play a role in affective temperament or personality in the general population. This is consistent with a polygenic quantitative genetic model as discussed above.

**Why Does Bipolar Disorder Exist? Do Mood Disorder Genes Convey a Selective Advantage?**

A possible selective advantage for mood disorders has long been speculated, particularly for bipolar disorder. Individuals with bipolar disorder may go through periods of hypomania or mania where their productivity is better than usual, or better than the general population. Bipolar disorder has long been associated with creativity, as illustrated by the mania-inspired artistic genius of Tchaikovsky, Lord Byron, Ernest Hemingway, and van Gogh, among many others. Many population-based studies support the familial connection between bipolar disorder and creativity. Milder spectrum forms of bipolar disorder, such as cyclothymic disorder, or bipolar spectrum traits, such as cyclothymic or hyperthymic temperaments may also convey greater productivity or creativity on a more common, less dramatic, and more consistent basis. It is easy to see how a need for less sleep, a greater drive to work, faster thoughts and speech, and charisma would be advantageous in aspects of today’s society. Hypersexuality is adequate alone from a genetic standpoint for such individuals to have an advantage in propagating their genes. Yet, bipolar disorder also results in great dysfunction and suffering.

Such a combination of positive and negative selective factors is not unusual in genetics. In the context of certain environmental conditions, selective advantages will tend to increase disease allele frequencies, while selective disadvantages will decrease them. The result is what is termed balanced selection. The frequencies of disease alleles in the population gradually change until the advantageous effects on selection are balanced by the deleterious
effects. In this way, selection by the environment determines the population allele frequency and the frequency of the disease. In the context of bipolar disorder, creativity, affective temperament, and certain personality traits, such as openness to experience, extraversion, and positive schizotypal traits, provide attractive targets for a balancing selection model. Such traits would be expected to increase with mild to moderate loading for genes causing risk for bipolar disorder. As genetic loading for illness increases, trait values would begin to decrease according to an inverted-U–shaped curve along with the increasing impairment associated with illness. This model is summarized in Figure 13.3-4 and suggests the influence of common variants distributed across the entire population, which is consistent both with the polygenic model of bipolar risk and with the observance of a stable worldwide prevalence rate. According to this model, first-degree relatives of patients and other allele carriers serve to perpetuate bipolar risk genes in the general population and benefit from the increased fitness that they confer. Such an idea has been difficult to test empirically. However, current methods that examine the correlation of the combined effects of all common genetic variants in the genome have begun to enable the direct testing of this idea, and an initial study demonstrated that bipolar disorder and creativity do indeed share genetic underpinning. Further progress in this area awaits the availability of potentially advantageous phenotypes for a sufficiently large cohort.

IDENTIFYING GENES FOR MOOD DISORDERS

Strategies for Gene Identification

The search for genes for mood disorders has, to date, focused primarily on bipolar disorder because of the stronger evidence for its genetic basis. In its early years, this search had a series of ups and downs of reported linkage findings and subsequent nonreplications likened to the highs and lows of the illness itself. However, the recent development of new methods for gene mapping has made this a very exciting time for psychiatric genetics. These methods will be addressed here specifically in relation to mood disorders. Two general strategies to disease gene identification have been employed: genome-wide mapping and candidate gene studies.
FIGURE 13.3–4. Balancing selection model of the bipolar spectrum. This figure provides an evolutionary and population genetics perspective on the bipolar spectrum. Shown is the proposed relationship of positive bipolar spectrum traits, such as creativity and affective temperaments, and the underlying shared genetic vulnerability. According to this model, positive traits increase with genetic loading for bipolar disorder (BP) up to a threshold, beyond which they begin to diminish according to an inverted-U–shaped curve along with the increasing impairment associated with illness. Polygenic risk reflects the combined influence of common genetic variants. This common variation is maintained in the population by clinically unaffected individuals, including first-degree relatives of patients and other allele carriers, who benefit from the increased fitness conferred by the associated positive, adaptive traits. The selective advantage in these individuals may greatly outweigh any selective disadvantage in severely ill individuals who are far fewer in number.

In genome-wide studies, markers are selected so as to cover the entire genome and are each tested for their genetic involvement in disease. The two primary advantages of this approach are that it is comprehensive, since all chromosomal regions are tested, and it is agnostic with no hypotheses regarding disease mechanism required. Genes are simply identified based on their position in the genome relative to the tested markers. This enables the discovery of new genes and mechanisms not previously suspected. However, this approach has some significant disadvantages. It may be quite expensive, requires very large sample sizes, and once a region is identified it may be difficult to identify the specific gene and risk variant.

The other major approach to disease gene identification is the candidate gene approach. In this approach, a specific gene is chosen based on its known role in systems relevant to disease. DNA markers are then genotyped and tested for genetic association. This approach
has the advantage of being simpler and more focused. However, since it is not systematic or genome-wide and also requires a hypothesis, it is less likely to result in novel discoveries.

Initially, genome-wide studies were conducted using genetic linkage. In this strategy, several hundred or several thousand markers that cover the genome are examined in families segregating the disease. Markers that are consistently inherited along with disease indicate chromosomal regions that may harbor disease genes. However, such regions may be quite large (10 to 20 Mb) and include hundreds of genes, such that identifying the specific gene may be difficult. Similarly, many linkage peaks may include multiple susceptibility genes, which further complicates disease gene mapping. While linkage has had some success in finding reproducible chromosomal regions, only a few specific genes have emerged from this work. It is felt by many experts that though linkage may work well for simple Mendelian traits, it may not be very powerful for complex or polygenic disorders, such as mood disorders. It may be the wrong tool for illnesses that are highly heterogeneous or have small gene effect sizes.

Over the past decade, GWAS have increasingly replaced linkage to become standard practice. It had long been known that genetic association was more powerful in detecting small gene effects than linkage. In genetic association, the frequencies of the alleles for a marker are compared between cases with the illness and controls. If an allele is more common in cases than controls then it may be involved in the illness. Association may be detected if the DNA variant used as a marker is the actual functional mutation itself or if it is simply very close to the actual mutation. The most common kind of DNA variant is a single nucleotide polymorphism (SNP), which consists of a single base substitution in the DNA sequence. The abundance and ease of genotyping SNPs has led to them becoming the most commonly used marker for association studies. As association requires the marker to be very close to the mutation, on the order of 1 to 10 kilobases, a very high density of markers is required to cover the genome. Several developments made this possible. First, the second phase of the Human Genome Project, called the HapMap Project, identified millions of SNPs and determined their frequency in different populations. Secondly, microarray technologies were developed that enabled the genotyping of hundreds of thousands of SNPs simultaneously on a chip for very low cost. Thus, it is now possible to genotype one million SNP markers spanning the genome.

Mood disorders likely result from a mixture of effects, ranging from rare variants of large effect to many common variants of small effect. Interactions among risk variants, as well as interactions of risk variants with the environment, are also likely to play a role in susceptibility. Although the mode of transmission in mood disorders appears very complex, genome-wide investigations through GWAS and sequencing may help resolve questions as to which variants contribute risk and how they are transmitted. While GWAS may be useful in identifying common risk variants, sequencing of many individuals will be needed to identify rare variants contributing to risk.

**Linkage Studies**

Numerous linkage studies of bipolar disorder have been conducted in a wide range of family samples that vary in the number of families, size of families, genetic strategy (e.g., sibling pair), and geographical and ethnic origin. These studies have implicated many different chromosomal regions meeting statistical significance, with some having been replicated with statistical significance. Across studies, linkage has been demonstrated for 4p, 6q, 8q, 16p,
18p, 18q, 21q, and Xq. The 22q region was first implicated in psychiatric illness by the observation of psychotic and mood symptoms in adolescents with a 22q11 deletion syndrome called velocardiofacial syndrome. The accumulation of multiple complete linkage scans has also enabled the application of meta-analysis methods to examine the results of multiple studies and calculate statistics that test the strength of a finding across multiple data sets. One such study examining 11 published genome scans of bipolar disorder identified 13q and 22q as the two regions with strongest evidence for linkage and as those most clearly replicated. Temperament traits have also been examined for linkage, as they have been proposed to represent the primary expression of the genes underlying illness. It has been argued that such traits are a more powerful phenotype for linkage and other gene mapping studies because they are closer to the genetic effect, and as quantitative traits, they convey more information. One study of bipolar families identified linkage for hyperthymic temperament on 1q, 2p, 6q, and 14q; for dysthymic temperament on 3p and 13q; and for irritable temperament on 6q.

While fewer linkage studies have examined major depression, several chromosomal regions, including 2q, 3q, 12q, 15q, and 18q, have been reported for a recurrent, early-onset form of illness that appears to be more heritable. Neuroticism is a personality trait, characterized by anxiety and dysphoria, and related to risk for major depression. Linkage of neuroticism has been reported for several chromosomal regions, including 1q, 4q, 6p, and 11p. Another personality trait related to depression, Harm Avoidance, has been mapped to 8p.

**Candidate Gene Association Studies**

Numerous candidate genes have also been examined for their possible role in the susceptibility to mood disorders. These candidates are selected largely because of their role in signal transduction, catecholamine or serotonin neurotransmission in particular. Other genes have been examined in association studies because they reside regions linked to illness, or they have shown association in other disorders, like schizophrenia.

The serotonin transporter (SLC6A4) is probably the most studied gene in psychiatric genetics. It is of great interest because it mediates the reuptake of serotonin and modulates synaptic serotonin levels; it is also the site of action of SSRI antidepressants. The promoter of the gene contains a repeat region that varies in the number of repeats between two major alleles. The short form of the repeat has been shown to express less serotonin transporter mRNA and protein than the long form and is associated with response to SSRI antidepressants. Alone it shows a relatively weak association with major depression and bipolar disorder. However, a prospective study measuring life events and the incidence of depression demonstrated that negative life events, such as death of a spouse or parent, strongly correlated with risk for major depression in those who carried the short form of the gene. This was one of the first demonstrations of an interaction between environmental stresses and a specific gene. It also emphasizes the importance of considering environment when examining gene effects.

Another candidate gene of high interest is brain-derived neurotrophic growth factor (BDNF), which is involved in the development and maintenance of catecholaminergic neurons. BDNF has been associated with bipolar and unipolar mood disorders and schizophrenia. A Val/Met substitution has been identified in the gene that affects processing of the peptide. This gene is particularly intriguing because it is a growth factor involved in brain development and neuronal maintenance. Antidepressants and lithium have been shown to increase its expression, and it likely plays a role in their neuroprotective functions.
Many candidate genes for mood disorder have been associated with multiple phenotypes. DRD4 and SLC6A3 (DAT1) have been associated with both mood disorder and ADHD. Most prominent is the overlap between genes for bipolar disorder and schizophrenia, as shown in Table 13.3-1. DAOA, NRG1, and DISC1 were each identified first through positional cloning studies of schizophrenia. Subsequently, they were shown to also be associated with bipolar disorder. These results are consistent with the family data and linkage data, where a large number of linkage peaks identified for bipolar disorder have also been reported for schizophrenia. They suggest that bipolar disorder and schizophrenia are more related in terms of genetics and mechanism than had been previously thought, as discussed below.

Table 13.3-1. Chromosomal Regions and Genes Associated with Bipolar Disorder or Shared between Bipolar Disorder and Schizophrenia

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Bipolar Disorder Only</th>
<th>Bipolar Disorder and Schizophrenia</th>
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<tbody>
<tr>
<td>Mania</td>
<td>Psychosis</td>
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<tr>
<td>Mood cycling</td>
<td>Cognitive deficits</td>
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<tr>
<td>Depression</td>
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<td></td>
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<tr>
<td>Linkage regions</td>
<td>4p16</td>
<td>6q21–25</td>
</tr>
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<td>16p</td>
<td>22q11–13</td>
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<tr>
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<td>21q21</td>
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<td>Xq25</td>
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<table>
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<th>Candidate genes</th>
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<th>Bipolar Disorder and Schizophrenia</th>
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</thead>
<tbody>
<tr>
<td>SLC6A3 (5p15.33)</td>
<td>DISC1 (1q42.2)</td>
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<tr>
<td>HTR4 (5q32)</td>
<td>DTNBP1 (6p22.3)</td>
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<td>DRD4 (11p15.5)</td>
<td>NRG1 (8p12)</td>
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<td>DRD2 (11q32.2)</td>
<td>BDNF (11p14.1)</td>
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<td>HTR2A (13q14.2)</td>
<td>DAOA (13q33.2)</td>
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<td>SLC6A4 (17q11.2)</td>
<td>COMT (22q11.21)</td>
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<td>MAOA (Xp11.3)</td>
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<th>Bipolar Disorder and Schizophrenia</th>
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<tr>
<td>VRK2 (2p16.1)</td>
<td>LMAN2L (2q11.2)</td>
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<td>TRANK1 (3p22.2)</td>
<td>ITIH1/3/4 (3p21.1)</td>
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<td>ADCY2 (5p15.31)</td>
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<td>SLC25A17 (22q13.2)</td>
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<td>MPP5 (7p15.3)</td>
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<td>IMMP2L (7q31.1)</td>
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<td></td>
<td>ADD3 (10q25.1)</td>
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<td>HLF (17q22)</td>
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<td>NCAN (19p13.11)</td>
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<td>MACROD2 (20p12.1)</td>
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Genome-wide Association Studies

The advent of GWAS has completely revolutionized the field of psychiatric genetics. GWAS gained primacy over linkage several years ago but have only recently begun to provide replicable results. As described above, this technology enables the genotyping of hundreds of thousands of markers simultaneously, thereby allowing association studies to systematically cover the genome. Many of the early GWAS did not yield strong evidence for association for any single gene, likely due to the use of sample sizes that were underpowered to detect small genetic effects. However, several genes began to show trends toward association across multiple studies, lending confidence to the results. A calcium channel, CACNA1C showed such correspondence between multiple studies, as did the gene encoding ankyrin G (ANK3). Other reported genes included the epidermal growth factor gene and diacylglycerol kinase eta (DGKH).

In 2007 the Psychiatric Genomics Consortium (PGC) was formed to combine GWAS datasets across the major psychiatric disorders in the hopes of identifying robust associations to genes and pathways underlying risk. By using a dataset consisting of more than 16,000 bipolar patients and controls, the Bipolar Working group of the PGC was able to confirm association to CACNA1C and ANK3 and identify a novel association to teneurin transmembrane protein 4 (TENM4). More recent analyses in an even larger sample of more than 52,000 individuals implicated 19 genes and regions, most of which reflect novel associations, as shown in Table 13.3-1. While the Depression Workgroup was initially unable to identify significant associations in a sample of over 53,000 individuals, ongoing efforts to increase the sample’s size have finally begun to bear fruit, with nine significant associations now identified in a sample totaling over 219,000 patients and controls. The large difference in the number of subjects needed to detect associations reflects the higher phenotypic complexity and lower heritability of major depression compared to bipolar disorder, as well as gender differences and a greater role of gene–environment interactions. However, it is anticipated that with increased sample sizes for mood disorders, additional genes will be identified that collectively explain a higher portion of the variation in disease risk. This phenomenon was successfully demonstrated by the Schizophrenia Workgroup, whereby quadrupling the sample to more than 150,000 patients and controls resulted in the identification of more than 100 additional significant associations and more than 30 percent of the risk for schizophrenia now explained by common genetic variants. It is expected that mood disorders will follow a similar pattern.

Several studies have shown that the specificity of the phenotype is much more important than large sample sizes in genetic analyses of complex disorders. The thought is that by using a more specific phenotype, the grouping of subjects in the analysis is more clinically similar and therefore more likely to share the same genetic influences. Thus, a better understanding and better utilization of subclinical phenotypes and comorbid states may lead to more powerful analyses for gene discovery. For example, a GWAS of temperament in a large bipolar sample revealed genome-wide significant associations to three distinct regions for the hyperthymic and irritable temperaments, where analysis of bipolar disorder as a phenotype failed to demonstrate significance to any region. This study demonstrates the potential power of quantitative phenotypes that may better index the underlying genetic and biological processes. Similarly, a recent study of comorbid eating disorders in the same bipolar disorder sample implicated the FXR1/SOX2-OT region, albeit at a level slightly below genome-wide significance. However, this region demonstrated genome-wide significance in two independent and very large GWAS evaluating eating disorders and schizophrenia,
respectively. Thus, an analysis of a small sample with a specific phenotype was able to replicate a prior association observed in related samples. Finally, another study examined the presence of comorbid externalizing disorders as a subclinical phenotype of bipolar disorder. Externalizing disorders included alcohol and substance abuse/dependence, pathological gambling, antisocial personality disorder, ADHD, and conduct disorder and were present in over 60 percent of the bipolar sample. The presence of such disorders significantly predicted a more severe course of illness characterized by an early age of onset of symptoms, more rapid mood switching, rapid cycling, more episodes of both depression and mania, and increased suicidality. This phenotype thus holds potential promise as a more severe bipolar phenotype to be evaluated in larger samples.

It is noteworthy that very little overlap is seen between the chromosomal regions implicated by linkage and GWAS of bipolar disorder. This is likely a reflection of the types of risk variants captured by each method. GWAS can only identify risk variants that are relatively common in the population, generally those with frequencies of 1 to 5 percent. While linkage can, in theory, identify both common and rare variants, the lack of convergence with GWAS data may be an indication that prior linkage studies have primarily detected rare variants in families. However, this remains to be verified through sequencing, as discussed below.

Studies of Rare Variation

While GWAS has begun to define some of the common variation contributing to risk for mood disorders, recent data suggest that many psychiatric disorders, including mood disorders, may result from multiple rare mutations of stronger effects. It is important to keep in mind that common SNPs currently explain only about 30 percent of the heritability of bipolar disorder, with the remaining genetic variance still to be discovered. This has been termed the “missing heritability,” and rare variation has been proposed as the primary constituent. In this model, genetic variants are rare because they are the result of relatively recent mutations, and enough generations have not passed for them to be positively selected and increase in frequency or negatively selected against as deleterious and decrease in frequency. It is thought that rare variants may include more variants of large effect, such that in each individual, disease results from only one or a few variants, yet each variant is very rare in the population or even unique to a family.

Several different types of rare variants exist, ranging from large structural variants, such as copy number variants (CNVs), to single nucleotide variants (SNVs). CNVs have been proposed to explain a significant portion of the genomic variation in humans. CNVs typically comprise a region of DNA that is duplicated many times, and the number of duplications is variable from individual to individual. Some are relatively stable and inherited, while others are spontaneous mutations in which one or more copies are added or deleted. The mechanism for these insertions and deletions is unclear but likely results from an error in DNA replication. These insertions and deletions range from a few thousand base pairs (kilobases) to many millions of base pairs (megabases). Typically, parts of one or more genes are deleted or interrupted such that gene function is eliminated or substantially altered. The human population contains a large number of very rare CNVs distributed across the genome.

While CNVs have been shown to play a significant casual role for some psychiatric disorders, particularly schizophrenia and autism, the role of CNVs in mood disorders is likely less prominent. Studies to date suggest that inherited stable CNVs do not contribute significantly to the cause of bipolar disorder, however, spontaneous CNV mutations do occur
more often in bipolar families. One of the challenges in studying CNVs is their rarity; though it is possible to demonstrate an increased rate of CNVs in general, identifying specific causal CNVs is difficult. CNVs were originally studied using the same DNA chips used for GWAS. Differences in the signal intensity indicated differing numbers of copies of a region. However, this technology made it difficult to detect CNVs below a certain size range, typically 10,000 to 100,000 base pairs. Though there is a great deal of copy number variation below this size range, its contribution to bipolar disorder remains unclear.

In order to access variation below this size range, including SNVs, DNA sequencing must be performed. The last 15 years have brought a dramatic decrease in the cost of DNA sequencing from approximately $3 billion for the first genome to around a thousand dollars. Though still expensive, it has begun to make possible a complete examination of the genome. Studies of this nature come in two main varieties: exome sequencing and whole genome sequencing. By using methods that select for exonic DNA, all of the protein coding sequence in an individual, their exome, can be selectively sequenced. However, this enables only an examination of the 2 percent of the genome that codes for proteins and is unable to examine regulatory regions in the genome that control when genes are turned on or off. In order to fully examine the genome, including regulatory sequences, whole genome sequencing must be performed. For many years, it was felt that the 98 percent of the genome that does not code for proteins was largely without function, or “junk DNA.” However, more recently, this estimate has been reversed to indicate that almost all DNA is functional and has a role in regulation of gene expression.

To date, only a limited number of exome or whole genome sequencing studies have been performed. As most variants are rare, these analyses typically compare the number of rare variants or functional variants between cases and controls on a gene-by-gene level. One study examining families using whole genome sequencing identified an excess of functional variants in genes in pathways related to voltage-gated calcium channel function and GABA receptors. These results fit well with those from GWAS, suggesting that susceptibility genes are likely affected by both common and rare variants. These studies also suggest that most of the variants involved in bipolar disorder are in regulatory regions of DNA and that most families are segregating several variants. Whole genome sequencing is the tool that delivers almost complete genomic information. The heritable causes of bipolar disorder will reside somewhere in these data. However, this era of human genetics is just beginning. Much larger sample sizes will be necessary to detect the rare variants that explain some portion of the missing heritability.

**Molecular Pathways**

Having discovered SNPs associated with bipolar disorder, the next challenge is to translate this into actionable biological knowledge. What abnormalities in neuronal function result from the causative SNPs, and how does this result in the symptoms of bipolar disorder? One approach to this important problem is to test gene pathways for enrichment of evidence of association. A large number of pathways are tested for enrichment, and the function of those pathways that are enriched may inform the cause of disease. This approach has highlighted a number of pathways of relevance, including CRF signaling, beta-adrenergic signaling, phospholipase signaling, glutamate signaling, and histone methylation. Pathway analysis, though informative, has a number of limitations, including the current availability of a very incomplete collection of pathways. As much of the pathway information comes from studies of other tissues and diseases, their relevance to the CNS is unclear. Furthermore, the
pathways vary in quality, with some derived from direct protein–protein interaction experiments and others simply a correlation in levels of expression. As a result, many are large pathway categories comprising many genes, which, at this time, provide relatively limited information.

**Functional Validation of Key Genes**

Several significant SNPs and genes identified by GWAS have been shown to have an effect on biological functions relevant to psychiatric illness. These “post-GWAS” studies provide invaluable validation of the genetic results and begin to inform the biology of mood disorders. One of the most important findings to emerge from GWAS of bipolar disorder is the involvement of the voltage-gated calcium channel complex. Many subunits of this complex have shown association to bipolar disorder, and its role in triggering neurotransmitter release in response to action potentials places it in a key regulatory position. A functional effect of the primary subunit involved, CACNA1C, has been suggested by several fMRI studies of bipolar disorder. CACNA1C genotype has been associated with reward responsiveness in healthy controls, anterior cingulate and hippocampal activation in episodic recall in controls, and amygdalar activation to emotional stimuli. Another prominent finding from GWAS is the gene ANK3, or giant-ankyrin. Ankyrin plays a role in anchoring components on the cell surface to the underlying cytoskeleton. It has recently been shown to also play a role in synapse formation and forming subdomains around AMPA receptor complexes. Knockdown of gene expression of ANK3 in mice resulted in lower anxiety and more activity, both of which were reversed by lithium. Though it is still early days for these functional studies, these are critical and the direction for the future, if lists of associated genes are to be transformed to a useful model of bipolar disorder pathways.

**GENETIC OVERLAP BETWEEN MOOD AND OTHER DISORDERS**

The relationship between bipolar disorder and schizophrenia has been debated since the distinction was made by Emil Kraeplin in 1899. Are they distinct disease entities, or do they exist on a spectrum? The definition of a disease entity should be based primarily on disease mechanism. Genetics is only one aspect of disease mechanism, but it does inform the discussion. This question has been explored in family studies by asking whether bipolar and schizophrenia “breed true.” A seminal study of families of bipolar probands by Tsuang and colleagues revealed an increased risk for bipolar disorder, as well as a smaller but significant increase in the risk for schizophrenia. Similarly, in families of probands with schizophrenia, there is a clear increase in the risk for schizophrenia, as well as a smaller increase in the risk for bipolar disorder. This is consistent with the model of partial genetic overlap, wherein a portion of the genes for one illness also predisposes to the other. The Maudsley twin study supports this same conclusion. Patients were shown over time to vary in presentation, such that at some points they were diagnosed with bipolar disorder and at others with schizophrenia. Also, a substantial portion of the genetic variance was explained by genetic factors common to the two disorders.

This genetic commonality between schizophrenia and bipolar disorder bears on the nature of schizoaffective disorder. Though commonly observed clinically, schizoaffective disorder has been variously defined through the years. It is consistent with a spectrum of illness between bipolar disorder and schizophrenia, where schizoaffective disorder lies in the middle. The genetic relationship of schizoaffective disorder to mood disorders also involves the role of psychosis in the genetics of mood disorders. Studies examining familial risks in relatives of
schizoaffective patients have been undertaken in order to attempt to clarify this issue. However, they have led to largely inconsistent results, some finding an increased risk of schizophrenia and some an increased risk of bipolar disorder. A possible explanation is that schizoaffective disorder represents a mixture of patients, some with bipolar and some with schizophrenia diatheses. This is supported by data that find an increased rate of bipolar disorder among the relatives of probands with the bipolar subtype of schizoaffective disorder. Similarly, schizophrenia has been reported to be increased among the relatives of probands with the depressive type of schizoaffective disorder. However, at least from a genetic perspective, these results suggest that the Kraepelinian distinction between the disorders is only partially valid and that both schizophrenia and mood disorders lie at the extremes of a spectrum of a common genetic liability.

The partial genetic overlap between bipolar disorder and schizophrenia has been supported by the identification of chromosomal regions and genes involved in both disorders. Some of this genetic overlap is shown in Table 13.3-1. One study investigated the contribution of common genetic variation to several psychiatric disorders, as well as the degree of overlap between them. Such studies use GWAS data to estimate the contribution of common variants, or the SNP heritability. This study revealed that common variants contribute approximately 25 percent of the risk for bipolar disorder and that 68 percent of this risk is shared with schizophrenia, as shown in Figure 13.3-5. These estimates therefore reflect a total genetic overlap, or coheritability, of about 17 percent due to common variants. Furthermore, many of the genes from the most recent GWAS conducted by the PGC Bipolar Working Group reflect shared associations with schizophrenia, as shown in Table 13.3–1, and likely contribute to this observed coheritability. Both bipolar disorder and schizophrenia also show significant overlap with major depression, with more than 40 percent of the common variation being shared between these disorders. These numbers are likely to increase with increasingly larger sample sizes for these types of analyses. It is also important to note that these heritability and coheritability estimates do not account for the potential effects of rare risk variants, some of which may also be shared between disorders. This may account for the significantly lower heritability estimates observed using GWAS data compared to those obtained from twin and population-based studies.
Genetic relationships between psychiatric disorders. This figure illustrates the genetic relationship between bipolar disorder (BP), major depression (MDD), and schizophrenia (SZ), each of which are indicated with respect to their prevalence rate. GWAS data were to evaluate the proportion of the genetic variance in each disorder that is due solely to common variation, or the SNP heritability. A common genetic vulnerability of >20% was shown for all three disorders, as indicated in bold text. These SNP heritability values are much lower than the heritability estimates derived from twin and population-based samples, which include all types of genetic variation and indicate a heritability of about 60% (vs. 25%) for bipolar disorder, 37% (vs. 21%) for major depression, and >60% (vs. 23%) for schizophrenia. Some genes are less specific and contribute to risk across multiple phenotypes. This is reflected in the shared common genetic variance, or coheritability, of 68% for bipolar disorder and schizophrenia and >40% for major depression with both disorders.

Genetic overlap with mood disorders has also been hypothesized for other psychiatric disorders. ADHD, for example, may share some genetic risk factors with bipolar disorder. Risk for ADHD has been shown to be elevated in the children of bipolar probands, and the risk for bipolar disorder is elevated in the parents of ADHD probands. Distinguishing these two disorders is a common diagnostic dilemma that may result in part from shared genetic contributions and mechanisms. However, studies of SNP coheritability have not revealed a significant genetic overlap as might be expected from the family data. The reason for this is unclear, but it may involve samples that are too small to detect an effect or perhaps a more prominent role for rare variants.
PHARMACOGENETICS

One of the first clinical applications of genetics in psychiatry may come from the newly emerging field of pharmacogenetics. Medication responses in mood disorders frequently have robust individual differences. Though response has been related to certain clinical factors, genetic differences likely play a major role. Much of the focus of this field to date has been on drug metabolism. Genetic variation in the cytochrome P450 system influences the degradation of a number of drugs. This can result in wide variation in serum level in different patients on the same dose. Monitoring such effects may help explain the lack of efficacy of drugs in some patients or predict possible toxicity due to high serum drug levels in poor metabolizers. Much, if not most, of the variation in response is likely due not to hepatic metabolism, but rather variation in genes that are drug targets or involved in the pathways modulated by drugs. One of the most intriguing aspects of pharmacogenetics is the implication for disease mechanism. A drug may work in one patient with depression and not another because the two patients have illnesses that are biochemically distinct. In other words, a drug may be effective only in a subset of patients whose illness involves dysfunction of the pathway that is modulated by the drug. A gene variant may predict response because it is associated with a form of mood disorder that involves that pathway. In this way, drug response may be a powerful phenotype for dissecting mechanistically different forms of illness. Alternatively, the gene variant may impact the ability of the drug to modulate its target pathway and have little effect on disease vulnerability.

Several other genes have been reported to predict drug response in mood disorder. A G protein subunit gene (GNB3) has been reported to predict response to antidepressants and lithium. BDNF and the gene for its receptor, NTRK2, have been associated with lithium response. In addition to influencing SSRI response, the serotonin transporter has also been reported to predict antidepressant-induced mania and antidepressant response to sleep deprivation. The risk for antidepressant-induced mania has also been shown to be associated with this gene. Recently, GWAS results have been reported for lithium response, including a large collaborative sample of over 2,500 patients retrospectively assessed for lithium response. This study identified a long noncoding RNA (lncRNA) significantly associated with lithium response, which was replicated in a smaller prospective sample. The intriguing aspect of this finding is that the lncRNA likely regulates the expression of a group of genes that may provide further information regarding genes involved in lithium response.

Other studies have focused on the clinical effectiveness of a panel of SNPs associated with drug response. These panels largely comprised SNP variants in CYP 450 enzymes along with some pharmacodynamics SNPs. When doctors and patients were randomized as to whether the doctor received the results of such tests, the group with the pharmacogenetics data had superior outcome. Much of this effect resulted from avoiding medications that the patient could not metabolize and would thus cause intolerable side effects. Although research in this area is still in its infancy, it promises a powerful tool for future clinicians who one day may use a DNA test panel to optimize the selection of medications for individual patients, thereby reducing the trial and error involved in medication treatment.

GENETIC COUNSELING

Based on the observation of psychiatric illness in their own families or the increasing public awareness of psychiatric genetics, patients frequently ask clinicians two questions: Are mood disorders genetic? What is the risk to my children or grandchildren? The answer to the first
question is easy: Yes, mood disorders are genetic, as is evidenced by the large body of epidemiological data summarized in this chapter. However, it is important that patients understand that mood disorders are only in part genetic. The twin studies argue strongly that only 70 to 80 percent of the etiology of mood disorders is genetic. Therefore, it is a predisposition to illness that is inherited and interacts with other nonheritable factors.

The risk to children and grandchildren is the more difficult question and the one that deserves the greatest consideration. The family data indicate that if one parent has a mood disorder, a child will have a risk for mood disorder of between 10 and 25 percent. If both parents are affected, this risk roughly doubles. It is important to take a careful family history to more accurately predict risk for a specific family. Several factors from the family history should be considered. The more members of the family that are affected, the greater the risk to a child. The risk is also greater if the affected family members are first-degree relatives, rather than more distant relatives. A family history of bipolar disorder conveys a greater risk for mood disorders in general and, specifically, a much greater risk for bipolar disorder. The presence of more severe illness in the family also likely conveys a greater risk. These factors should be considered together in forming an estimate of risk for the concerned parent.

Equally important to providing the estimate of risk is providing guidance in interpreting and responding to that information. Patient’s reactions to risk information will vary greatly depending on his or her own personal experience with the illness. Some will be relieved that it is so low, whereas others will be fearful that it is so high. It is important to emphasize that their child carries a risk or predisposition to illness, rather than a certainty of illness. It is also useful to emphasize the range of illness, from mild to severe, that could result, as well as the availability and efficacy of treatment. Ultimately, the use of such information in family planning is a highly personal decision. Some patients may choose to not have children. For existing children, it is important to educate parents about the typical age of onset, presenting symptoms, and the importance of early recognition and treatment. However, this must be balanced with the goal of not labeling the child or being overly protective.

FUTURE DIRECTIONS AND IMPLICATIONS OF IDENTIFYING SUSCEPTIBILITY GENES

Though much is understood about the familiality and heritability of mood disorders, the identification of specific genes has been challenging. Studies to date have reproducibly identified a number of genes; though, these genes together explain only a small portion of the genetic variance. It remains unclear how many genes are involved and how the illness is transmitted.

New technologies are now being used that may yield answers to some of these questions. GWAS have shown that common variants contribute significantly to heritability. Yet, mood disorders may not be primarily polygenic and the result of common alleles. It appears likely that they are highly heterogeneous and that cases may result from either many common variants or very rare mutations of strong effect. To identify these very rare variants, each individual would need to be fully sequenced. As discussed above, these studies are just beginning but already have begun to provide information about the relationship between common and rare variants in disease causation.

The availability of large datasets generated by DNA sequencing thousands of subjects and millions of SNPs will also enable the testing for a variety of interactions. It is very likely that
much of the genetic variance is explained by gene–gene interactions. Genes may interact to produce a risk for illness greater than the sum of their individual effects. It is presently, unclear how important such interactions are for mood disorders. Detection of interaction effects is only possible with large datasets. Ultimately, a more comprehensive understanding of the genetics of mood disorder may entail complex models of the interaction of numerous genes. As a better understanding of environmental effects becomes available, these will be incorporated into such models. Although some environmental effects may be nonspecific, it seems likely that at least some will reflect specific gene–environment interactions. Such interactions may be difficult to detect and will add substantial complexity to the overall model of mood disorder genetics. At this point, it seems promising that most genes for mood disorders can be identified through such large, though tractable, projects.

What will be the implications of this knowledge? The most immediate impact may well be on public opinion. Psychiatrically ill persons have long experienced the stigma and discrimination that portions of the public impose out of fear and ignorance. The acceptance of major mental illnesses as brain disorders has been slow. The definitive identification of genetic causes may have a highly beneficial impact on public understanding and acceptance.

This knowledge should also have a dramatic impact on the understanding of pathophysiology and approaches to treatment for mood disorders. Most current theories of pathophysiology are based on the mode of action of therapeutic agents, which were, for the most part, discovered serendipitously. The site of action of therapeutic drugs is not necessarily either the site of the genetic defect or the primary site of the pathophysiology. The identification of disease genes may point to entirely new systems involved in the pathophysiology or components of currently implicated systems that were not previously known. It is hoped that such an understanding may lead to the rational drug design long sought by patients, clinicians, and pharmaceutical companies. The result may be new drugs that act via completely novel mechanisms, possibly with greater efficacy and specificity.

The identification of disease genes will likely have a major impact on diagnosis and nosology. Just as the diagnosis of jaundice has given way to a classification scheme based on pathophysiology, it is likely that, in the future, the diagnosis of major mood disorders may be specific to disease mechanism. Mechanism-specific diagnoses may dictate the use of different, more specific, and more effective treatments. Finally, such knowledge will carry with it danger and responsibility. Premorbid DNA testing that would indicate the degree of genetic vulnerability to major mood disorders could become available. Those with psychiatric disorders will then face the same issues of genetic testing currently faced by families with Huntington disease or breast cancer: Will at-risk family members want such information? How will they use it? How will they cope with it? How can psychiatrists assist them in these decisions? Finally, how can patients be protected from discrimination based on such information?

In summary, genetic studies promise a new era of understanding and treatment of mood disorders. Identification of genes alone will not elucidate pathophysiology but will merely point the way for the application of modern neuroscience methods in the equally large task of understanding mechanisms. Recent results suggest that such guidance may not be far away.
REFERENCES


13.4 Mood Disorders: Clinical Features

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TERMINOLOGY

Mood disorders are characterized by pervasive dysregulation of mood and psychomotor activity and by related biorhythmic and cognitive disturbances. The rubric of affective disorder, which, in some European classifications, also subsumes morbid anxiety states, is increasingly being replaced by the nosologically more delimited concept of mood disorder. Thus, mood disorder is now the preferred term in the WHO’s tenth edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and the American Psychiatric Association’s (APA’s) fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Official mood disorder categories in current use include bipolar disorders (with manic or hypomanic, depressive, or mixed episodes) and major depressive disorders and their respective attenuated variants known as(1)
cyclothymic and dysthymic disorders (called persistent depressive disorder in DSM-5). The term unipolar is avoided in DSM-5 because major depressive disorder, especially when early in age at onset, is an unstable diagnosis and is liable to switch to bipolar. Conditions that, in earlier editions of these manuals, were categorized as endogenous depression, involutinal melancholia, and psychotic depressive reaction have been incorporated into major depressive disorder. Although the neurotic–endogenous distinction has been officially deleted, the term melancholic features is now used to qualify major depressive disorders in which biological concomitants predominate. The United States and international classifications recognize the common occurrence of mixed anxiety–depressions, which underscores the value of the broader affective disorder rubric. It is uncertain whether classic neurasthenic conditions, which have recently reemerged and overlap to some extent with the so-called chronic fatigue syndrome, should be classified under this broad rubric.

**RECENT DIAGNOSTIC TRENDS**

The reshuffling and reclassification of various affective conditions into the mood disorders chapter of the APA classification in DSM-5 have, on balance, considerably broadened their boundaries. This change reflects, in part, developments in pharmacotherapy that have resulted in considerable alleviation of suffering for persons whose illnesses fall short of and sometimes beyond the boundaries of classic mood disorders. As a result, many individuals with recurrent mood disorders who would have been disabled can now expect to lead a life relatively free of major episodes and major personal and occupational disruptions. Such gratifying results have, in turn, helped to destigmatize this group of disorders. Destigmatization has been further facilitated by published self-revelations of famous persons with depressive and bipolar disorders. Unfortunately, access to competent mental health care is not available to large segments of the population. Moreover, destigmatization, which has led to global efforts to detect and to treat mood disorders—particularly depression—in public and private sectors, may have had unintended sequelae. Despite the obvious public health advantages of such destigmatization, some authorities nonetheless now contend that a global depression-centric perspective has emerged in psychiatric and general medical sectors at the expense of bipolar disorders and may have led to overtreatment with antidepressants and unmasking of latent bipolar disorders. Others believe that the opposite to be true—that it is bipolar disorder that is overdiagnosed and mood stabilizers that are overused. The data, however, indicate that, on balance, it is the continuing underdiagnosis of bipolar disorder that presents the greatest threat to public health. Indeed, recent epidemiologic data suggest considerable disability in untreated or inadequately treated bipolar disorder.

**SPECTRUM OF MOOD DISORDERS**

The foregoing considerations notwithstanding, the increasing clinical diagnosis of major depressive and bipolar disorders should not be dismissed as mere therapeutic fad. External validating strategies, such as familial-genetic studies and prospective follow-up, can now be used to buttress the broadened concept of mood disorders, including that of bipolar disorder. New research comparing monozygotic and dizygotic twins has demonstrated that the genetic propensity to mood disorders embraces entities that extend beyond endogenous depression (melancholia) to subsume a larger variety of depressions, including some encountered in persons in the community who have never received psychiatric treatment. Although such data might seem counterintuitive to those who would restrict depression to a core primary “biological” disease, they suggest that the constitutional predisposition for affective dysregulation occurs in as many as one of every three persons. That ratio is similar to the
proportion of those who progress to a full depressive syndrome after bereavement, rhesus monkeys developing depressive-like behavior after a separation paradigm, and dogs that develop learned helplessness after inescapable shock. The fact that these rates are considerably higher than those observed in clinical populations suggests that many people possess protective factors against major depressive episodes; alternatively, the data suggest that other factors determine which person with emotional distress becomes a clinical case. A great deal might therefore be revealed about the nature of pathological affective processes through the study of self-limiting affective conditions on the border of mood disorders.

Evidence from long-term prospective studies indicates that the course of mood disorders consists of various gradations of affective oscillations from the subsyndromal level to the syndromic level. Major episodes represent an operational convention to define a clinical threshold. Subchronic course, dominated by subthreshold symptoms, occurs in 50 to 60 percent. This is equally true for major depressive disorder and bipolar disorders. Detecting the illness in its subthreshold stage and treating interepisodic subthreshold phases are important clinical considerations.

The suffering and dysfunction resulting from mood disorders are among the most common reasons for consulting psychiatrists and other physicians. In fully developed cases of depression, all activity stops—including creative powers—and life is grim and in total disarray, as portrayed in Albrecht Dürer’s engraving (shown in Fig. 13.4–1) of interest, the ladder and the angel-like portrayal of the melancholic subject in this engraving promise that the illness that can bring descent into the hell of depression can also permit ascent into the heavens and creativity. Such creativity, however, is largely limited to a few talented individuals with the milder forms of bipolarity, such as bipolar II and at the temperamental level. Many with the manic extremes of the illness have poor judgment and insight, refuse treatment, and suffer a deteriorative course.

All great physicians of the past, beginning with Hippocrates, have devoted considerable space in their general medical texts to the clinical characterization of melancholic and manic states, as well as their alternations in the same patient. The relationship of anxious and melancholic states was also known. A broad spectrum of affective disturbances—ranging from the relatively mild temperamental variants (represented in the official US nosology by dysthymic and cyclothymic disorders) to their severest forms (including what today is considered mood disorder with mood-congruent and mood-incongruent psychotic features)—has been described in classical medical and psychiatric treatises. Finally, classical authors noted that melancholia and certain physical diseases shared seasonal exacerbation, and they described the common occurrence of alcohol indulgence, especially in individuals prone to mania. These boundary problems continue to pose challenges today, with the addition of substance use disorders.
FIGURE 13.4–1. *Melancholia* by Albrecht Dürer (1471 to 1528).
AFFECTS, MOODS, TEMPERAMENTS, AND MORBID MOOD STATES

Ethological Considerations

Affects and moods refer to different aspects of emotion. Affect is communicated through facial expression, vocal inflection, gestures, and posture and (according to current ethological research) is intended to move human beings and other primates to appraise whether an individual is satisfied, distressed, disgusted, or in danger. Thus, joy, sadness, anger, and fear are basic affects that serve a communicative function in primates as well as many in other mammalian species.

Affects tend to be short-lived expressions reflecting momentary emotional contingencies. Moods convey sustained emotions; their more enduring nature means that they are experienced long enough to be felt inwardly. Moods are also manifested in subtle ways, and their accurate assessment often requires empathic understanding by the interviewer. The words that persons use to describe their inner emotions may coincide with the technical terms used by researchers or clinicians and often vary from one culture to another. Furthermore, the inward emotion and the prevailing affective tone may be discordant. This conflict could be due to deliberate simulation (i.e., the person does not wish to reveal his or her inner emotion), or it could result from a pathological lesion or process that has altered the emotions and their neural substrates. Thus, evaluating moods and affective expression requires considerable clinical experience. Such evaluation is obviously of great importance in differential diagnosis. Finally, it is of great usefulness in the therapeutic process; the admonition to “go after the affect” in psychotherapy helps to find where it hurts, thereby making treatment possible.

Sadness and Joy

The normal emotions of sadness and joy are part of everyday life and should be differentiated from major depressive disorder and mania. Sadness, or normal depression, is a universal human response to defeat, disappointment, or other adversities. The response may be adaptive, in an evolutionary sense, by permitting withdrawal to conserve inner resources, or it might signal the need for support from significant others. Transient depressive periods also occur as reactions to certain holidays or anniversaries, as well as during the premenstrual phase and the first week postpartum. Termed, respectively, holiday blues, anniversary reactions, premenstrual tension, and maternity blues, they are not psychopathological per se, but individuals predisposed to mood disorder may develop clinical depression during such times.

Grief

Normal bereavement or grief, considered the prototype of reactive depression, occurs in response to significant separations and losses, such as death, divorce, romantic disappointment, leaving familiar environments, forced emigration, or civilian catastrophes. DSM-5 tends to limit the concept of normal grief to loss due to the death of a loved one—a condition that it considers as an exclusionary criterion for major depression. However, the work of Elie Karam and colleagues showed that bereavement and other losses associated with the civil war in Lebanon served as potent forces in depression formation. The same was true for the losses due to the earthquake in Armenia. The boundary behavior and clinical depression are blurred in reactions to such complex losses. In addition to depressed affect that
is appropriate to the loss, bereavement reactions are characterized by the prominence of sympathetic arousal and restlessness believed to represent, from an evolutionary perspective, physiological and behavioral mechanisms to facilitate the search for the lost object. Like other adversities, bereavement and loss do not generally seem to cause depressive disorder, except in individuals predisposed to mood disorder. Reactions to major catastrophes might represent a partial exception.

Elation

The positive emotion of elation is popularly linked to success and achievement. However, paradoxical depressions may also follow such positive events, possibly because of the increased responsibilities that often have to be faced alone. Elation is conceptualized psychodynamically as a defense against depression or as a denial of the pain of loss, as exemplified by maniacal grief, a rare form of bereavement reaction in which elated hyperactivity may replace the expected grief. The character of the “merry widow” in opera seems to be of similar derivation.

Other pseudomanic states include the brief energetic and unusually lucid periods encountered in dying patients or in those who need to take superhuman action in the face of unusual duress, both of which have been conceptualized as a flight into health. In predisposed persons, such reactions might be the prelude to a genuine manic episode. Sleep deprivation, which commonly accompanies major stressors, might represent one of the intermediary mechanisms between stressor and adverse clinical outcome.

Affective Temperaments

Another mediating factor between normal and pathological moods is temperament. Most persons have a characteristic pattern of basal affective oscillations that defines their temperament. For instance, some are easily moved to tears by sad or happy circumstances, whereas others tend to remain placid. Normally, oscillations in affective tone are relatively minor, tend to resonate with day-to-day events, and do not interfere with functioning. Some persons exhibit greater variability of emotional responses whereby, with no obvious provocation, the person alternates between normal mood and sadness or elation. Temperament traits tend to cluster into basic types. A worrying temperament associated with generalized anxiety disorder is often complicated by depressive episode: It overlaps considerably with the depressive temperament; such inclination to melancholy makes the person more easily sink into weary and sad moods and occurs in 3 to 6 percent of the general population. The hyperthymic temperament, in which the person is naturally inclined toward cheerful moods, has been reported in 2 to 5 percent; the cyclothymic temperament, swinging between cheerful and sad moods, characterizes 4 to 6 percent of young adults. All four types have an early insidious onset and tend to persist throughout adult life. Of interest, these temperaments may be the prelude to episodes of depressive or hypomanic and manic polarity, which underscores the inherent instability of temperamental inclinations. Marked irritable-explosive traits occur in 2 to 3 percent of young persons and tend to attenuate by middle age. Current data suggest that such traits often coexist with the mood–labile cyclothymic type, representing the dark “borderline” side of this temperament.

An examination of the traits associated with these temperaments can provide the rationale for the hypothesis about the social and evolutionary functions that they subserve (Table 13.4-1). Thus, the person with a depressive temperament is hard working, dependable, sensitive to the
suffering and needs of others, and suitable for jobs that require long periods of devotion to meticulous detail; such persons are said to shoulder the burdens of existence without experiencing its pleasures. A person with the hyperthymic temperament, endowed with high levels of energy, extroversion, and humor, assumes leadership positions in society or excels as a performer in media or entertainment; such persons are also successful from a Darwinian perspective in that they are adept in amorous advances and engender a large number of offspring. In talented persons, the cyclothymic temperament, which alternates between sadness and elation, could provide the inspiration for love and for the emotional intensity needed for composing music, writing poetry, and painting. A person with the irritable temperament might be best suited for a military career or even revolutionary action. The danger with persons with extreme temperaments is that they could swing too far in one or the other direction or in both directions (i.e., major depressive, manic, or mixed episodes). Use of such substances as alcohol, caffeine, and other stimulants might further destabilize affective regulation in persons with those attributes. Some adolescent girls with irritable cyclothymia might develop the extreme emotional disequilibrium that, in contemporary psychiatry, is considered borderline personality disorder. Temperament concepts can enrich understanding of the boundary between normal moods and emotional disorders and can supplement the DSM-5 descriptors of personality disorders with valuable information about individual vulnerability and assets. A new instrument—the Temperament Evaluation of Memphis, Pisa, Paris and San Diego—has been developed in an autoquestionnaire version (TEMPS-A) and validated in at least 12 languages.

Table 13.4–1. Attributes, Assets, and Liabilities of Depressive and Hyperthymic Types Derived from Classic Concepts of Temperaments

<table>
<thead>
<tr>
<th>Depressive</th>
<th>Hyperthymic</th>
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<tbody>
<tr>
<td>Gloomy, incapable of fun, complaining</td>
<td>Cheerful and exuberant</td>
</tr>
<tr>
<td>Humorless</td>
<td>Articulate and jocular</td>
</tr>
<tr>
<td>Pessimistic and given to brooding</td>
<td>Overoptimistic and carefree</td>
</tr>
<tr>
<td>Guilt-prone, low self-esteem, and preoccupied with inadequacy or failure</td>
<td>Overconfident, self-assured, boastful megalomaniac</td>
</tr>
<tr>
<td>Introverted, with restricted social life</td>
<td>Extroverted and people seeking</td>
</tr>
<tr>
<td>Sluggish, living a life out of action</td>
<td>High energy level, full of plans</td>
</tr>
<tr>
<td>Few but constant interests</td>
<td>Versatile with broad interests</td>
</tr>
<tr>
<td>Passive and “sensitive”</td>
<td>Overinvolved and meddlesome</td>
</tr>
<tr>
<td>Reliable, dependable, and devoted</td>
<td>Uninhibited and stimulus seeking</td>
</tr>
</tbody>
</table>

**Morbid Mood States**

Mood disorders represent abnormal or extreme variations in mood and associated manifestations and are characterized by the following features: pathological mood change, endoreactive moods, recurrence, and impairment.

**Pathological Mood Change.** Pathological moods are distinguished from their normal counterparts by being out of proportion to any concurrent stressor or situation; being unresponsive to reassurance; being sustained for weeks, months, and, sometimes, years; and having a pervasive effect on the person, such that judgment is seriously compromised by the mood.
Endoreactive Moods. Depression and mania are diagnosed, respectively, when sadness or elation is overly intense and continues beyond the expected impact of a stressful life event. Indeed, the morbid mood might arise without apparent or significant life stress. The pathological process in mood disorders is thus partly defined by the ease with which an intense emotional state is released and, especially, by its tendency to persist autonomously even when the offending stressor is no longer operative. Rather than being endogenous (i.e., occurring in the absence of precipitants), mood disorders are best conceptualized as endoreactive (i.e., once released, they tend to persist autonomously). The homeostatic dyscontrol of mood, which is part of a more pervasive mood dysregulation, resists reversal to the habitual baseline affective tone.

Recurrence. In a more descriptive vein, what sets mood disorders apart from their normal emotional counterparts is the clustering of signs and symptoms into discrete syndromes that typically recur on an episodic basis or pursue an intermittent, subthreshold course over the span of many years, if not a lifetime. Cyclic course and, in some cases, regular periodic recurrence are other signs of mood dysregulation that are particularly relevant to bipolar disorder.

Impairment. Normative reactions to adversity and stress, including biological stress, typically consist of transient admixtures of anxiety and dysphoria that are best captured under the DSM-5 rubric of adjustment disorder with mixed anxiety and depressed mood. That is, self-limiting reactions are best qualified broadly as normal affective states that produce little, if any, impairment in the main areas of functioning.

Although anxiety, irritability, and anger do occur in various types of mood disorders, pathologically sustained mood states of depression and elation characterize those disorders. Morbid mood states (mood disorders) then consist of protracted emotional reactions that deepen or escalate, respectively, into clinical depression or mania, with a tendency to recur or to evolve into unremitting chronicity in 15 to 20 percent of cases. The contribution of temperamental peculiarities to such outcomes should be apparent. The impaired functioning characteristic of mood disorders is thus based on a combination of factors, including severity, autonomy, recurrence, and chronicity of the clinical features.

To recapitulate, dysregulation in mood disorders can take different forms. It could be expressed as a single severe episode that persists autonomously for many months and sometimes years, or it might recur with episodes of varying severity, years apart or in rapid succession, with or without interepisodic remission. In general, the earlier the age at onset, the more likely are recurrences, especially those of bipolar nature. Thus, depending on the course of the illness, impairment could be state dependent and could occur during an episode, or it could extend into the interepisodic period. According to National Institute of Mental Health (NIMH) estimates, on average, a woman with bipolar disorder spends 12 years in florid episodes (often hospitalized), loses 14 years from a productive career and motherhood, and has her life curtailed by 9 years. More recent weekly prospective observations over up to two decades in the NIMH Collaborative Depression Study have shown that patients with bipolar disorder I are symptomatic 47 percent of the time, and bipolar disorder II patients are symptomatic 53 percent of the time, much of it spent in subthreshold depression. In this study, unipolar major depressive disorder was even more pervasive, with subacute chronicity 59 percent of the time.
Recent observations have also revealed another pattern of impairment. In dysthymic and cyclothymic disorders, which represent an intensification of temperamental instability, impairment is not due to the severity of the mood disturbance per se but to the cumulative impact of the dysregulation beginning in the juvenile or early adult years and continuing unabated or intermittently over long periods; hence, the frequent confusion with character pathology. Here, the impairment is more subtle but nonetheless is pervasive. Persons with cyclothymic disorder tend to be dilettantes, whereas those with dysthymic disorder often lead morose and colorless lives. The fundamental causes of mood disorders must be sought in the preclinical expressions in the offspring of adults with these disorders.

**PSYCHOPATHOLOGY**

**Depressive Syndrome**

Like other illnesses, depressive disorder clusters into signs and symptoms that constitute what DSM-5 and ICD-10 term *major depressive episode* (Table 13. 4–2). These criteria attempt to set an operational threshold for depressive disorder based on a specified number of items and their temporal patterns. The diagnosis of clinical depression cannot be accomplished by a checklist: The DSM-5 diagnostic criteria for major depressive disorder provide a general guide. Only after an in-depth phenomenological approach can a clinician ascertain the diagnosis of a depressive disorder. Disturbances in all four spheres (mood, psychomotor activity, cognitive, and vegetative) should be ordinarily present for a definitive diagnosis of major depressive disorder.

**Mood Disturbances.** Mood change, usually considered the sine qua non of morbid depression, manifests in a variety of disturbances, including (1) painful arousal, (2) hypersensitivity to unpleasant events, (3) insensitivity to pleasant events, (4) insensitivity to unpleasant events, (5) reduced anticipatory pleasure, (6) anhedonia or reduced consummatory pleasure, (7) affective blunting, and (8) apathy. The phenomenology and psychometric properties of this broad range of mood disturbances are under investigation at the Salpêtrière Hospital in Paris. The focus in the description that follows is primarily on painfully aroused mood (depression) and diminished capacity for pleasure (anhedonia), two mood disturbances given selective weight in DSM-5 and ICD-10.

**DEPRESSED MOOD.** The term *depressed mood* refers to negative affective arousal, variously described as *depressed, anguished, mournful, irritable, or anxious.* These descriptions tend to trivialize a morbidly painful emotion, typically experienced as worse than the severest physical pain. Thus, depressed mood has a somatic quality that, in the extreme, is indescribably painful. Even when not so severe, depressive suffering is qualitatively distinct from its “neurotic” counterparts, taking the form of groundless apprehensions with severe inner turmoil and torment. This description is particularly apt for middle-aged and elderly persons, who were once considered to be experiencing *involutional melancholia.* The sustained nature of the mood permits no respite, although it tends to lift somewhat in the evening. Suicide may represent an attempt to find deliverance from such unrelenting psychic torment; death can be conceived as comforting.

Patients with a milder form of the malady typically seen in primary care settings might deny experiencing mournful moods and instead complain of physical agony from headache epigastic pain, precordial distress, and so on, in the absence of any evidence of diagnosable physical illness. Such conditions have been described as *depressio sine depressione* or
masked depression. In such cases, which are commonly observed in older patients, the physician should corroborate the presence of mood disturbance by the depressed affect in the patient’s facial expression, vocal inflection, and overall appearance.

ANHEDONIA AND LOSS OF INTEREST. Paradoxically, the heightened perception of pain in many persons with depressive disorder is accompanied by an inability to experience normal emotions. Patients exhibiting the disturbance may lose the capacity to cry, a deficit that is reversed as the depression is lifting.

Table 13.4–2. DSM-5 Criteria for Major Depressive Disorder

<table>
<thead>
<tr>
<th>A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.</th>
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<tbody>
<tr>
<td>Note: Do not include symptoms that are clearly attributable to another medical condition.</td>
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<tr>
<td>1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, and hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)</td>
</tr>
<tr>
<td>2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).</td>
</tr>
<tr>
<td>3. Significant weight loss when not dieting or weight gain (e.g., a change or more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)</td>
</tr>
<tr>
<td>4. Insomnia or hypersomnia nearly every day.</td>
</tr>
<tr>
<td>5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings or restlessness or being slowed down).</td>
</tr>
<tr>
<td>6. Fatigue or loss of energy nearly every day.</td>
</tr>
<tr>
<td>7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).</td>
</tr>
<tr>
<td>8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).</td>
</tr>
<tr>
<td>9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.</td>
</tr>
</tbody>
</table>

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A–C represent a major depressive episode (MDE).

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness, or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of an MDE in addition to the normal response to a significant loss should also be considered. This decision inevitably requires the exercise of clinical judgment based on the individual’s history and the cultural norms for the expression of distress in the context of loss.¹

D. The occurrence of the MDE is not better explained by schizoaffective disorder, schizophrenia, schizotypal disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.
In evaluating anhedonia, inquiring whether the patient has lost the sense of pleasure is not enough; the clinician must document that the patient has actually given up previously enjoyed pastimes. When mild, anhedonia evidences with a decreased interest in life. Later, patients complain that they have lost all interest in things. This is best illustrated in Hamlet’s disgust: “How weary, stale, flat, and unprofitable seem to me all the uses of the world” (William Shakespeare, *Hamlet*, Act I, Scene II). In the extreme, patients lose their feelings for their children or spouses, who once were a source of joy. Thus, the hedonic deficit in clinical depression might represent a special instance of a more pervasive inability to experience emotions.
Patients with severe depression may complain of being emotionally cut off from others and experience depersonalization and a world that seems strange to them (derealization). The impact of the loss of emotional resonance can be so pervasive that patients may denounce values and beliefs that had previously given meaning to their lives. For instance, members of the clergy might present with the complaint that they no longer believe in the Church and that they have lost God. The inability of the person with depressive disorder to experience normal emotions (commonly observed among young depressed patients) differs from the flat affect of patient with schizophrenia, in that the loss of emotions is itself experienced as painful; that is, the patient suffers immensely from the inability to experience emotions.

**Psychomotor Disturbances.** In depression, psychomotor changes consist of abnormalities in the motor expression of mental and emotional activity. In severe cases, these changes manifest in specific facial features (Fig 13.4-2).

**PSYCHOMOTOR AGITATION.** Although agitation (pressured speech, restlessness, hand wringing, and hair pulling) is the more readily observed abnormality, it appears to be less specific to the illness than retardation (slowing of psychomotor activity). Psychophysiological studies have documented that such slowing often coexists with agitation.

**PSYCHOMOTOR RETARDATION.** Underlying many of the deficits seen in clinical depression, some authorities believe psychomotor retardation to be the core, or primary, pathology in mood disorders. Morbid depression—what patients describe as being “down”—can be understood in terms of moderate-to-extreme psychomotor slowing. The patient experiences inertia, being unable to act physically and mentally. Recent brain imaging research that has revealed subcortical (extrapyramidal system) disturbances in mood disorders tends to support the centrality of psychomotor dysfunction in these disorders.

Long neglected in psychopathological research, psychomotor retardation can be measured with precision. The Salpêtrière Retardation Scale developed by Daniel Widlocher and colleagues places special emphasis on the following disturbances: (1) paucity of spontaneous movements; (2) slumped posture with downcast gaze (Fig. 13.4–3); (3) overwhelming fatigue (patients complain that everything is an effort); (4) reduced flow and amplitude of speech and increased latency of responses, often giving rise to monosyllabic speech; (5) a subjective feeling that time is passing slowly or has stopped; (6) poor concentration and forgetfulness; (7) painful rumination or thinking that dwells on a few (usually unpleasant) topics; and (8) indecisiveness or an inability to make simple decisions.

DSM-5 places greater emphasis on the more easily observable objective or physical aspects of retardation. For the patient, however, the subjective sense of slowing is as pervasive and disabling. This more psychological dimension of retardation is most reliably elicited from depressed persons with good verbal skills.

Ms. A, a 34-year-old literature professor, presented to a mood clinic with the following complaint: “I am in a daze, confused, disoriented, staring. My thoughts do not flow, my mind is arrested. . . . I seem to lack any sense of direction, purpose. . . . I have such an inertia, I cannot assert myself. I cannot fight; I have no will.”
Less linguistically sophisticated patients would simply complain of an inability to perform household chores or difficulty in concentrating on their studies. Such psychomotor deficits, in turn, underlie depressed patients’ diminished efficiency or their inability to work.

**FIGURE 13.4–2.** The Swiss neuropsychiatrist Otto Veraguth described a peculiar triangle-shaped fold in the nasal corner of the upper eyelid. The fold, often associated with depression, is referred to as Veraguth’s fold. The photograph illustrates this physiognomic feature in a 50-year-old man during a major depressive episode. Veraguth’s fold may also be seen in persons who are not clinically depressed, usually while they are harboring a mild depressive affect. Distinct changes in the tone of the corrugator and zygomatic facial muscles accompany depression, as shown in electromyograms. (Courtesy of Heinz E. Lehmann, M.D.)

**PSEUDODEMENTIA.** The slowing of mental functions can be so pronounced in elderly persons that they experience memory difficulties, disorientation, and confusion.

**STUPOR.** Psychomotor slowing in young persons is sometimes so extreme that patients might slide into a stupor, unable to participate even in basic biological functions, such as feeding themselves. Such an episode is often the precursor of bipolar disorder, which later declares itself in a manic episode. Today, depressive disorder is diagnosed in its earlier stages, and subtle stupor is much more likely to be encountered clinically.

A 20-year-old male college student seen in the emergency room spoke of “being stuck—as if I have fallen into a black hole and can’t get out.” Further evaluation revealed that the patient was metaphorically describing his total loss of initiative and drive and was engulfed by the disease process. A clinician without the requisite phenomenological training might consider such a patient bizarre and perhaps even psychotic. Yet, the patient responded dramatically to fluoxetine (Prozac) and, in 2 weeks, was back in school.
Cognitive Disturbances. The cognitive view of depression considers negative evaluations of the self, the world, and the future (the negative triad) central to understanding depressed mood and behavior, but it is equally likely that the depressed mood colors perceptions of the self and others or that disturbed psychomotor activity leads to negative self-evaluations. Therefore, instead of being considered causal, the cognitive triad in depression is best approached empirically as a psychopathological manifestation of depression. Faulty thinking patterns are clinically expressed as (1) ideas of deprivation and loss; (2) low self-esteem and self-confidence; (3) self-reproach and pathological guilt; (4) helplessness, hopelessness, and pessimism; and (5) recurrent thoughts of death and suicide.

The essential characteristic of depressive thinking is that the patient views everything in an extremely negative light. The self-accusations are typically unjustified or are blown out of proportion, as in the case of a middle-aged woman who was tormented by guilt because, as a child, she had not repaid a nickel that she had borrowed from a classmate. Some of the thoughts may verge on the delusional. For instance, an internationally renowned scientist complained that he was “nothing.” Self-evaluations that indicate an extremely low image of one’s self might, nonetheless, reflect an accurate perception of one’s impairment from psychomotor retardation.

MOOD-CONGRUENT PSYCHOTIC FEATURES. In depressive disorders with psychotic features, negative thinking acquires grossly delusional proportions and is maintained with such conviction that the thoughts are not amenable to change by evidence to the contrary.
According to Kurt Schneider, delusional thinking in depression derives from humankind’s four basic insecurities—those regarding health, financial status, moral worth, and relationship to others. Thus, severely depressed patients may have delusions of worthlessness and sinfulness, reference, and persecution: They believe that they are being singled out for their past mistakes and that everyone is aware of their incompetence. Persecutory ideation in depression is often prosecutory, in that it derives from the belief that one deserves punishment for such transgressions. A severely depressed man may feel so incompetent in all areas of functioning, including the sexual sphere, that he may suspect his wife of having an affair (delusion of infidelity).

Other depressed persons believe that they have mismanaged their finances in such a way that their children will starve (delusions of poverty); that they are harboring an occult illness, such as cancer or the acquired immune deficiency syndrome (AIDS) (delusions of ill health); or that parts of their bodies are missing (nihilistic delusions). In more severe illness, the patient might feel that the world has changed and that calamity and destruction await everyone. In rare tragic instances, a parent with such delusions might kill his or her young children to save them from moral or physical decay and then commit suicide. In women with psychotic depression, infanticide is most likely to occur in the postpartum period, often leading to all types of inappropriate interpretations in the media. Finally, a minority of depressed persons have fleeting auditory or visual hallucinations with extremely unpleasant content along the lines of their delusions (e.g., hearing accusatory voices or seeing themselves in coffins or graveyards). All of these psychotic experiences are genuine affective delusions or hallucinations. They are mood congruent in the sense that they are phenomenologically understandable in light of the prevailing pathological mood.

MOOD-INCONGRUENT PSYCHOTIC FEATURES. Sometimes so-called first-rank or schneiderian-type symptoms can arise in the setting of a major depressive episode.

A 42-year-old civil servant said that she was so paralyzed by depression that she felt that she had no personal initiative and volition left; she believed that some malignant force had taken over her actions and that it was commenting on every action that she was undertaking. The patient recovered fully with thymoleptic medication. There is no reason to believe that, in this patient, the feelings of somatic passivity and running commentary indicated a schizophrenic process.

Thus, with proper phenomenological probing, certain classes of apparently mood-incongruent psychotic experiences can be understood as arising from the pathological mood and the profound changes in psychomotor activity that accompany them. (In other instances, the clinician must seek a history of alcohol or substance use disorder or withdrawal as a putative explanation for mood incongruence in psychotic depression.) In brief, incidental schneiderian first-rank symptoms should not distract from the diagnosis of an affective psychosis if otherwise typical signs and symptoms of mood disorder are present.

HOPELESSNESS AND SUICIDE. Given that most, if not all, clinically depressed patients find themselves locked in the private hell of their negative thoughts, it is not surprising that many untreated or inadequately treated patients give up hope of ever recovering and kill themselves. The suicide attempt is not, however, undertaken in the depth of melancholia. When asked if she had any suicide plans, a severely depressed patient replied, “Doctor, I don’t exist—I am already dead.”
Thus, the risk of suicide is less pronounced during acute severe depression. Emil Kraepelin observed that it is when psychomotor activity is improving, yet mood and thinking are still dark, that the patient is most likely to muster the requisite energy to commit the suicidal act. Aaron Beck’s work has shown that hopelessness on mental status evaluation in a patient recovering from depression should alert the clinician to the possibility of such an outcome. The discovery of a therapeutic modality that could achieve improvement in psychomotor, mood, and cognitive components in tandem will constitute a major clinical advance.

There is no basis for the common belief that inquiring about suicide provokes such behavior. On the contrary, patients are often relieved that the physician appreciates the magnitude of their suffering. Suicidal ideation is commonly expressed indirectly (e.g., in a wish not to wake up or to die from a malignant disease). Some depressed persons are tormented with suicidal obsessions and are constantly resisting unwanted urges or impulses to destroy themselves. Others might yield to such urges passively (e.g., by careless driving or by walking into high-speed traffic). A third group harbors elaborate plans, carefully preparing a will and taking out insurance. Deliberate planning indicates a high suicidal risk. The foregoing examples are not exhaustive; they are meant to remind clinicians with depressed patients to be alert always to the possibility of suicide.

Vegetative Disturbances. The Greeks considered depression a somatic illness and ascribed it to black bile; hence, the term melancholia. The mood change in depressive disorder is accompanied by measurable alterations of biorhythms that implicate midbrain dysfunction. Once the changes occur, they tend to be independent of the environment throughout much of the episode, and, as a consequence, they do not respond to interpersonal feedback of a pleasant or upbeat nature. The biological concomitants of melancholia include profound reductions in appetite, sleep, and sexual functioning, as well as alterations in other circadian rhythms, especially matinal worsening of mood and psychomotor performance. These disturbances are central to the concept of melancholia, a form of depression in which such biological concomitants predominate. An equally prominent subgroup of depressed persons exhibits a reversal of the vegetative and circadian functions, with increases in appetite and sleep—and sometimes in sexual functioning—and an evening worsening of mood; in this atypical pattern, patients characteristically exhibit mood reactivity and sensitivity to rejection. Marked retardation might herald a manic switch, whereas atypicality should raise the suspicion of bipolar II disorder.

ANOREXIA AND WEIGHT LOSS. The most reliable somatic indicators of depressive disorder include anorexia and weight loss. In addition to being a hypothalamic-based disturbance in depression, anorexia might be secondary to blunted olfactory or taste sensations or a decreased enjoyment of food, or (rarely) it might result from a delusional belief that the food has been poisoned.

Inanition, especially in elderly persons, can lead to malnutrition and electrolyte disturbances that represent medical emergencies in their own right. If weight loss is severe, especially after 40 years of age, the psychiatrist should first use appropriate medical consultation to rule out the likelihood of an occult malignancy.

WEIGHT GAIN. Overeating, decreased activity, or both may result in weight gain. In middle-aged patients, it may aggravate pre-existing diabetes mellitus, hypertension, or coronary artery disease. In younger patients, especially women, weight problems may
conform to a bulimic pattern that is often the expression of the depressive phase of a bipolar disorder with infrequent hypomanic periods (bipolar II disorder).

INSOMNIA. Sleep disturbance, a cardinal sign of depression, often is characterized by multiple awakenings, especially in the early hours of the morning, rather than by difficulty falling asleep. The light sleep of a depressed person, in part a reflection of the painful arousal of the disorder, tends to prolong the depressive agony over 24 hours. Thus, deep stages of sleep (III and IV) are decreased or deficient. The attempt to overcome the problem by drinking alcohol may initially succeed but ultimately aggravates the sleep patterns and insomnia. This is also true for sedative–hypnotic agents, which are often prescribed by the busy general practitioner who has not spent enough time diagnosing the depressive condition. Although sedatives (including alcohol) effectively reduce the number of awakenings in the short term, they are not effective in the long run because they further diminish stage III and stage IV sleep. They are not antidepressants, and they tend to prolong the depression.

HYPERSOMNIA. Young depressed patients, especially those with bipolar tendencies, often exhibit excessive sleep and have difficulty getting up in the morning.

Kevin, a 15-year-old boy, was referred to a sleep center to rule out narcolepsy. His main complaints were fatigue, boredom, and a need to sleep all the time. Although he had always started the day somewhat slowly, he now could not get out of bed to go to school. That alarmed his mother, prompting sleep consultation. Formerly a B student, he had been failing most of his courses in the 6 months before referral. Psychological counseling, predicated on the premise that his family’s recent move from another city had led to Kevin’s isolation, had not been beneficial. Extensive neurological and general medical workup had also proven negative. He slept 12 to 15 hours per day but denied cataplexy, sleep paralysis, and hypnagogic hallucinations. During psychiatric interview, he denied being depressed but admitted that he had lost interest in everything except his dog. He had no drive, participated in no activities, and had gained 30 pounds in 6 months. He believed that he was “brain damaged” and wondered whether it was worth living like that. The question of suicide disturbed him, as it was contrary to his religious beliefs. These findings led to the prescription of desipramine (Norpramin) in a dose that was gradually increased to 200 mg per day over 3 weeks. Not only did desipramine reverse the presenting complaints, but it also pushed him to the brink of a manic episode. The affective nature of the disorder in such patients is often unrecognized, and their behavior is attributed to “laziness.” The vignette also illustrates the emergence of manic behavior during antidepressant treatment. Such shifts in polarity are common in major depressive disorder and necessitate revising the diagnosis to a bipolar disorder. Hypersomnia associated with lethargy should actually raise strong suspicion of bipolar disorder in young depressive patients. In the elderly, organic or brain pathology should be suspected.

CIRCADIAN DYSREGULATION. Many circadian functions, such as temperature regulation and cortisol rhythms, are disrupted in major depressive disorder. Disturbances of sleep rhythms, however, have received the greatest research focus. These include deficits in stage IV or delta sleep, as well as more intense REM activity in the first one-third of the night. More specific to depressive disorders—whether suffering from insomnia or hypersomnia—nearly two-thirds of patients exhibit a marked shortening of REM latency, the period from the onset of sleep to the first REM period. This abnormality is observed throughout the depressive episode and may also be seen during relatively euthymic periods in persons with recurrent depression. The occurrence of short REM latency in the younger, clinically well relatives of the affectively ill suggests that neurophysiological abnormalities might precede the overt psychopathological manifestations of the illness; on closer scrutiny,
these “well” relatives are often found to meet criteria for subthreshold mood conditions, such as dysthymic disorder, intermittent depression, or labile temperament.

Few data exist on the consistency of sleep electroencephalographic (EEG) abnormalities in patients from episode to episode. However, clinical experience suggests that a patient observed over time (even during the same episode) may exhibit insomnia and morning worsening of mood and activity during one period of the disorder and hypersomnia extending to late morning hours during another period. In either case, persons with depressive disorder are characteristically tired in the morning, which means that even prolonged sleep is not refreshing for them. The propensity to exhibit such divergent patterns of sleep disturbance is more likely in bipolar disorders. Patients with major depressive disorder tend to exhibit insomnia more stereotypically episode after episode; despite extreme fatigue, they rarely oversleep. Such fatigue coexisting with negative affective arousal is even more exhausting.

SEASONALITY. Another classic biorhythmic disturbance in mood disorders is seasonal (especially autumn–winter) accentuation or precipitation of depression. Most of those patients experience increased energy and activation, if not frank hypomania, in the spring. In the fall and winter, they complain of fatigue, tend to crave sugars, and overeat and oversleep. The hypersomnia in some of these patients is associated with delayed (rather than short) REM latencies. These data suggest dysregulation of circadian rhythms in depressive disorders rather than mere phase advance. Given the biphasic nature of the clinical phenomenology, some autumn–winter depressions belong to the bipolar spectrum (type II). Although autumn–winter depression has received the greatest attention, there also exist summer depressions; the former appear to be related to reduction in daylight (photoperiods), and the latter appear to be related to increased temperature.

SEXUAL DYSFUNCTION. Decreased sexual desire is seen in depressed men and women. In addition, some women experience temporary interruption of their menses. Depressed women are often unresponsive to lovemaking or are disinclined to participate in it, a situation that could lead to marital conflict. Psychotherapists might mistakenly ascribe the depression to the marital conflict and might devote unnecessarily zealous psychotherapeutic attention to conjugal issues. Decreased or lost libido in men often results in erectile failure, which may prompt endocrinological or urological consultation. Again, depression may be ascribed to the sexual dysfunction rather than the reverse, and definitive treatment may be delayed by the focus on the sexual complaint. In the past, some men with depressive disorder were subjected to permanent penile implants before receiving more definitive treatment of their depression. This is less likely to occur in the sildenafil (Viagra) era, but even treatment with such agents would not necessarily resolve erectile disorder in clinically depressed patients without competent treatment of the mood disorder. SSRIs typically aggravate the sexual dysfunction, whereas bupropion (Wellbutrin) tends to improve it.

A small subgroup of persons with depressive disorder may exhibit increased sexual drive or activity of a compulsive nature. These patients tend to have other atypical features as well; hence, the increased sexual drive can be considered the fifth reverse vegetative sign (after evening worsening of mood, initial insomnia, hypersomnia, and weight gain). Several patients have derived temporary reversal of their depression after intense sexual encounters. In these depressed persons, increased sexual drive, intensity, or both may indicate a mixed episode of bipolar disorder (type II). Further scrutiny in such cases often reveals a premorbid cyclothymic or hyperthymic temperament. Current data suggest that, depending on the
breadth of the criteria used, 30 to 70 percent of depressions with atypical features belong to the bipolar spectrum.

**Manic Syndrome**

As with clinical depression, the psychopathology of mania (Table 13.4–3) can be conveniently discussed under mood, psychomotor, circadian, and cognitive disturbances. The clinical features of mania are generally the opposite of those of depression. Thus, instead of lowered mood, thinking, activity, and self-esteem, there is elevated mood, a rush of ideas, psychomotor acceleration, and grandiosity. Despite those contrasts, the two disorders share such symptoms as irritability, anger, insomnia, and agitation. Actually, an excess of the latter symptoms of escalating intensity suggests a mixed phase or mixed episode of mania and depression occurring simultaneously. Manic and mixed episodes represent the hallmark of what was once termed *manic-depressive psychosis* and is currently termed *bipolar I disorder*.

Table 13.4–3. Manic Episode

<table>
<thead>
<tr>
<th>A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. During the period mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:</td>
</tr>
<tr>
<td>1. Inflated self-esteem or grandiosity.</td>
</tr>
<tr>
<td>2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).</td>
</tr>
<tr>
<td>3. More talkative than usual or pressure to keep talking.</td>
</tr>
<tr>
<td>4. Flight of ideas or subjective experience that thoughts are racing.</td>
</tr>
<tr>
<td>5. Distraction (i.e., attention to easily drawn to unimportant or irrelevant external stimuli), as reported or observed.</td>
</tr>
<tr>
<td>6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).</td>
</tr>
<tr>
<td>7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).</td>
</tr>
<tr>
<td>8. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.</td>
</tr>
<tr>
<td>9. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.</td>
</tr>
</tbody>
</table>

*Note:* A full manic episode that emerges during antidepressant treatment (e.g., medication and electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient for a manic episode and therefore, a bipolar I diagnosis.

*Note:* Criteria A–D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

Although milder or hypomanic features (Table 13.4–4) can contribute to success in business, leadership roles, and the arts, recurrences of even mild manic symptomatology are typically disruptive. The elated mood tends to produce overoptimism concerning one’s abilities, which, coupled with the impulsivity characteristic of mania, often leads to disaster. Thus, accurate and early diagnosis is paramount.

Classic mania, as formulated in the DSM-5, operationalism of manic episode is relatively easy to recognize. Misdiagnosis was once rampant in North American practice as clinicians confused severe mania with schizophrenia and confused its milder variants with normality or with narcissistic and sociopathic personality disorders. Like the misdiagnosis of depressive
conditions, such errors of clinical judgment are due to a lack of familiarity with the phenomenology of the classic illness. Again, DSM-5 criteria provide only a guideline. The actual diagnosis requires careful history and phenomenological understanding by an empathetic observer. The manic patient lifts the observer’s mood and makes the examiner smile and even laugh but can also be irritating. The patient’s speech is fast and may even appear to the novice psychiatry student as “loose,” but it also can often be witty. Finally, the behavior is typically dramatic, expansive, and jesting. Current research indicates that social disinhibition and pathological overfamiliarity with strangers represent cardinal features of mania and can be contrasted with the withdrawal of most schizophrenic patients. For the experienced clinician, the overall Gestalt experienced in the presence of manic patients is emotionally and qualitatively distinct from that of persons with schizophrenia or frontal lobe diseases; the latter conditions tend to leave the examiner cold. These considerations become clearer when the clinical observer systematically examines the psychopathology of mania in the areas of mood, behavior, and thinking.

**Mood Disturbance.** Mood disturbance in mania represents a contrast to that observed in depression, but not entirely.

**MOOD ELEVATION.** The mood in mania is classically one of elation, euphoria, and jubilation, typically associated with laughing, punning, and gesturing.

**LABILITY AND IRRITABILITY.** The prevailing positive mood in mania is not stable, and momentary crying or bursting into tears is common. In addition, the high is so excessive that many patients experience it as intense nervousness. When crossed, patients can become extremely irritable and hostile. Thus, lability and irritable hostility are as much features of the manic mood as is elation. In mixed manic states, they dominate the clinical picture, giving rise to what is now termed *dysphoric mania* (and what Kraepelin characterized as *anxious-depressive mania*).

**Psychomotor Acceleration.** Accelerated psychomotor activity, the hallmark of mania, is characterized by overabundant energy and activity and rapid, pressured speech. Subjectively, the patient experiences an unusual sense of physical well-being (eutonia).

**FLIGHT OF IDEAS.** Thinking processes are accelerated, subjectively experienced as flight of ideas, and thinking and perception are unusually sharp. The patient may speak with such pressure that associations are difficult to follow; such “clang” associations are often based on rhyming or chance perceptions and can be lightning fast. The pressure to speak may continue despite the development of hoarseness.

**IMPULSIVE BEHAVIOR.** Manic patients are typically impulsive, disinhibited, and meddlesome. Pathological familiarity with total strangers is also a feature not specifically listed in the DSM-5 schema for mania, yet it is one of its cardinal signs. They are intrusive in their increased involvement with others, leading to friction with family members, friends, and colleagues. They are distractible and move quickly, not only from one thought to another but also from one person to another, showing heightened interest in every new activity that strikes their fancy. They are indefatigable and engage in various activities in which they usually display poor social judgment. Examples include preaching or dancing in the street; abusing the use of long-distance calling; buying new cars, hundreds of records, expensive jewelry, or other unnecessary items; paying the bills of total strangers in bars; giving away
furniture; marrying impulsively; engaging in risky business ventures; gambling; and taking sudden trips. Such pursuits can lead to personal and financial ruin.

Table 13.4–4. Hypomanic Episode

| A. | A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day. |
| B. | During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree: |
| 1. | Inflated self-esteem or grandiosity. |
| 2. | Decreased need for sleep (e.g., feels rested after only 3 hours of sleep). |
| 3. | More talkative than usual or pressure to keep talking. |
| 4. | Flight of ideas or subjective experience that thoughts are racing. |
| 5. | Distraction (i.e., attention to easily drawn to unimportant or irrelevant external stimuli), as reported or observed. |
| 6. | Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation. |
| 7. | Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments). |
| C. | The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic. |
| D. | The disturbance in mood and the change in functioning is observable by other. |
| E. | The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic. |
| F. | The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment). |

Note: A fully hypomanic episode that emerges during antidepressant treatment (e.g., medication and electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of the treatment is sufficient evidence for hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.

Note: Criteria A–F constitute a hypomanic episode. Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

DELIRIOUS MANIA. Although not listed in DSM-5, an extremely severe expression of mania (once known as Bell’s mania) called delirious mania involves frenzied physical activity that continues unabated and leads to delirium and disorientation—a life-threatening medical emergency. This complication, the manic counterpart of stupor, is rare today.

WITH CATATONIC FEATURES. As a symptom, catatonia can be present in several mental disorders. The presence of catatonic features in patients with mood disorders may have prognostic and treatment significance. The hallmark of symptoms of catatonia—stuporousness, blunted affect, extreme withdrawal, negativism, and marked psychomotor retardation—can be seen in both catatonic and noncatatonic schizophrenia, major depressive disorder (often with psychotic features), and medical and neurological disorders. Clinicians often do not associate catatonic symptoms with bipolar I disorder because of the marked contrast between these symptoms of stuporous catatonia and the classic symptoms of mania.

VEGETATIVE DISTURBANCES. Vegetative disturbances are more difficult to evaluate in mania than in depression.
Hyposomnia. Hyposomnia is the cardinal sign of decreased need for sleep—the patient sleeps only a few hours but feels energetic on awakening. Some patients may actually go sleepless for several days. This could lead to dangerous escalation of manic activity, which might continue despite signs of physical exhaustion.

Inattention to Nutrition. There does not seem to be a clinically significant level of appetite disturbance as such, but weight loss may occur because of increased activity and neglect of nutritional needs.

Sexual Excesses. Hypersexuality is a cardinal sign of mania. The sexual appetite is typically increased and may lead to sexual indiscretion. Married women with previously unblemished sexual lives may associate with men below their social status. Men typically overindulge in alcohol, frequent bars, and may squander their savings on prostitutes. The sexual misadventures of manic patients result in marital disasters—hence the multiple separations or divorces that are almost pathognomonic of the disorder. The sexual excesses of bipolar patients are even more problematic today, in view of the specter of AIDS.

Cognitive Distortions. Manic thinking is overly positive, optimistic, and expansive.

GRANDIOSITY, LACK OF INSIGHT, AND POOR JUDGMENT. The patient exhibits inflated self-esteem and a grandiose sense of confidence and achievements. Behind that facade, however, may be a vague and painful recognition that the positive self-concepts do not represent reality. However, such insight (if present at all) is transient, and manic patients are notoriously refractory to self-examination and insight. Denial and lack of insight are cardinal psychological derangements of mania. It is this lack of insight—coupled with poor judgment—that leads manic patients to engage in activities that harm themselves and their loved ones. It also explains, in part, their nonadherence with medication regimens during the manic phase.

DELUSION FORMATION. Manic patients often harbor delusional beliefs, including delusions of exceptional mental and physical fitness and talent; delusions of wealth, aristocratic ancestry, or other grandiose identity; delusions of assistance (i.e., well-placed persons or supernatural powers are assisting their endeavors); or delusions of reference and persecution, based on the belief that enemies are observing or following them out of jealousy at their special abilities. At the height of mania, patients may even see visions or hear voices congruent with their euphoric mood and grandiose self-image (e.g., they might see images of heaven or hear cherubs chanting songs to praise them). The denial characteristic of mania—and the frequently psychotic nature of episodes—means that clinicians must routinely obtain diagnostic information about past episodes from significant others. Lack of insight also unfortunately means that hospitalization must often be arranged on an involuntary basis.

MOOD-INCONGRUENT PSYCHOSIS. Psychosis in the setting of mania and mixed manic episodes is typically mood congruent. The sense of physical well-being and mental alacrity is so extraordinary that it is understandable why manic patients believe that they possess superior powers or perhaps are great scientists or famous reformers. Moreover, their senses are so vivid that reality appears richer and more exotic and can be easily transformed into a vision.

Likewise, their thoughts are so rapid and vibrant that they feel that they can hear them. Thus, certain first-rank schneiderian-type symptoms that have been traditionally considered mood
incongruent can be understood phenomenologically to arise from the powerful mental experiences of mania

A 37-year-old engineer had experienced three manic episodes for which he had been hospitalized; all three episodes were preceded by several weeks of moderate psychomotor retardation. Although he had responded to lithium (Eskalith) each time, once outside the hospital, he had been reluctant to take it and eventually refused to do so. Now that he was “euthymic,” after his third and most disruptive episode during which he had badly beaten his wife, he could more accurately explain how he felt when manic. He experienced mania as “God implanted in him,” so he could serve as “testimony to man’s communication with God.” He elaborated as follows: “Ordinary mortals will never, never understand the supreme manic state which I’m privileged to experience every few years. It is so vivid, so intense, so compelling. When I feel that way, there can be no other explanation: To be manic is, ultimately, to be God. God himself must be supermanic: I can feel it when mania enters through my left brain like laser beams, transforming my sluggish thoughts, recharging them, galvanizing them. My thoughts acquire such momentum, they rush out of my head, to disseminate knowledge about the true nature of mania to psychiatrists and all other ordinary mortals. That’s why I will never accept lithium again—to do so is to obstruct the divinity in me.” Although he was on the brink of divorce, he would not yield to his wife’s plea to go back on lithium.

The vignette illustrates the possibility that even some of the most psychotic manifestations of mania represent explanatory delusions, the patient’s attempt to make sense of the experience of mania. Many manic patients abuse alcohol and stimulants to enhance their mental state; mood incongruence can sometimes be explained on that basis.

HYPOMANIA VERSUS MANIA. Nonpsychotic and nondisruptive variants of mania are much more common and are recognized by DSM-5 as hypomanic episodes. They are the historical clinical marker for bipolar II. Diagnostically, history of hypomania is preferably obtained from significant others who have observed the patient; the experience is often pleasant, and the subject may be unaware of it or may tend to deny it. Others experience irritable or dysphoric hypomanic episodes, which may be difficult to recognize clinically because of a stereotype that emphasizes the positive aspects of hypomania. Some patients feel that they benefit from the energy and confidence of hypomania. This is true if hypomania is mild and “sunny.” But, many patients, especially those with “darker” irritable activation, experience impairment in occupational and interpersonal functioning over time. DSM-5 stipulates a minimum duration of 4 days for hypomania; however, current evidence indicates that bipolar II disorders with long (4 or more days) and short (2 to 3 days) hypomania are indistinguishable on the basis of bipolar family history. It is, therefore, recommended that the threshold for detecting the duration of hypomania be set at 2 days. Ultimately, the duration of hypomanic experiences might be less important than the fact that they recur. In other words, the occurrence of brief recurrent hypomanias, even if their duration is 1 day, interspaced with major depressive episodes can be taken as presumptive evidence for bipolar II. Finally, although DSM-5 states that treatment-emergent hypomania in a depressed patient does not count toward a diagnosis of bipolarity, prospective observations show that nearly all such episodes are followed eventually by spontaneous hypomania (or mania); moreover, family history for bipolar disorder is comparable in patients with spontaneous and antidepressant-associated hypomania. In brief, antidepressant-associated hypomanias are best considered as a genetically less penetrant variant of bipolarity (which, in the literature, are often referred to as bipolar III disorders).
DIAGNOSTIC CLASSIFICATION

The classification of mood disorders in DSM-5 subsumes a large variety of patients seen in private, public, ambulatory, and inpatient settings. The main demarcation in that large clinical terrain is between bipolar and depressive disorders. Thus, bipolar disorders range from the classic manic and depressive episodes, often of psychotic intensity (bipolar I disorder), to recurrent major depressive episodes alternating with hypomanic episodes (bipolar II disorder) and cyclothymic mood swings. Likewise, depressive disorders include those with psychotic severity, melancholia, atypical features, and dysthymic variants.

Major and specific attenuated subtypes are distinguished on the basis of severity and duration. In dysthymic and cyclothymic disorders, a partial mood syndrome consisting of such subthreshold features as subdepressive and hypomanic periods is maintained, intermittently or continuously, for at least 2 years. Subdepressive periods dominate in dysthymia; in cyclothymia, they alternate with brief hypomania. The onset is typically in adolescence or childhood, and most persons with these diagnoses first seen clinically in young adulthood have had low-grade mood symptoms for 5 to 10 years. Major mood disorders, which generally begin much later in life, require the presence of a full manic episode or a full depressive episode—sustained for at least 1 and 2 weeks, respectively—and an episodic course, typically permitting recovery or remission from episodes. As many as one-third of persons with major depressive disorders fail to achieve full symptomatic recovery and should thus be qualified as chronic or in partial remission.

Dichotomy or Continuum?

Although, in the extreme, bipolar and depressive disorders can be discriminated clinically and therapeutically (Table 13.4–5), clinical observations testify to a vast overlap between those extremes. Thus, the distinctions among the various affective subtypes are not as hard and fast as DSM-5 attempts to portray. For instance, full-blown bipolar disorder can be superimposed on cyclothymic disorder that tends to persist after the resolution of manic or major depressive episodes. Even more common is major depressive disorder complicating cyclothymic disorder, which should be reclassified as an important course variant of bipolar II disorder. Likewise, recent evidence indicates that dysthymic disorder may precede major depressive disorder in as many as one-third of cases. Moreover, as much as 50 percent of persons with major depressive disorder during long-term prospective follow-up develop hypomanic or manic episodes and should be reclassified as having bipolar disorder. In some, if not many, instances, apparent switching of polarity might simply be due to earlier misclassification of bipolar disorder as major depressive disorder. Finally, unexpected crossing from dysthymic disorder to hypomanic or manic episodes has also been described, suggesting that some forms of dysthymic disorder are subaffective precursors of bipolar disorder. The concept of sub-bipolar dysthymia (not a formal category in DSM-5) can bring clinical attention to this subgroup of patients. Such observations are in line with Kraepelin’s historic attempt to bring all mood disorders under one rubric. Epidemiological studies in the community have also shown much fluidity among various subthreshold and major mood disorders.
Heterogeneity undoubtedly exists among mood disorders. However, the classic unipolar–bipolar distinction might not be the best way to capture it. The foregoing observations suggest that much of the recurrent depressive terrain might be pseudo-unipolar (i.e., soft bipolar). The clinical significance of these considerations lies in the fact that many DSM-5 subtypes of mood disorders are not pure entities, and considerable overlap and switches in polarity take place. They also provide some rationale, for instance, for why lithium or other mood stabilizer augmentation may be effective in some apparently unipolar depressions; such patients do not necessarily experience brief spontaneous hypomanic episodes but instead often exhibit a high baseline level of hypothyamic traits. Finally, several studies have shown that bipolar patients with cyclothymic premorbid adjustment and interepisodic adjustment are at considerable risk of antidepressant-induced rapid cycling, defined as a rapid succession of major episodes with few or no intervals of freedom.

As Kraepelin illustrated in his monograph, course is best captured graphically (Fig 13.4–4). Kraepelin, after diagramming 18 illustrative patterns for the entire spectrum of manic-depressive illness, declared that the illness pursued an indefinite number of courses. Although not represented in the official US and international classifications, some of these course patterns are of considerable interest today. For instance, a biphasic course (a sequence in which episodes of opposite polarity succeed each other and then are followed by a free interval) is relevant to treatment response. Thus, depression followed by mania or hypomania—compared to mania or hypomania followed by depression—appears, on the basis of replicated studies, to be less responsive to lithium.
FIGURE 13.4–4. Graphs depicting prototypical courses. A: Course of major depressive disorder, recurrent, with no antecedent dysthymic disorder and a period of full remission between the episodes. This pattern predicts the best future prognosis. B: Course of major depressive disorder, recurrent, with no antecedent dysthymic disorder but with prominent symptoms persisting between the two most recent episodes (i.e., partial remission is attained). C: Rare pattern (present in fewer than 3 percent of persons with major depressive disorder) of major depressive disorder, recurrent with antecedent dysthymic disorder but with full interepisode recovery between the two most recent episodes. D: Course of major depressive disorder, recurrent, with antecedent dysthymic disorder and no period of full remission between the two most recent episodes. This pattern, commonly referred to as double depression, is seen in approximately 20 to 25 percent of persons with major depressive disorder. (From American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Text rev. Washington, DC: American Psychiatric Association; 2000, with permission.)

DEPRESSIVE DISORDERS

The broad category of depressive disorders includes major depressive disorder, dysthymic disorder, and depressive disorder not otherwise specified.

**Major Depressive Disorder**

Episodes usually begin over a prodromal period of weeks to months. The DSM-5 diagnosis of major depressive disorder requires one of the following: (1) dysphoric mood or (2) decreased interest in usual activities. The full range of signs and symptoms are listed in Table 13.4–2. Such symptoms must be sustained for at least 2 weeks, and cannot be explained by another process known to cause depressive symptoms, such as normal bereavement, certain physical conditions commonly associated with depression, or another mental disorder. It can be a single episode or, commonly, recurrent, or both.

**Comorbid Physical Disease.** The foregoing considerations raise the question of whether major depressive disorder should be limited to depressions of unknown etiology (i.e., those without documented physical causes). The DSM-5 approach has basically been that, when the cause is known, the condition should be diagnosed as mood disorder due to a general medical condition that must be specified or substance-induced mood disorder. The problem with this approach is that many common medical factors historically associated with depression do not seem to be causative in the etiological sense but rather are triggering agents in otherwise
predisposed persons. This is analogous to the situation with life events, which no longer are used in making distinctions between reactive and endogenous subtypes of depression. A more troubling implication is that major depressive disorders without demonstrable physical disease are not medical or otherwise biological. More important, there appears to be no reliable or valid way for a clinician to decide that a depressive condition is due to a specified medical condition. In brief, the designation due to a general medical condition is cumbersome and redundant. Major depressive disorder should be considered to represent the final common pathway of multifactorial interacting factors—physical and psychological—a syndrome that should be diagnosed irrespective of presumed cause.

**Diagnostic Threshold.** Another question concerning the definition of major depressive disorder relates to the threshold at which a constellation of depressive features becomes a condition distinct from the ordinary blues. Within the current definition, if a person responds to a setback with lowered spirits and self-doubt, difficulty in sleeping and concentration, and decreased sexual interest for 14 days, he or she would qualify for the diagnosis of a major depressive disorder of mild intensity. Many clinicians would consider such a condition a relatively minor departure from normality, probably no more than an adjustment disorder. Obviously, criteria other than signs, symptoms, and duration are necessary to differentiate a major depressive disorder from adjustment reactions to life situations. The presence of the following characteristics might assist in such a differentiation:

- By definition, a major depressive disorder should be incapacitating. Previously, much attention was paid to the interpersonal consequences of depression. Recent evidence indicates that measurable deficits in work performance are often early manifestations. Afflicted persons also do not benefit from taking leisure time, and, hence, prescribing vacations is futile.
- Major depressive disorder is usually perceived as a break from a person’s usual or premorbid self, which can be so striking that patients may feel as though they are losing their minds. The important point is that the patient and significant others can usually relate the onset of the illness to a given month or quarter of a year, which is not true, for instance, for dysthymic disorder.
- Major depressive disorder is often experienced by the patient as qualitatively distinct from grief or other understandable reactions to loss or adversity. William James described it as follows:

  There is a pitch of unhappiness so great that the goods of nature may be entirely forgotten, and all sentiment of their existence vanish from the mental field. For this extremity of passion to be reached, something more is needed than adversity; the individual must in his own person become the prey of pathological melancholy. Such sensitiveness and susceptibility of mental pain is a rare occurrence where the nervous constitution is entirely normal: one seldom finds it in a healthy subject even where he is the victim of the most atrocious cruelties of outward fortune; it is an active anguish, a sort of psychical neuralgia wholly unknown to healthy life.

Two additional features, when present, would further validate the diagnosis of major depressive disorder.

- History of past episodes.
- Consecutive-generation family history of mood disorder—especially when a large number of family members are afflicted with depression or mood disorder—is characteristic of clinical depression. For instance, one study that prospectively followed persons with minor or neurotic depression found that such pedigrees predicted the development of future
major episodes. In clinical practice, these factors would strongly weigh whether depression is taken seriously.

**Single-Episode and Recurrent Subtypes.** A significant minority—perhaps one-third—of all major depressive episodes do not recur. Such patients tend to be older and less likely to have a positive family history for mood disorders and have a more protracted (1 to 2 years) course of the disorder. Patients with single-episode major depressive disorder should be distinguished from those experiencing their first episodes of recurrent major depressive disorder. The latter group tends to be younger, and the disorder is more likely to have been preceded by a depressive temperament or dysthymic disorder. Those who switch to bipolar disorder are more likely to have experienced recurrent depressions (5 or more episodes).

Research has established that recurrent major depressive disorders are more familial than their single-episode counterparts. The average length of episodes is 6 months, whereas the mean interval between episodes tends to vary (typically years). The mean number of major episodes over a lifetime, according to retrospective and prospective studies, is five to six, in contrast to an average of eight to nine major episodes in bipolar disorder. These figures are probably underestimates, in that they are typically ascertained on the basis of clinical referral or hospitalization, or both.

**Melancholic Features.** *Melancholic features* is a qualifying phrase for major depressive disorders in which anhedonia, guilt, and psychomotor–vegetative disturbances dominate the clinical picture. In addition, severe suicidal ideation may be present.

**Atypical Features.** Reverse vegetative signs with rejection sensitivity, often contrasted to melancholia on phenomenological and pharmacological grounds, represent a major depressive disorder qualifier occurring in as many as one-third of all major depressive disorders. Atypical features are so common in bipolar disorder, especially bipolar II disorder, that some consider them to be clinical markers for soft bipolar disorders. Although there is no consensus on this question, before diagnosing major depressive disorder in such cases, it is clinically wise to exclude bipolar II disorder, especially where hostile–labile features predominate.

**Psychotic Features.** From 10 to 15 percent of major depressive disorders, usually from the rank of those with melancholic features, develop into delusional depressions. In young persons, they tend to be retarded, even stuporous, and are best considered initial episodes of a bipolar disorder until proven otherwise. More typically, psychotic depression that develops for the first time after 50 years of age often presents with severe agitation, delusional guilt, hypochondriacal preoccupations, early-morning awakening, and weight loss. The premorbid adjustment of such patients is classically characterized as *obsessoid.* Their mournful-anxious mood and agitation are autonomous, being refractory to psychological interventions, and they endure great psychic suffering. Except for the fact that generally one to two episodes occur in late-onset (so-called involutional) depressions, they represent a severe variant of DSM-5 melancholia. Kraepelin’s postulation of a cerebrovascular basis for such cases makes the ventricular enlargement and white matter opacities reported in psychotic depressions of some interest. Their etiological specificity for persons with late-onset psychotic depression has been controversial, however, because younger (more bipolar) persons with psychotic depression may exhibit similar findings. Brain imaging findings tend to be correlated with the neurocognitive deficits observed in psychotic depressions. Those features do not seem to define a distinct depressive subtype but one of greater severity that some authorities now
classify as *vascular depressions*. Finally, despite attempts to suggest a neurochemical uniqueness based largely on the need for antipsychotic treatment in the acute phase of many of those patients, familial and other external validations have failed to support psychotic depression as a separate entity; Emerging data, nonetheless, might eventually force a change in this convention. For instance, William Coryell and collaborators in the NIMH Collaborative Depression Study showed that psychotic depression was the most consistent unipolar subtype across episodes. Alan Schatzberg’s work, originally conducted at Harvard, likewise underscored the uniqueness of psychotic depression based on neuroendocrine and putative neurochemical considerations. Finally, consideration should be given to Athanasios Koukopoulos’ clinical formulation that many agitated psychotic depressions might represent mixed states (i.e., activated depressions that belong to the bipolar spectrum).

**Chronic Depression.** The symptom profile in chronic depressions usually displays low-grade intensity rather than severe syndromic chronicity. Severe depressive disorder, in its psychotic forms, is so agonizing that the patient is at risk of committing suicide before the disorder has a chance to become chronic. More commonly, the psychotic symptoms respond to medication or to ECT, but residual depressive symptoms may linger for a long time. In other persons with chronic depressions, the chronicity arises from more mundane (nonpsychotic) major depressive episodes, representing depressive residua following one or several clinical episodes that fail to remit fully. Instead of the customary remission within 1 year, the patients are ill for years. The level of depression varies, fluctuating between syndromic illness and milder symptoms. Recent landmark analyses from the NIMH Collaborative Depression Study by Lewis Judd and colleagues actually showed that as many as 60 percent of patients with major depressive disorder have a subthreshold fluctuating chronic course.

Rather than exhibiting a frankly depressive mood, many persons with chronic depression experience deficits in their ability to enjoy leisure and display an attitude of irritable moroseness. They also show a sense of resignation, generalized fear of an inability to cope, adherence to rigid routines, and inhibited communication. Such deficits, along with the irritable humor, tend to poison their conjugal lives: Their marriages are typically in a state of chronic deadlock, leading neither to divorce nor to reconciliation. In other patients, the residual phase is dominated by somatic features, such as sleep and other vegetative or autonomic irregularities. That these interpersonal, conjugal, and autonomic manifestations represent unresolved depression is shown by persistent sleep EEG (especially REM and delta phase) abnormalities that are indistinguishable from their acute counterparts. Unfortunately, self-treatment with ethanol or iatrogenic benzodiazepine dependence rather than definitive treatment of the ongoing low-grade depression is common.

Failure to recover from major depressive disorder is associated with increased familial loading for depression, disabled spouses, deaths of immediate family members, concurrent disabling medical disease, use of depressant pharmacological agents, and excessive use of alcohol and sedative–hypnotic agents. Social support is often eroded in persons with residual depression through the death or illness of significant others. Therefore, a thorough medical evaluation and socially supportive interventions should be essential ingredients of the overall approach to these patients.

Interpersonal disturbances in such patients are usually secondary to the distortions produced by longstanding depression. Therefore, observed pathological characterological changes—clinging or hostile dependence, demanding tendencies, touchiness, pessimism, and low self-esteem—are best considered as *postdepressive personality* changes. A dangerous
stereotypical thinking holds that, because a patient has not responded adequately to standard treatments (the illness has become chronic), the disorder must have a characterological substrate. The long duration of the disorder often leads the patient to identify with the failing functions of depression, producing the self-image of being a depressed person. This self-image itself represents a malignant cognitive manifestation of the depressive disorder and dictates vigorous treatment targeted at the mood disorder.

**Dysthymic Disorder (Persistent Depressive Disorder in DSM-5)**

Dysthymia, called Persistent Depressive Disorder in DSM-5 (Table 13.4–6), is distinguished from chronic depressive disorder by the fact that it is not a sequel to well-defined major depressive episodes. Instead, in the most typical cases, patients complain that they have always been depressed. Thus, most cases are of early onset, beginning in childhood or adolescence and certainly by the time patients reach their 20s. A late-onset subtype, much less prevalent and not well characterized clinically, has been identified among middle-aged and geriatric populations, largely through epidemiological studies in the community.

**Table 13.4–6. DSM-5 Diagnostic Criteria for Dysthymia**

This disorder represents a consolidation of DSM-IV-defined chronic major depressive disorder and dysthymic disorder.

A. Depressed mood for most of the day, for more days than not, as indicated by either subjective account or observation by others, for at least 2 years.
   **Note:** In children and adolescents, mood can be irritable, and duration must be at least 1 year.

B. Presence, while depressed, of two (or more) of the following:
   1. Poor appetite or overeating.
   2. Insomnia or hypersomnia.
   3. Low energy or fatigue.
   4. Low self-esteem.
   5. Poor concentration or difficulty making decisions.
   6. Feelings of hopelessness.

C. During the 2-year period (1 year for children or adolescents) of the disturbance, the individual has never been without the symptoms in Criteria A and B for more than 2 months at a time.

D. Criteria for a major depressive disorder may be continuously present for 2 years.

E. There has never been a manic episode or hypomanic episode, and criteria have never been met for cyclothymic disorder.

F. The disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.

G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hypothyroidism).

H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
   **Note:** Because the criteria for a major depressive episode include four symptoms that are absent from the symptom list for persistent depressive disorder (dysthymia), a very limited number of individuals will have depressive symptoms that have persisted longer than 2 years but will not meet criteria for persistent depressive disorder. If full criteria for a major depressive episode have been met at some point during the current episode of illness, they should be given a diagnosis of major depressive disorder. Otherwise, a diagnosis of other specified depressive disorder or unspecified depressive disorder is warranted.
Table 13.4–6. (continued) DSM-5 Diagnostic Criteria for Dysthymia

**Specify if:**
- With anxious distress (p. 184)
- With mixed features (pp. 184–185)
- With melancholic features (p. 185)
- With atypical features (pp. 185–186)
- With mood-congruent psychotic features (p. 186)
- With mood-incongruent psychotic features (p. 186)
- With peripartum onset (pp. 186–187)

**Specify if:**
- In partial remission (p. 188)
- In full remission (p. 188)

**Specify if:**
- Early onset: If onset is before 21 years of age.
- Late onset: If onset is at age 21 years or older.

**Specify if** (for most recent 2 years of persistent depressive disorder):
- With pure dysthmic syndrome: Full criteria for a major depressive episode have not been met in at least the preceding 2 years.
- With persistent major depressive episode: Full criteria for a major depressive episode have been met throughout the preceding 2-year period.
- With intermittent major depressive episodes, with current episode: Full criteria for a major depressive episode are currently met, but there have been periods of at least 8 weeks in at least the preceding 2 years with symptoms below the threshold for a full major depressive episode.
- With intermittent major depressive episodes, without current episode: Full criteria for a major depressive episode are not currently met, but there has been one or more major depressive episodes in at least the preceding 2 years.

**Specify current severity:**
- Mild (p. 188)
- Moderate (p. 188)
- Severe (p. 186)

Although the dysthyemic disorder category in DSM-5 can occur as a secondary complication of other psychiatric disorders, the core concept of dysthyemic disorder refers to a subaffective disorder with (1) low-grade chronicity for at least 2 years, (2) insidious onset with origin often in childhood or adolescence, and (3) persistent or intermittent course. Although not part of the formal definition of dysthyemic disorder, the family history is typically replete with depressive and bipolar disorders, which is one of the more robust findings supporting its link to primary mood disorder.

**Social Adjustment.** Dysthyemic disorder is typically an ambulatory disorder compatible with relatively stable social functioning. However, the stability is precarious; recent data document that many patients invest whatever energy they have in work, leaving none for leisure and family or social activities, which results in marital friction. These empirical findings on the work orientation of persons with dysthyemic disorder echo earlier formulations in the German and Japanese literature. For instance, Kraepelin described such persons as follows: “Life with its activity is a burden which they habitually bear with dutiful self-denial without being compensated by the pleasures of existence.”

The dedication of persons with dysthyemic disorder to work has been suggested to be an overcompensation and a defense against their battle with depressive disorganization and inertia. Nevertheless, Ernst Kretschmer suggested that such persons are the “backbone of
society,” dedicating their lives to jobs that require dependability and great attention to detail. Epidemiological studies have demonstrated that some persons with protracted dysthymic complaints, extending over many years, have never experienced clear-cut depressive episodes. Some of them may seek outpatient counseling and psychotherapy for what some clinicians might consider existential depression, with feelings of being empty and lacking any joy in life outside of their work. Such persons have been described as leading “monocategorical existences.” Others present clinically because their low-grade dysphoria has intensified into a major depression disorder.

**Course.** An insidious onset of depression dating back to late childhood or the teens, preceding any superimposed major depressive episodes by years or even decades, represents the most typical developmental background of dysthymic disorder. A return to the low-grade depressive pattern is the rule after recovery from superimposed major depressive episodes, if any; hence, the designation double depression as a prominent course pattern. This pattern, commonly seen in clinical practice, consists in the baseline dysthymic disorder fluctuating in and out of depressive episodes. The more prototypical patients with dysthymic disorder often complain of having been depressed since birth or of feeling depressed all the time. They seem, in the apt words of Kurt Schneider, to view themselves as belonging to an “aristocracy of suffering.” Such descriptions of chronic gloominess in the absence of more objective signs of depression earn these patients the label of characterological depression. The description is further reinforced by the fluctuating depressive picture that merges imperceptibly with the patient’s habitual personality makeup. This conceptual uncertainty notwithstanding, given the confluence of data on the efficacy of many classes of antidepressants, patients with dysthymia should not be denied the potential benefit of antidepressants.

**Clinical Picture.** The profile of dysthymic disorder overlaps with that of major depressive disorder but differs from it in that symptoms tend to outnumber signs (more subjective than objective depression). This means that marked disturbances in appetite and libido are uncharacteristic, and psychomotor agitation or retardation is not observed. This all translates into a depression with attenuated symptomatology. However, subtle endogenous features are not uncommonly observed: inertia and anhedonia that are characteristically worse in the morning.

Although dysthymic disorder represents a more restricted concept than its parent, neurotic depression, it is still quite heterogeneous. Anxiety is not a necessary part of its clinical picture, yet dysthymic disorder is often diagnosed in patients with anxiety and neurotic disorders. That clinical situation is perhaps to be regarded as a secondary or anxious dysthymia or, in the framework of Peter Tyrer, as part of a general neurotic syndrome. For greater operational clarity, it is best to restrict dysthymic disorder to a primary disorder, one that cannot be explained by a nonmood disorder. The essential features of such primary dysthymic disorder include habitual gloom, brooding, lack of joy in life, and preoccupation with inadequacy. Dysthymic disorder then is best characterized as longstanding, fluctuating, low-grade depression experienced as part of the habitual self and representing an accentuation of traits observed in the depressive temperament. Sleep EEG data indicate that many persons with dysthymic disorder at baseline exhibit the sleep patterns of those with acute major depressive disorder, providing support for the constitutional nature of the disorder. Further evidence for that position comes from studies demonstrating high rates of familial affective disorder in dysthymic disorder or depressive temperament, or both.
The clinical picture of dysthymic disorder that emerges from the foregoing description is quite varied, with some patients proceeding to major depression, whereas others manifest the pathology largely at the personality level. The foregoing considerations suggest that a clinically satisfactory operationalism of dysthymia must include symptomatic, cognitive, and trait characteristics.

A 27-year-old male grade-school teacher presented with the chief complaint that life was a painful duty that had always lacked luster for him. He said that he felt “enveloped by a sense of gloom” that was nearly always with him. Although he was respected by his peers, he felt “like a grotesque failure, a self-concept I have had since childhood.” He stated that he merely performed his responsibilities as a teacher and that he had never derived any pleasure from anything he had done in life. He said that he had never had any romantic feelings; sexual activity, in which he had engaged with two different women, had involved pleasureless orgasm. He said that he felt empty, going through life without any sense of direction, ambition, or passion, a realization that itself was tormenting. He had bought a pistol to put an end to what he called his “useless existence” but did not carry out suicide, believing that it would hurt his students and the small community in which he lived.

**Dysthymic Variants.** Dysthymia is not uncommon in patients with chronically disabling physical disorders, particularly among elderly adults. Dysthymia-like clinically significant subthreshold depression lasting 6 or more months has also been described in neurological conditions, including stroke. According to a recent WHO conference that generated a book, this condition aggravates the prognosis of the underlying neurological disease and therefore deserves pharmacotherapy. Ongoing studies should provide more explicit clinical recommendations on this topic.

Prospective studies on children have revealed an *episodic course* of dysthymia with remissions, exacerbations, and eventual complications by major depressive episodes, 15 to 20 percent of which might even progress to hypomanic, manic, or mixed episodes postpuberty. Persons with dysthymic disorder presenting clinically as adults tend to pursue a chronic unipolar course that may be complicated by major depression. They rarely develop spontaneous hypomania or mania. However, when treated with antidepressants, some of them may develop brief hypomanic switches that typically disappear when the antidepressant dose is decreased. In this special subgroup of persons with dysthymic disorder, the family histories are often positive for bipolar disorder. These patients represent a clinical bridge between major depressive disorder and bipolar II disorder.

**Other Specified Depressive Disorder and Unspecified Depressive Disorder**

**Minor Depressive Disorder.** In so-called minor depression, observed in primary care settings, the depression is subthreshold, milder than major depressive disorder, and yet not protracted enough to be considered dysthymic. These varied manifestations of depression argue for a continuum model (Fig. 13.4–5) as originally envisaged by Kraepelin. Lewis Judd and collaborators at the University of California at San Diego have suggested that subthreshold depressive symptoms—without necessarily meeting the criterion for mood change—might actually represent the most common expressions of a depressive diathesis. From such a subsyndromal symptomatic depressive base, individuals predisposed to depressive illness are said to fluctuate in and out of the various DSM-5 and subthreshold subtypes of depressive disorders. This viewpoint is presently most cogent for subsyndromal symptomatic depression that follows major depressive disorder, a strong predictor of subsequent frequent relapse or chronic course. There is an important message for the clinician here: Treat subsyndromal symptomatic depression residual to major depressive disorder.
Premenstrual Dysphoric Disorder. In view of the higher prevalence of depressive disorders in women, premenstrual affective changes—dysphoria, tension, irritability, hostility, and labile mood—have received clinical and, more recently, research attention. The attempt to establish a specific premenstrual dysphoric disorder beyond this more normative premenstrual tension has neglected the occurrence of premenstrual eutonia, increased energy, and sexual drive. The not uncommon occurrence of these positive emotions, along with the labile mixed affective manifestations, tends to point toward a bipolar phenomenon. Although women with severe premenstrual complaints appear to have higher rates of lifetime major mood disorders, a recent twin study found that genetic and environmental factors contributing to premenstrual depression and major depressive disorders are largely distinct. Furthermore, events such as migraine, epileptic attacks, and panic states may, in some instances, be associated with the premenstrual phase. The foregoing considerations suggest the hypothesis that premenstrual psychobiological changes exacerbate different neuropsychiatric disorders to which women are otherwise predisposed. Whether the exaggerated premenstrual variability in emotional equilibrium constitutes a specific mood disorder or a more familiar affective disorder variant (e.g., mixed panic–depressive, bipolar) must await more-definitive studies. Premenstrual accentuation or precipitation of bipolar episodes, especially of a mixed dysphoric nature, is described in the clinical literature.

Recurrent Brief Depressive Disorder. Recurrent brief depressive disorder derives from British work on young adults with frequent suicide attempts and epidemiological studies conducted in a young adult cohort in Zurich. It is described as short-lived depressions that usually recur on a monthly basis but are not menstrually related. They could coexist with major depressive disorder or dysthymic disorder and with hypomania. Again, the existence of hypomanic-prone recurrent brief depressive disorder argues for a bridge between depressive and bipolar II disorders. Such patients are believed to be more prevalent in primary care than
in psychiatric settings. Those seen in psychiatric settings are likely to be given Axis II diagnoses, such as borderline personality disorder. The current nosological status of recurrent brief depressive disorder is uncertain, but it testifies to Kraepelin’s observation that many transitional forms link the depressive temperament to affective episodes:

A permanent gloomy stress in all the experiences of life usually perceptible already in youth, and may persist without essential change throughout the whole of life (or) there is actually an uninterrupted series of transitions to periodic melancholia in which the course is quite indefinite with irregular fluctuations and remissions.

**Reactive Depression.** Classically, *reactive depression* is defined as resulting from a specific life event. In an ideal case, the depression would not have occurred without the event (e.g., love loss) to which it is a reaction. It continues as long as the event is present, and it terminates with the reversal of the event (e.g., return of the lover). Depressions exhibiting all of those features are almost never seen in clinical practice. With interpersonal support, most people can face life’s reverses, which explains why reactive depression tends to be self-limiting. Hence, adjustment disorder is the more appropriate diagnosis for many cases of reactive depression.

**Chronic Demoralization.** Conceptually, however, one can envision chronically unsatisfactory life situations that might lead to chronic helplessness. However, such a condition, which could warrant the designation of chronic reactive depression, is a contradiction in terms. The question often raised is why a person would continue to stay in the situation. Sometimes psychodynamic authors invoke the concept of masochism to explain why certain persons cannot rid themselves of painful life situations, implying that they somehow contribute to their maintenance. Current thinking is that some of those presumed self-defeating traits are more situation specific than previously believed and might resolve with the elimination of the situation. So-called self-defeating features then are best considered psychodynamic mechanisms rather than indicators of a specific personality. At the present stage of knowledge, they do not deserve to be raised to the level of a nosological entity (hence, their non-inclusion in DSM-5). Chronic adjustment disorder might describe the chronic demoralization observed among some individuals stuck in chronically unsatisfactory life situations. Others might fulfill the criteria for dysthymia. Finally, if the chronically unsatisfactory life conditions involve conjugal violence and trauma, PTSD may be the appropriate diagnosis.

**Neurasthenia.** A century-old term developed by the American neuropsychiatrist George Beard, *neurasthenia* refers to a more chronic stage of anxious–depressive symptomatology. The anxiety generated by overstimulation is so excessive that it is replaced by a chronic disposition to irritability, fatigue (especially mental fatigue), lethargy, and exhaustion. It is as if the patient’s mind refuses to take on new stresses. The clinical picture described by Beard suggests that anxious manifestations were pre-eminent in his time. They included headache, scalp tenderness, backache, heavy limbs, vague neuralgias, yawning, dyspepsia, palpitations, sweating hands and feet, chills, flushing, sensitivity to weather changes, insomnia, nightmares, pantophobia, asthenopia, and tinnitus.

Although the diagnosis of neurasthenia is now used more in China than in the rest of the world, the recent worldwide popularity of the concept of chronic fatigue syndrome attests to the clinical acumen of classic physicians. Despite much energy invested in finding a viral or immunological cause, current descriptions tend to suggest an anxiety or mood disorder basis
for many, but certainly not all, of those with the syndrome. Some patients with neurasthenia would meet the criteria for major depressive disorder with atypical features and history of panic and phobic disorders. What circumstances would lead anxiety or depression to manifest primarily in fatigue is as elusive as it was 100 years ago. Like many other patients presenting to primary care settings with somatic complaints, those with chronic fatigue tend to denounce psychiatric diagnoses as inadequate explanations for their ills.

**Postpsychotic Depressive Disorder of Schizophrenia.** A postpsychotic depression can occur during the residual phase of schizophrenia. It is characterized by the persistence of negative symptoms or positive symptoms that are in an attenuated form (e.g., odd beliefs, unusual perceptual experiences). The depression is characterized by loss of interest or pleasure and sad or depressed mood. Most typically, the Major Depressive Episode follows immediately after remission of the active phase of the psychotic episode. Sometimes it may follow after a short or extended interval during which there are no psychotic symptoms. Mood symptoms due to the direct physiological effects of a drug of abuse, a medication, or a general medical condition are not counted toward postpsychotic depressive disorder of schizophrenia.

In all postpsychotic depressions, one must first exclude a missed bipolar diagnosis. Negative symptoms due to classic antipsychotics—especially depot phenothiazines and those due to the residuum of schizophrenia once positive symptoms are brought under control—should be distinguished from the depressive episodes that complicate the course of schizophrenia in young, intelligent patients. This phenomenon is so common (at least 30 percent of patients with schizophrenia) that it can be considered as part of the natural course of schizophrenia rather than a separate nosological entity.

**BIPOLAR DISORDERS**

There are several types of bipolar disorder categories included in DSM-5. Some are categorized on a descriptive level such as bipolar I disorder, bipolar II disorder, cyclothymic disorder, and unspecified bipolar disorder; some are classified according to etiology such as substance or medication induced bipolar disorder and bipolar disorder due to another medical condition. The clinical picture for each is similar regardless of etiology.

Tables 13.4–3 through 13.4–5 describe the syndromes of depression, mania and hypomania that make bipolar disorder I or bipolar II.

**Bipolar I Disorder**

Typically beginning in the teenage years, the 20s, or the 30s, the first episode of bipolar I disorder could be manic, depressive, or mixed. One common mode of onset is mild retarded depression or hypersonomnia for a few weeks or months, which then switches into a manic episode. Others begin with a severely psychotic manic episode with schizophreniform features; only when a more classic manic episode occurs is the affective nature of the disorder clarified. In a third group, several depressive episodes occur before the first manic episode. A careful history taken from significant others often reveals hyperthymic or cyclothymic traits that antedated the frank onset of manic episodes by several years, if not longer.
Single manic episode (describes patients having a first episode of mania (most such patients eventually develop depressive episodes). The remaining subcategorization is used to specify the nature of the current or most recent episode in patients who have had recurrent mood episodes. For clinicians and researchers alike, it is more meaningful to chart a patient’s course in color over time—for example, using red for manic, blue for depressive, and violet for mixed episodes, with hypomanic, dysthymic, and cyclothymic periods drawn in the appropriate colors on a smaller scale between the major episodes. Life events, biological stressors, and treatment can be indicated by arrows on the time axis. This approach, originally championed by Kraepelin, is routinely used in mood or bipolar clinics to chart retrospectively the past course of illness in mood disorders, especially bipolar disorders. Robert Post at the NIMH has developed this approach into systematic clinical science. Its adoption for clinical use was recommended by an international conference that took place in Barcelona. Recent data from the NIMH Collaborative Depression Study—using a prospective method of life charting—of bipolar I disorder clinical cohorts followed in five major US medical centers show more depression, especially its subthreshold variants, during an average of 12 years of follow-up. These patients were actually symptomatic nearly 50 percent of the weeks through the entire follow-up, suggesting a more pervasive course of illness than previously appreciated. Although such data indicate some degree of tertiary care bias in favor of patients willing to be retained in a long-term study, they underscore a clinical reality faced by many clinicians in their daily practice (see Fig. 13.4–6).

On average, manic episodes predominate in youth, and depressive episodes predominate in later years. Although the overall sex ratio is approximately 1:1, men, on average, undergo more manic episodes, and women experience more mixed and depressive episodes. Bipolar I disorder in children is not as rare as previously thought; however, most reported cases are in boys, and mixed manic (dysphoric–explosive) and rapid-cycling presentations are the mode. Childhood-onset depression must also be considered a major risk for ultimate bipolar transformation. This is based on the following characteristics: (1) early age at onset; (2) even sex ratio; (3) prominence of irritability, labile moods, and explosive anger, suggesting mixed episodes; (4) questionable response to antidepressants, hypomanic switches, or both; (5) high recurrence rate after depression; and (6) familial affective loading. Mania can also first appear after 65 years of age, although a diligent search often reveals a past mild, forgotten, or untreated depressive or excited episode in earlier years.

Acute Mania. Mania typically escalates over a period of 1 to 2 weeks; more-sudden onsets have also been described. The DSM-5 criteria stipulate (1) a distinct period that represents a break from premorbid functioning, (2) a duration of at least 1 week, (3) an elevated or irritable mood, (4) at least three or more classic manic signs and symptoms, and (5) the absence of any physical factors that could account for the clinical picture. The irritable mood in mania can deteriorate to cantankerous behavior, especially when the person is rebuffed. Such patients are among the most aggressive seen in the emergency room. Florid grandiose psychosis with paranoid features, a common presentation of mania, further contributes to the aggression. Alcohol use, observed in at least 50 percent of bipolar I patients (often during the manic phase), further disinhibits the patient and might lead to a dangerous frenzy. Such patients may attack loved ones and hurt them physically. So-called crimes of passion have been committed by patients harboring delusions of infidelity on the part of spouses or lovers, usually when the patient is under the influence of alcohol.

The genesis of delusional, hallucinatory, even first-rank, psychotic experiences in mania has already been described. Recent research has documented that most types of formal thought
disorders are common to schizophrenic and mood psychoses; only poverty of speech content (vagueness) emerges as significantly more common in schizophrenia. In addition, posturing and negativism occur may occur during manic periods. Finally, even pseudodemented presentations, can occur. Mania is most commonly expressed as a phase of bipolar I disorder, which has strong genetic determinants. The evidence does not permit separating recurrent mania without depressive episodes from that type as a distinct nosological entity.

**Secondary Mania.** Although there is some suggestion that postpartum mania without depression is distinct from familial bipolar I disorder (in which depressive, manic, and especially mixed manic episodes occur in the postpartum period), the evidence for a distinct puerperal mania is not compelling. Mania without prior bipolarity can arise in the setting of such somatic illnesses as thyrotoxicosis, systemic lupus erythematosus or its treatment with steroids, rheumatic chorea, multiple sclerosis (MS), Huntington disease, cerebrovascular disorder, diencephalic and third ventricular tumors, head trauma, complex partial seizures, syphilis, and (most recently) AIDS. The family history is reportedly low in such cases, suggesting a relatively low genetic predisposition and, thus, a lower risk of recurrence. These patients do not easily fit into the DSM-5 category of mood disorder due to a general medical condition) because most of the conditions appear to be cerebral. Such factors must always be diligently sought in manias of late life.

Less well-defined forms of mania are the so-called reactive manias. Personal loss and bereavement are hypothesized to be triggering factors, and the reaction is conceptualized psychodynamically as a denial of loss. Although such explanations may be plausible in individual cases, no systematic data suggest that these patients differ in family history from persons with other manias. The same is generally true for depressed patients who switch to
hypomania or mania after the abuse of stimulant drugs, treatment with antidepressants, or sleep deprivation. In all of these situations, a bipolar diathesis is usually manifest in a family history of mania or in spontaneous excited episodes during prospective observation. First-onset manic episodes can also occur in persons who abruptly abstain from alcohol after one or more decades of chronic use and then develop classic bipolar I disorder.

**Chronic Mania.** About 5 percent of bipolar I disorder patients have a chronic manic course. These cases commonly represent deterioration of course dominated by recurrent manic episodes grafted onto a hyperthymic baseline. Noncompliance with pharmacological treatment is the rule. Recurrent excitement is personally reinforcing, subjective distress is minimal, and insight is seriously impaired. Thus, the patient sees no reason to adhere to treatment. Episodic or chronic alcohol abuse, prevalent in such patients, has been suggested as a contributory cause of the chronicity. Some authorities further consider comorbid cerebral pathology to be responsible for nonrecovery (and increased mortality) from manic excitement occurring in late life.

Grandiose delusions (e.g., delusions of inventive genius or aristocratic birth) are not uncommon in chronic mania and may lead to the mistaken diagnosis of paranoid schizophrenia. Because of their social deterioration, Kraepelin subsumed such patients under the category *manic dementia*. Organic factors, such as head trauma and chronic alcohol abuse, may contribute to the deterioration. Nonschizoid premorbid adjustment, a family history of bipolar I disorder, and the absence of flagrant formal thought disorder can be marshaled in establishing the affective basis of these poor-prognosis manic states.

**Bipolar Mixed Phase.** Momentary tearfulness and even depressed mood are commonly observed at the height of mania or during the transition from mania to retarded depression. These transient labile periods, which occur in most bipolar I disorder patients, must be contrasted with mixed episodes proper.

The latter, variously referred to as *mixed mania* or *dysphoric mania*, are characterized by dysphorically excited moods, irritability, anger, panic attacks, pressured speech, agitation, suicidal ideation, severe insomnia, grandiosity, and hypersexuality, as well as persecutory delusions and confusion. Severely psychotic mixed states that involve hallucinations and schneiderian symptoms risk being labeled *schizoaffective*. A correct diagnosis helps to avoid conventional antipsychotic drugs known to exacerbate the depressive component; in such patients, failure to use mood stabilizers can prolong the patient’s misery.

New research data from mood centers worldwide on mixed mania suggest that dysphoric mania—mania and full-blown depression occurring simultaneously—is relatively uncommon. Two to four depressive symptoms from the list of depressed mood, helplessness, hopelessness, fatigue, anhedonia, guilt, and suicidal ideation, impulses, or both in the setting of a manic syndrome appear to suffice for the diagnosis of mixed manic states, which occur in 50 percent of patients with bipolar disorder sometime during their lives. Mixed states occur predominantly in women in whom mania is superimposed on a depressive temperament or a dysthymic baseline. The emerging conceptualization of mixed mania is a manic state intruding on long-term depressive traits. Other mixed manic states, especially in men, often arise from the interaction of substance or alcohol use in bipolar I disorder.

**Depressive Phase.** Psychomotor retardation, with or without hypersomnia, marks the uncomplicated depressive phase of bipolar I disorder. Onset and offset are often abrupt,
although onset can also occur gradually over several weeks. Patients may recover into a free interval or may switch directly into mania. Switching into an excited phase is particularly likely when antidepressants have been used. However, not all patients develop mania after antidepressant treatment of bipolar depression. Some develop a mixed agitated depression; indeed, patients may be stuck for many months in a severe depressive phase with some manic admixtures, such as racing thoughts and sexual arousal. Delusional and hallucinatory experiences are less common in the depressive phase of bipolar I disorder than in the manic and mixed manic phases. Stupor is the more common psychotic presentation of bipolar depression, particularly in adolescents and young adults. Pseudodemented organic presentations appear to be the counterpart of stupor in elderly adults.

**Cyclothymic Disorder**

An attenuated bipolar disorder that typically begins insidiously before 21 years of age, cyclothymic disorder is characterized by frequent short cycles of subsyndromal depression and hypomania. The course of cyclothymia is continuous or intermittent, with infrequent periods of euthymia. Shifts in mood often lack adequate precipitants (e.g., sudden profound dejection with social withdrawal for a few days switching into cheerful, gregarious behavior). Circadian factors may account for some of the extremes of emotional lability, such as the person’s going to sleep in good spirits and waking up early with suicidal urges. The mood changes of cyclothymia are best described as endoreactive in the sense that endogenous over-reactivity seems to determine the sudden shifts in mood and behavior (e.g., falling in love with a person one has just met and as quickly falling out of love).

Mood swings in these ambulatory patients are overshadowed by the chaos that the swings produce in their personal lives. Repeated romantic breakups or marital failures are common because of interpersonal friction and episodic promiscuous behavior. Uneven performance at school and work is also common. Persons with cyclothymic disorder are dilettantes; they show great promise in many areas but rarely bring any of their efforts to fruition. As a result, their lives are often a string of improvident activities. Geographical instability is a characteristic feature; easily attracted to a new locale, job, or love partner, they soon lose interest and leave in dissatisfaction. Polysubstance abuse, which occurs in as many as 50 percent of such persons, is often an attempt at self-treatment. Suicidality has emerged as a public health hazard in adolescents. Many such youth, often labeled “borderline,” may actually suffer from undiagnosed temperament expression of bipolar disorder.

**Bipolar II Disorder**

Research conducted during the last three decades has shown that, between the extremes of manic-depressive illness defined by at least one acute manic episode, which could be mood congruent or incongruent (bipolar I disorder), and strictly defined major depressive disorder without any personal or family history of mania (pure unipolar disorder), there exists an overlapping group of intermediary forms characterized by recurrent major depressive episodes and hypomania. Current data worldwide indicate that bipolar II disorder is actually more prevalent than bipolar I disorder. This certainly appears to be true in the outpatient setting, in which an average of 50 percent (and in one French national study up to 65 percent) of persons with major depressive disorder have been reported to conform to the bipolar II disorder pattern. The depressive phase of bipolar disorder, especially as expressed in bipolar II and its “soft” expressions, has emerged as a major public health problem.
The following self-description provided by a 34-year-old poet illustrates the pattern:

I have known melancholy periods, lasting months at a time, when I would be literally paralyzed: All mental activity comes to a screeching halt, and I cannot even utter one word. I become so dysfunctional that I was once hospitalized. Although the paralysis creeps into me insidiously—often lasting months—it typically reverses within hours. I am suddenly alive and vibrant, I cannot turn off my brain neither during the day nor at night; I usually go on celebrating like this for many days, needing no more than few hours of slumber each day.

This vignette is nearly identical to the autobiographical description provided by the British poet William Cowper three centuries earlier:

I have known many a lifeless and unhallowed hour … long intervals of darkness interrupted by short returns of peace and joy. . . . For many succeeding weeks to rejoice day and night was all my employment. Too happy to sleep much, I thought it was lost time that was spent on slumber.

Although some hypomanias last for weeks, the hypomania at the end of depressive episodes in most bipolar II disorder patients does not last long; it is usually measured in days. As discussed earlier, hypomanias with short duration (less than 4 days) are familially similar to those with longer duration (more than 4 days). Another common form of bipolar II disorder is major depressive disorder superimposed on cyclothymic disorder, in which hypomania precedes and follows major depressive disorder, with the entire interepisodic period characterized by cyclothymic mood instability. Such patients tend to have an unstable course, stormy interpersonal relationships, and more irritable and hostile hypomanic episodes—hence the confusion with borderline personality disorder. Current data indicate that cyclothymic and noncyclothymic bipolar II disorder have similar rates of familial bipolarity, which suggests that the borderline characterological features represent a complication of the unstable course that cyclothymia imparts to bipolar II disorder. Such individuals with unstable course have a high risk of suicide—indeed, based on research in Budapest, it appears that the high burden of suicide in mood disorders appears to be due to bipolar II disorder. Descriptively, hypomania in bipolar II disorder can be defined as mini manic episodes occurring spontaneously. Bipolar II disorder—especially when major depressions are superimposed on cyclothymia—is thus best characterized as cyclical or cyclothymic depression.

The depressive episodes of patients with bipolar disorder often have admixtures (e.g., flight of ideas and increased drives and impulsivity in sexual and other domains). These are best regarded as depressive mixed states, which are basically ignored in the DSM-IV-TR schema. Depressive mixed states are not as severe as dysphoric mixed states but are refractory to antidepressants nonetheless, and, according to current data, are overrepresented in suicide. Current Italian research conducted by Franco Benazzi and the author of this chapter indicates that such depressive mixed states occur in as much as 60 percent of cases of bipolar II disorder and as much as 30 percent of cases of “unipolar” major depressive disorder. Both groups have similar rates of familial bipolarity, suggesting that one of three patients with “unipolar” depression belongs to the bipolar II spectrum.

**Hypomania.** The common denominator of the soft spectrum of bipolar disorders is the occurrence of hypomania as episode or trait. Hypomania refers to a distinct period of at least a few days of mild elevation of mood, sharpened and positive thinking, and increased energy and activity levels, typically without the impairment characteristic of manic episodes. It is not merely a milder form of mania. Hypomania occurring as part of bipolar II disorder rarely progresses to manic psychosis and insight is relatively preserved. Hypomania is distinguished
from mere happiness in that it tends to recur (happiness does not!) and can sometimes be mobilized by antidepressants. In cyclothymic disorder, it alternates with mini depressions; in hyperthymic temperament, it constitutes the person’s habitual baseline. These definitions, developed by empirical research, recognize three patterns of hypomania: Episodes heralding the termination of a retarded depressive state (bipolar II disorder), cyclic alternation with mini depressions (cyclothymic disorder), and an elevated baseline of high mood, activity, and cognition (hyperthymic or chronic hypomanic traits).

Because hypomania is experienced as a rebound relief from depression or as a pleasant, relatively short-lived, ego-syntonic mood state, persons with bipolar II disorder rarely report it spontaneously. Skillful questioning is thus required to make the diagnosis of soft bipolar conditions; as in mania, collateral information from family members is crucial. In interviewing the patient, it is customary to use questions along these lines: “Have you had a distinct sustained high period when your mood was so intense that you felt nervous, you were endowed with such energy that others could not keep up with you, and when your thinking and perceptions were unusually vivid or rapid?” Many bipolar patients react to inquiries about “high moods” or “high periods” with a negative: “I am not a manic-depressive!” Benazzi and the author have recently shown that it is best first to inquire about signs and symptoms referring to behavioral activation and to items related to mood. Once energized periods are remembered, the patient is more likely to recall the mood change associated with these periods.

Clinical and epidemiological studies in the United States and Europe have revealed a rich range of hypomanic manifestations including an increase in cheerfulness and jocularity; gregariousness and people seeking; greater interest in sex; talkativeness, self-confidence, and optimism; and decreased inhibitions and sleep need. The clinician must ascertain that those experiences are not due to stimulant or alcohol withdrawal. Depressive and hypomanic periods are often not easily discerned because chronic caffeine use, stimulant abuse, or both may complicate the depression. In such instances, diagnosis should be deferred for 1 month after detoxification. Cocaine and stimulant use is also not uncommon in hypomania, especially in patients with hyperthymic traits, and constitutes an attempt to augment the baseline energy and mood rather than self-treatment of low moods. When in doubt, direct clinical observation of hypomania—sometimes elicited by antidepressant pharmacotherapy—provides definitive evidence for the bipolar nature of the disorder.

Seasonal Patterns. Seasonality is observed in many cyclic depressions, often with autumn or winter anergic depression and energetic periods in the spring. This natural propensity explains why phototherapy may provoke mild hypomanic switches. Seasonal depressions conform, in large measure, to the bipolar II disorder or bipolar III disorder pattern. Furthermore, preliminary evidence suggests that treatment with classic antidepressants disrupts the baseline seasonality, with the depressive phase appearing in the spring and summer. The changes that antidepressants induce in seasonal depressions probably represent a special variant of the rapid-cycling phenomenon.

Temperament and Polarity of Episodes. New systematic clinical observations have revealed that bipolar II disorder (characterized predominantly by depressive attacks) arises more often from a hyperthymic or cyclothymic baseline, whereas bipolar I disorder (defined by manic attacks) not uncommonly arises from the substrate of a depressive temperament. In line with these observations, a prospective 11-year NIMH study of major depressive disorder patients who switched to bipolar II disorder showed that mood-labile (cyclothymic) and
energetic–active (hyperthymic) temperament traits were highly specific (86 percent) and reasonably sensitive (42 percent) predictors of such an outcome.

Bipolarity is conventionally defined by the alternation of manic (or hypomanic) and depressive episodes. The foregoing data on temperaments suggest that a more fundamental characteristic of bipolarity is the reversal of temperament into its “opposite” episode (in the case of the bipolar II disorder spectrum, from cyclothymia and hyperthymia to major depression). Such findings suggest that the intrusion of cyclothymic and hyperthymic traits into a depressive episode may underlie the instability of the bipolar II disorder subtype and could partly explain why bipolar II depression often has mixed features. These considerations may have important implications for preventing recurrence. For instance, a prospective study of the onset of bipolar disorder in the offspring or siblings of adults with the disorder found that children with depressive onsets as their first episode (which were usually treated with antidepressants) had significantly higher rates of recurrence than those with manic or mixed onsets (treated with lithium) during a 3-year prospective observation. It appears that temperamental instability in the depressive group might have predisposed them to the cycling effect of antidepressants.

Alcohol and Substance Abuse. New evidence supports the high prevalence of alcohol and substance abuse in mood disorder subtypes, especially those with interepisodic cyclothymia and hyperthymia. The relation appears to be particularly strong in the teenage and early adult years, when the use of such substances often represents self-medication for the mood instability. It is not just self-treatment of selected symptoms associated with the down or up phases (e.g., alcohol to alleviate the insomnia and nervousness characteristic of both phases), it also augments certain desired ends (e.g., stimulants to enhance high-energy performance and sexual behavior associated with hypomania). Alcohol may be sought both for its disinhibiting effects and for sedation to calm the nervousness of the high periods. How many patients display alcohol and substance abuse secondary to an underlying bipolar diathesis remains to be determined. However, in view of findings suggesting a link between polysubstance abuse and suicide in adolescents with bipolar familial backgrounds, the use of mood stabilizers in these adolescents should be strongly considered. Although alcohol and stimulant use continues into adult years in a considerable number of bipolar disorder patients, such use is often unrelated to familial alcoholism and frequently tends to dwindle during long-term follow-up, which supports the self-medication hypothesis.

Rapid-Cycling Bipolar Disorder. Rapid cycling is defined as the occurrence of at least four episodes of retarded depression and hypomania (or mania) per year. Thus, rapid cyclers are rarely free of affective symptoms and experience serious vocational and interpersonal incapacitation. Lithium is only modestly helpful to those patients, as are traditional antipsychotic agents; most antidepressants readily induce excited episodes and thus aggravate the rapid-cycling pattern. A balance among mood stabilizers, atypical antipsychotic drugs, and antidepressants may be difficult to achieve. Antidepressants should be avoided because every provoked hypomania is followed by depression, and the roller coaster is further prolonged. Many such patients require frequent hospitalization because they develop explosive excitement and precipitous descent into severe psychomotor inhibition. The disorder is a roller coaster nightmare for the patient, significant others, and the treating physician. Treating these patients is an art, Lamotrigine (Lamictal), a mood stabilizer that stabilizes “from below,” has been reported to be efficacious in this group of patients.
As expected, rapid cycling commonly arises from a cyclothymic substrate, which means that most rapid cyclers have bipolar II disorder. Factors favoring its occurrence include (1) female gender, (2) borderline hypothyroidism, (3) menopause, (4) temporal lobe dysrhythmias, (5) alcohol, minor tranquilizer, stimulant, or caffeine abuse, and (6) long-term, aggressive use of antidepressant medications. Most clinically identified patients are bipolar II women in middle age or upper socioeconomic status. Rapid cycling is uncommon from a bipolar I disorder base.

**Leadership and Creativity.** Persons with hyperthymic temperament and soft bipolar conditions in general possess assets that permit them to assume leadership roles in business, the professions, civic life, and politics. Increased energy, sharp thinking, self-confidence, and eloquence represent the virtues of an otherwise stormy life.

Creative achievement is relatively uncommon among those with the manic forms of the disorder, which are too severe and disorganizing to permit the necessary concentration and application. Notable artistic achievements are found among those with soft bipolar disorders, especially cyclothymic disorders. Psychosis, including severe bipolar swings, is generally incompatible with creativity. That conclusion tends to refute the romantic tendency to idolize insanity as central to the creative process. Because talent is the necessary ingredient of creativity, how might soft bipolarity contribute? The simplest hypothesis is that depression might provide insights into the human condition, and the activation associated with hypomania helps in producing the artistic work. A more profound interpretation suggests that the repeated self-doubt that comes with recurrent depression might be an important ingredient of creativity because original artistic or scientific expression is often initially rejected and the self-confidence that accompanies repeated bouts of hypomania can help in rehearsing such ideas or expressions until they are perfected. Finally, the tempestuous object relations associated with bipolarity in the parent’s or the patient’s life often create the unique biographical landmarks that might be immortalized in an artistic medium.

**Ultrarapid Cycling.** In these patients, hypomanic or manic and depressive episodes alternate rapidly over a few days. In many, the alternation occurs in a regular fashion. The episodes in such cycling patients have greater amplitudes than in cyclothymia, leading to marked impairment. They can be considered as intermediary between cyclothymia and full-blown rapid cycling. Of considerable theoretical and methodological interest, they are difficult to manage clinically. Some individuals with this condition learn to change their work days such that they coincide with the hypomanic periods.

**Recurrent Brief Hypomania.** This hypomanic counterpart of recurrent brief depressive disorder is best conceptualized as a variant of soft bipolarity described previously. It tends to coincide with cyclothymic depression, in which hypomanias are short (less than 4 days).

**Hysteroid Dysphoria.** Hysteroid dysphoria combines reverse vegetative signs with the following characteristics: (1) giddy responses to romantic opportunities and an avalanche of dysphoria (angry-depressive, even suicidal, responses) to romantic disappointment; (2) impaired anticipatory pleasure, yet the capability to respond with pleasure when such is provided by others (i.e., preservation of consummatory reward); and (3) craving for chocolate and sweets, which contain phenylethylamine compounds and sugars believed to facilitate cellular and neuronal intake of the amino acid L-tryptophan, hypothetically leading to synthesis of endogenous antidepressants in the brain. The use of the epithet *hysteroid* was used to convey that the apparent character pathology was secondary to a biological
disturbance in the substrates governing affect, drives, and reward. The intense, unstable life of the patient with hysteroid dysphoria suggests links to cyclothymic disorder or bipolar II disorder. This suggestion is further supported by the Columbia group’s tendency to subsume those patients under atypical depressions (some of which, as indicated, have bipolar affinities). Like patients with bipolar depression, they respond preferentially to monoamine oxidase inhibitors (MAOIs). In brief, hysteroid dysphoria appears to be a variant of bipolar II disorder with cyclothymic-irritable traits. Such patients are often relegated to the realm of borderline personality. Recent formulations deriving from the Pisa–San Diego Collaboration suggest that cyclothymic traits represent the underlying diathesis of atypical depression, borderline personality, and bipolar II.

**UNSPECIFIED MOOD DISORDERS**

After all diagnostic information has been obtained, some patients with affective symptoms do not meet the specific criteria for the mood conditions described thus far, nor do they fit the examples listed in the not otherwise specified categories for depressive and bipolar disorders. One example is that of individuals with acute suicidal ideation of an ego-dystonic nature, not accompanied by other affective symptoms. Family or close follow-up, or both, often suggests a more discrete mental condition. In general, such cases should be considered as undiagnosed mood disorders. However, two hybrid conditions that have not been specifically addressed elsewhere in this chapter can be conveniently discussed here.

**Mixed Anxiety–Depressive Disorder**

Both anxiety and depression can occur together when confronted with a major aversive life situation. The admixture implies that the psychopathology progresses from anxiety to depression, that the patient’s mental state is still in flux, and that the ongoing dynamics partly explains the subacute or chronic nature of the disorder. Anxious depression serves to point to the common presence of anxiety in depressive states, especially its greater visibility when the depression is less prominent. Patients with the latter presentation are reportedly most prevalent in general medical settings. This should not come as a surprise, because depressive symptoms that motivate medical consultation commonly complicate generalized anxiety states with a subthreshold level of symptomatology. Some authorities argue that neurotic depressions arise as maladaptive responses to anxiety and, on that basis, suggest retaining the neurotic depression rubric. Recent preliminary genetic data indirectly support the contention that certain (unipolar) depressive and (generalized) anxiety states are related. As currently defined, anxious depressions are heterogeneous. In patients refractory to anxiolytic or antidepressant treatment, practitioners must entertain the diagnosis of a complex bipolar II disorder with mixed features. Indeed, recent familial-genetic investigations suggest that bipolar II disorder with panic attacks might represent a special form of bipolar disorder.

**Atypical Depression**

Originally developed in England and under investigation at Columbia University in New York City, *atypical depression* refers to fatigue superimposed on a history of somatic anxiety and phobias, together with reverse vegetative signs (mood worse in the evening, insomnia, tendency to oversleep and to overeat). Experience suggests that another reverse vegetative sign is increased sexual interest and/or desire, although it remains undescribed in this literature. Sleep is disturbed in the first half of the night in many persons with atypical depressive disorder, and so irritability, hypersomnolence, and daytime fatigue would be
expected. The temperaments of these patients are characterized by sensitive traits. The MAOIs and serotonergic antidepressants seem to show some specificity for such patients, which is the main reason that atypical depression is taken seriously.

Other research suggests that reverse vegetative signs can be classified as (1) the anxious type just described or (2) a subtle bipolar subtype with protracted hyperphagic–hypersomnic–retarded dysthymic disorder with occasional brief, extroverted, hypomanic-type behavior, often elicited by antidepressants. Increasing evidence indicates considerable affinity between atypical depression and bipolar II and III disorders. Furthermore, many patients with dysthymic disorder exhibit atypical features at various times. Recent Italian research suggests that many patients with atypical depression meet criteria for brief hypomania or cyclothymic disorder. Such patients also resemble those with hysteroid dysphoria, the precursor of the construct of atypical depression.

**DIFFERENTIAL DIAGNOSIS**

A missed mood disorder diagnosis means that the disorder does not receive specific treatment, which has serious consequences. Many such persons drop out of school or college, lose their jobs, get divorced, or may commit suicide. Those with unexplained somatic symptoms are frequent users of the general health system. Others are unwell, despite interminable psychotherapy. Some, treated with conventional neuroleptics, develop tardive dyskinesia unnecessarily. As with other medical disorders for which specific treatments are available, accurate diagnosis and early treatment are within the purview of all physicians and mental health professionals. Psychiatrists, in particular, should develop the competence to detect the entire spectrum of mood disorders. Despite massive educational efforts, underdiagnosis and undertreatment of mood disorders remain serious problems worldwide. The most pernicious of these is downplaying the mood component because a personality disorder is given undue prominence.

Although much enthusiasm was generated three decades ago about the potential use of certain biological markers (e.g., REM latency, DST, and thyrotropin-releasing hormone [TRH] test) to corroborate the differentiation of mood disorder from adjacent disorders, no definitive progress justifies their routine use in clinical practice. The same is true, at least for now, for brain imaging, neuropsychological testing, and genetic screening. Faced with unusual or confusing presentations, a systematic clinical approach is still the best method in differential diagnosis (1) to detail all clinical features of the current episode, (2) to elicit a history of more typical major mood episodes in the past, (3) to assess whether the presenting complaints recur periodically or cyclically, (4) to substantiate adequate social functioning between periods of illness, (5) to obtain a positive family history for classic mood disorder and to construct a family pedigree, and (6) to document a history of unequivocal therapeutic response to thymoleptic medication or ECT in the patient or the family.

**Normal Bereavement**

Bereaved persons exhibit many depressive symptoms during the first 1 to 2 years after their loss, so how can the 5 percent of bereaved persons who have progressed to a depressive disorder be identified?
Grieving persons and their relatives perceive bereavement as a normal reaction, whereas those with depressive disorder often view themselves as sick and may actually believe they are losing their minds. Unlike the melancholic person, the grieving person reacts to the environment and tends to show a range of positive effects. Marked psychomotor retardation is not observed in normal grief. Although bereaved persons often feel guilty about not having done certain things that they believe might have saved the life of the deceased loved one (guilt of omission), they typically do not experience guilt of commission. Delusions of worthlessness or sin and psychotic experiences in general point toward mood disorder. Active suicidal ideation is rare in grief but common in major depressive disorder. “Mummification” (i.e., keeping the belongings of the deceased person exactly as they were before his or her death) indicates serious psychopathology. Severe anniversary reactions should alert the clinician to the possibility of psychopathology.

In another form of bereavement depression, the patient simply pines away, unable to live without the departed person, usually a spouse. Although not necessarily pathological by the foregoing criteria, such persons do have a serious medical condition. Their immune function is often depressed, and their cardiovascular status is precarious. Death can ensue within a few months of that of a spouse, especially among elderly men. Such considerations (highlighted in the work of Sidney Zisook and his colleagues at the University of California at San Diego) suggest that it would be clinically unwise to withhold antidepressants from many persons experiencing an intensely mournful form of grief. A case vignette illustrates this point:

A 75-year-old widow was brought to the treatment by her daughter because of severe insomnia and total loss of interest in daily routines after her husband’s death 1 year before. She had been agitated for the first 2 to 3 months and thereafter “sank into total inactivity—not wanting to get out of bed, not wanting to do anything, not wanting to go out.” According to her daughter, she was married at 21 years of age, had four children, and had been a housewife until her husband’s death from a heart attack. Past psychiatric history was negative; premorbid adjustment had been characterized by compulsive traits. During the interview, she was dressed in black, appeared moderately slowed, and sobbed intermittently, saying “I search everywhere for him … I don’t find him.” When asked about life, she said “Everything I see is black.” Although she expressed no interest in food, she did not seem to have lost an appreciable amount of weight. Her DST result was 18 mg/dL. The patient declined psychiatric care, stating that she “preferred to join her husband rather than get well.” She was too religious to commit suicide, but, by refusing treatment, she felt that she would “pine away … find relief in death and reunion.”

Anxiety Disorders

Anxiety symptoms, including panic attacks, morbid fears, and obsessions, are common during depressive disorders, and depression is a common complication of anxiety states. Systematic British studies have shown that early-morning awakening, psychomotor retardation, self-reproach, hopelessness, and suicidal ideation are the strongest clinical markers of depression in that differential diagnosis. On follow-up of depressed patients, the manifestations tend to remit, whereas those with anxiety states continue to exhibit marked tension, phobias, panic attacks, vasomotor instability, feelings of unreality, and perceptual distortions, as well as hypochondriacal ideas. A predominance of such anxiety features antedating the present illness suggests the diagnosis of an anxiety disorder. Because anxiety
disorders rarely first appear after 40 years of age, a late appearance of marked anxiety features strongly favors the diagnosis of melancholia. The clinical picture is often one of morbid groundless anxiety with somatization, hypochondriasis, and agitation. The depressive nature of the illness is further supported by a superior response to ECT. Periodic monosymptomatic phobic and obsessional states exist that can be regarded as affective equivalents on the basis of a family history of mood disorders and their response to thymoleptic agents. Recent data from a large clinical series suggest that 15 percent of cases have hypomanic symptoms; these patients are best considered to have bipolar II disorder and are treated with lithium salts. Social phobias often usher in adolescent depression, even a bipolar II disorder; the latter is particularly likely when the phobia is paired with alcohol abuse.

The psychopathological differentiation of anxiety and depressive states has not been entirely resolved. Cognitive factors may differentiate them best (Table 13.4–7). Although recurrent (especially retarded) major depressive disorder is a distinct disorder from anxiety states, at least some forms of depression may share a common diathesis with anxiety disorders, particularly generalized anxiety disorders. Before assigning patients to such a putative mixed anxiety–depressive group (not yet an official nosological entity), the clinician must note that anxiety that arises primarily during depressive episodes is best considered as epiphenomenal to depressive disorder. The same is generally true for anxiety symptoms that occur in a person with depressive disorder who is using alcohol or sedative–hypnotic or stimulant drugs. Finally, anxiety symptoms could be prominent features of mixed bipolar states, as well as complex partial seizures.

Table 13.4–7. Unique Cross-Sectional Profiles of Clinical Anxiety and Depression

<table>
<thead>
<tr>
<th>Anxiety</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypervigilance</td>
<td>Psychomotor retardation</td>
</tr>
<tr>
<td>Severe tension and panic</td>
<td>Severe sadness</td>
</tr>
<tr>
<td>Perceived danger</td>
<td>Perceived loss</td>
</tr>
<tr>
<td>Phobic avoidance</td>
<td>Loss of interest—anhedonia</td>
</tr>
<tr>
<td>Doubt and uncertainty</td>
<td>Hopelessness—suicidal</td>
</tr>
<tr>
<td>Insecurity</td>
<td>Self-deprecation</td>
</tr>
<tr>
<td>Performance anxiety</td>
<td>Loss of libido</td>
</tr>
<tr>
<td></td>
<td>Early-morning awakening</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
</tr>
</tbody>
</table>

**Major Depressive Disorder versus Bipolar Disorder**

This “internal” boundary question of whether a patient has major depressive disorder versus bipolar disorder has been discussed extensively throughout this work. With the increasing availability of mood-stabilizing agents, it has emerged as a major challenge in clinical practice. Numerous studies have shown that bipolar disorder is confused not only with personality, substance use, and schizophrenic disorders but also with depressive and anxiety disorders. Prospective and other systematic studies have shown that each of the following features—especially in combination—is predictive of bipolar disorder:
► Early age at onset
► Psychotic depression before 25 years of age
► Postpartum depression, especially one with psychotic features
► Rapid onset and offset of depressive episodes of short duration (less than 3 months)
► Recurrent depression (more than five episodes)
► Depression with marked psychomotor retardation
► Atypical features (reverse vegetative signs)
► Seasonality
► Bipolar family history
► High-density three-generation pedigrees
► Trait mood lability (cyclothymia)
► Hyperthymic temperament
► Hypomania associated with antidepressants
► Repeated (at least three times) loss of efficacy of antidepressants after initial response
► Depressive mixed state (with psychomotor excitement, irritable hostility, racing thoughts, and sexual arousal during major depression)

More broad indicators of bipolarity include the following conditions, none of which, by itself, clinches a bipolar diagnosis but should raise clinical suspicion in that direction: Agitated depression, cyclical depression, episodic sleep dysregulation, or a combination of these; refractory depression (failed antidepressants from three different classes); depression in someone with an extroverted profession; periodic impulsivity, such as gambling, sexual misconduct, and wanderlust, or periodic irritability, suicidal crises, or both; and depression with erratic personality disorders.

**Personality Disorders**

The state dependency of most personality measures is well documented. In general, clinicians should refrain from using personality disorder labels in describing patients with active affective illness and should focus instead on competent treatment of the mood disorder. Unfortunately, such advice is not always heeded. Even in patients with chronic or subthreshold mood disorders, personality maladjustment is best considered postaffective, arising from the distortions and conflicts that affective disturbances produce in the life of the patient. The most problematic of the personality labels used in patients with mood disorders is borderline personality disorder, usually applied to teenage and young adult women. Table 13.4–8 shows that the overlap between borderline personality and mood disorders is extensive, so that giving a *borderline* diagnosis to a person with mood disorder is redundant. Use of personality disorder diagnoses may lead to a neglect of the mood disorder or, perhaps, half-hearted treatment of the mood disorder; failure to respond would then be blamed on the patient’s “self-defeating character” or “resistance to getting well,” thus exculpating the clinician.

Although more systematic research is needed on the complex interface of personality and mood disorders, clinically, they are often inseparable. As with alcohol and substance use disorders, it is generally preferable to diagnose mood disorders at the expense of personality disorders, which should not be difficult to justify in most cases that satisfy the validating strategies outlined previously. When features of personality and mood disorders coexist, it is good practice to defer personality disorder diagnoses and to embark on competent treatment of the concurrent mood disorder. Although not all personality disturbances recede with the competent treatment of mood disorders, so many experienced clinicians have seen such
disturbances melt away with the successful resolution of the mood disorder that erring in favor of mood disorders is justified.

A 19-year-old single woman presented with the chief complaint that “all men are bastards.” Since her early teens, with the onset of her menses, she had complained of extreme variability in her moods on a nearly daily basis; irritability with hostile outbursts was her main affect, although more-protracted hypersomnic depressions with multiple overdoses and wrist slashings had led to at least three hospitalizations. She also had migrainous headaches that, according to her mother, had motivated at least one of those overdoses. Despite her tempestuous and suicidal moods that led to these hospitalizations, she complained of “inner emptiness and a bottomless void.” She had used heroin, alcohol, and stimulants to overcome this troubling symptom. She also gave history of ice cream craving and frequent purging. She was talented in English and wrote much-acclaimed papers on the American confessional poet Anne Sexton. She said that she was mentally disturbed because of a series of stepfathers who had all forced “oral rape” on her when she was between 11 and 15 years of age. She subsequently gave herself sexually to any man that she met in bars, no longer knowing whether she was a “prostitute” or a “nice little girl.” On two occasions, she had inflicted cigarette burns inside her vagina “to feel something.” She had also engaged in a “brief lesbian relationship” that ultimately left her “emptier” and guilt ridden; nonetheless, she now believed that she should burn in hell because she could not get rid of “obsessing” about the excitement of mutual cunnilingus with her much older female partner. The patient’s mother, who owned an art gallery, had been married five times and gave a history of unmistakable hypomanic episodes; a maternal uncle had died from alcohol-induced cirrhosis. The patient’s father, a prominent lawyer known for his “temper and wit,” had committed suicide. The patient was given phenelzine (Nardil), eventually raised to 75 mg per day, at which point the mother described her as “the sweet daughter she was before age 13.” At her next premenstrual phase, the patient developed insomnia, ran away from home at night, started “dancing like a go-go girl, met an incredibly handsome man” of 45 years of age (a pornography shop owner), and had a clandestine marriage to him. After many dose adjustments, she is now maintained on a combination of lithium (900 mg per day) and divalproex (Depakote; 750 mg per day). The patient now attends college and has completed four semesters in art history. In addition to control of her irritable and suicidal moods, bulimic and migraine attacks have abated considerably. Her marriage has been annulled on the basis that she was not mentally competent at the time of the wedding. She is no longer promiscuous and now expresses fear of intimacy with men that she is attracted to. She is receiving individual psychotherapy for this problem.

Table 13.4–8. Overlap of Borderline Personality Disorder and Mood Disorders

<table>
<thead>
<tr>
<th>Familial</th>
<th>High rates of mood disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenomenology</td>
<td>Dysthymic disorder</td>
</tr>
<tr>
<td></td>
<td>Cyclothymic disorder</td>
</tr>
<tr>
<td></td>
<td>Bipolar II disorder</td>
</tr>
<tr>
<td></td>
<td>Mixed state</td>
</tr>
<tr>
<td>Pharmacological response</td>
<td>Worsening on most antidepressants</td>
</tr>
<tr>
<td></td>
<td>Stabilization on anticonvulsants</td>
</tr>
<tr>
<td>Prospective course</td>
<td>Major mood episodes</td>
</tr>
<tr>
<td></td>
<td>Suicide</td>
</tr>
</tbody>
</table>
This case illustrates the intimate relationship among atypical depression, borderline personality, and bipolar II disorder. These three conditions may share an underlying psychobiological or genetic diathesis. The complaint is often heard that, even when a mood disorder is diagnosed in a “borderline” patient, response to antidepressants is disappointing. The problem is that affective disorders in these patients usually conform to bipolar II disorder—often complicated by ultrarapid cycling—and many clinicians trained in an earlier era, including some with biological orientation, may lack sufficient experience in the art of pharmacologically managing patients who markedly deviate from classic bipolar I disorder. Recently, lamotrigine has shown promise for such patients.

**Alcohol and Substance Use Disorders**

The high comorbidity of alcohol and substance use disorders with mood disorders cannot be explained as merely the chance occurrence of two prevalent disorders. Self-medication for mood disorders is insufficiently appreciated by psychiatrists and other professionals who deal with addiction. Given the clinical dangers of missing an otherwise treatable disorder, mood disorder should be seriously considered as the primary diagnosis if marked affective manifestations persist or escalate after detoxification (e.g., 1 month). This consideration also pertains to cyclothymic disorder and dysthymic disorder, which appear particularly likely to invite self-medication. The clinical validating strategies listed previously can further buttress a mood disorder diagnosis.

The DSM category of substance-induced mood disorder is difficult to validate clinically because, in the absence of an affective diathesis, detoxification should, in principle, rapidly clear affective disturbances in persons whose primary problem is that of substance abuse. A dual diagnosis of a mood disorder and a substance use disorder is a more realistic clinical approach to this group of patients. Bipolarity, particularly bipolar II disorder, should be sought in the interface of mood and substance use disorders.

A 27-year-old married businessman employed in an international family venture owned by his father presented with a court-ordered request for psychiatric treatment. He had been found “bringing” cocaine across the United States–Mexican border and was briefly jailed. He had used stimulants since his late teens to enhance his already high level of energy. His family was rich, and he had no difficulty affording cocaine. During the previous year, he had needed more cocaine because of greater moodiness and fleeting suicidal ideation, which he linked to increasing tensions between him and his father: “My father was never satisfied with me and demanded greater and greater performance from me.” His arrest by police was a major embarrassment for him and his family and motivated his compliance with psychiatric hospitalization to detoxify him. He had not had cocaine for 10 days, exhibited marked lability of mood, and gradually sank into a severe hypersomnic-retarded depression of stuporous proportions. He was treated in an inpatient unit with tranylcypromine (Parnate) 20 mg twice a day, and, within 10 days, he switched into hypomania, his mind “exploding with creativity and confidence,” marked jocularity and witticisms that entertained other patients, and marked seductiveness toward the nurses. His wife recalled that the patient previously had several such periods naturally (i.e., “off cocaine”), which had strained their marriage due to “brief sexual liaisons.” Reducing the tranylcypromine dose by 50 percent did not eliminate the hypomanic behavior, and lithium, 900 mg per day, was added. He has since been maintained on a combination of tranylcypromine and lithium for 4 years; he has not relapsed into cocaine use, and, following a few psychoeducational sessions involving father and spouse, relationships with family and spouse have been less tempestuous. (Since then, consultation was sought by the patient’s 60-year-old mother, an attractive, sophisticated woman who confessed that for years she had been engaged in “love relationships” with young artists, with, apparently, her husband’s “tacit consent”; since at least her mid-20s, she, by history, would meet the criteria for bipolar II disorder, only treated “on the couch,”
and her sister and brother had received treatment of “alcohol excesses.”) The patient stated that pharmacotherapy, which did require adjustment now and then, helped in balancing the “rough edges” of his “high-nervous temperament” and his “periodic lapse into paralyzing fatigue states that occurred at stressful times.” If it had been assumed that these mood states were merely due to cocaine withdrawal, the patient’s bipolar II disorder would never have been treated. There is emerging interest in treating dually diagnosed patients with anticonvulsant mood stabilizers and their judicious combination. Among the antidepressants, bupropion (Wellbutrin) is a suitable agent to “replace” stimulant craving; serotonin reuptake inhibitors can be useful for concurrent social phobia and anxious components. The intention is to attenuate any withdrawal phenomena from substances of abuse and to reduce craving while treating any underlying or emerging bipolar diathesis.

Physical Disease

Somatic complaints are common in depressive disorders. Some, such as vegetative disturbances, represent the hypothalamic pathology that is believed to underlie a depressive disorder. Autonomic arousal, commonly associated with depression, could explain such symptoms as palpitations, sweating, and headache. In some instances, the physical symptoms might reflect delusional experiences. The clinician must be vigilant about the likelihood that somatic complaints in depression can also reflect an underlying physical illness. Table 13.4–9 lists the most common medical conditions that have been associated with depression. When depressive symptoms occur in the setting of physical illness, it is not always easy to determine whether they constitute a genuine depressive disorder. Before diagnosing depression, psychiatrists must ensure that they are not dealing with pseudodepression: (1) functional loss due to physical illness; (2) vegetative signs, such as anorexia and weight loss, as manifestations of such an illness; (3) stress and demoralization secondary to the hospitalization; (4) pain and discomfort associated with the physical illness; and (5) medication adverse effects. However, nonpsychiatric physicians who manage such patients must consider the diagnosis of depression in the presence of persistent anhedonia; observed depressed mood with frequent crying; observed psychomotor retardation or agitation; indecisiveness; convictions of failure, worthlessness, or guilt; and suicidal ideation. The physician should also suspect clinical depression in all patients who refuse to participate in medical care.

Diagnosing depression in medically ill elderly patients can be particularly difficult. This task should be undertaken diligently because it was recently reported that (especially in those with cardiovascular disease) mortality is accelerated by depression. Depressed elderly adults often deny being depressed but complain of anxiety, fatigue, and worsening memory. Hypochondriacal symptoms and pain are common. Patients may exhibit extreme negativism and querulousness when invited to participate in medical procedures; others develop poor fluid and food intake out of proportion to their physical conditions.

Another important diagnostic problem at the interface of mood disorder and physical disease is the rare development of malignancy in patients with an established mood disorder. Patients who had responded well to a given antidepressant during previous episodes now have an unsatisfactory response to the same medication. Even a small dose may cause such alarming symptoms as agitation, dizziness, depersonalization, and illusions, which might indicate an occult malignancy, perhaps in the abdomen or the brain. The psychiatrist should always be vigilant about the development of life-threatening physical diseases in patients with pre-established depressive disorder.
A 55-year-old woman had four previous episodes of severe depression that had responded to ECT, amitriptyline (Elavil), or a combination in her native city in the Middle East. She immigrated to the United States at 43 years of age and encountered several major stresses, including an unfamiliarity with English, her daughter dating a man of Chinese extraction, and a complicated series of operations for uterine prolapse. Then, her husband confessed that he had had an affair with a much younger woman. For months, the patient had complained of intermittent fatigue and expressed hostility toward her husband. He had slapped her on her face on two occasions. Her ensuing fifth depressive episode (with pain localized to her face) appeared fully “understandable,” but her physician’s prescription of 25 mg of amitriptyline resulted in dizzy spells that culminated in syncope. Citalopram (Celexa), 10 mg, did not fare any better. An extensive medical workup revealed a retroperitoneal lymphoma. She died 6 months later.

**Stupor.** Although less common today, stupor still raises a diagnostic problem in differentiating between a mood disorder and somatic disease, as well as other psychiatric disorders. Depressive stupor is relatively easy to distinguish from so-called hysterical mutism; in the latter, behavior is meaningfully directed to significant others in the patient’s environment. The rubric of catatonic stupor is best reserved for a phase of schizophrenia; in such patients, the schizophrenic origin of the catatonia might be apparent from the patient’s history. Otherwise, most acute-onset stupors are probably of affective origin. The main differential diagnosis here is from organic stupor (due to drugs or acute intracranial events); the physical and neurological examination is not always decisive in such cases, and diagnosis depends on a high index of suspicion of possible somatic factors.
Table 13.4–9. Pharmacological Factors and Physical Diseases Associated with Onset of Depression

<table>
<thead>
<tr>
<th>Pharmacological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroidal contraceptives</td>
</tr>
<tr>
<td>Reserpine (Serpalan), α-methyldopa</td>
</tr>
<tr>
<td>Anticholinesterase insecticides</td>
</tr>
<tr>
<td>Amphetamine or cocaine withdrawal</td>
</tr>
<tr>
<td>Alcohol or sedative–hypnotic withdrawal</td>
</tr>
<tr>
<td>Cimetidine (Tagamet), indomethacin (Indocin)</td>
</tr>
<tr>
<td>Phenothiazine antipsychotic drugs</td>
</tr>
<tr>
<td>Thallium, mercury</td>
</tr>
<tr>
<td>Cycloserine (Seromycin)</td>
</tr>
<tr>
<td>Vincristine (Oncovin), vinblastine (Veiban)</td>
</tr>
<tr>
<td>Interferon</td>
</tr>
<tr>
<td>Endocrine-metabolic</td>
</tr>
<tr>
<td>Hypothyroidism and hyperthyroidism</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Hypopituitarism</td>
</tr>
<tr>
<td>Addison disease</td>
</tr>
<tr>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Infectious</td>
</tr>
<tr>
<td>General paresis (tertiary syphilis)</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Influenza, viral pneumonia</td>
</tr>
<tr>
<td>Viral hepatitis</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
</tr>
<tr>
<td>Acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>Collagen</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
</tr>
<tr>
<td>Nutritional</td>
</tr>
<tr>
<td>Pellagra</td>
</tr>
<tr>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>Neurological</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Parkinson disease</td>
</tr>
<tr>
<td>Head trauma</td>
</tr>
<tr>
<td>Complex partial seizures</td>
</tr>
<tr>
<td>Sleep apnea</td>
</tr>
<tr>
<td>Cerebral tumors</td>
</tr>
<tr>
<td>Cerebrovascular infarction (and disease)</td>
</tr>
<tr>
<td>Neoplastic</td>
</tr>
<tr>
<td>Abdominal malignancies</td>
</tr>
<tr>
<td>Disseminated carcinomatosis</td>
</tr>
</tbody>
</table>

*Cholesterol is not mentioned because low levels as a factor in depression have been inconsistently reported.*
**Depressive Pseudodementia.** The geriatric equivalent of semistupor in younger persons with depressive disorder, depressive pseudodementia, is distinguished from primary degenerative dementia by its acute onset without prior cognitive disturbance, a personal or family history of past affective episodes, marked psychomotor retardation with reduced social interaction, self-reproach, diurnal cognitive dysfunction (worse in the morning), subjective memory dysfunction in excess of objective findings, circumscribed memory deficits that can be reversed with proper coaching, and a tendency to improve with sleep deprivation. Current clinical considerations have revealed “maniform” pseudodementia as well, some of which might be in the early stages of a dementing disease and manifesting with such manifestations as mood lability, aggressivity, and sexual disinhibition in the setting of memory decline and confusion. Family history of bipolar disorder or past history of mild manic-like expressions helps in distinguishing these patients from those with depressive pseudodementia. The distinction is important because antidepressants and anti-Alzheimer agents often worsen the maniform conditions, which instead often respond favorably to anticonvulsant mood stabilizers. The definitive diagnosis in all such cases will be revealed during prospective follow-up. The main clinical message here is not to miss treatable and/or potentially reversible depressive and bipolar states in elderly patients with dementiform manifestations or early and even mid-stage dementia.

**Chronic Fatigue Syndrome.** Chronic fatigue syndrome is a complex differential diagnostic problem in view of the subtle immunological disturbances presumably associated with it. The following self-report by such a patient illustrates many of the uncertainties marking the present knowledge of the interface between the syndrome and mood disorders.

I am a 39-year-old, never-married woman, trained as a social worker but currently on disability. I have experienced extreme lethargy and fatigue for many years. I have always felt foggy-headed and had trouble thinking and concentrating. My complaint is of fatigue not of depression. My body feels like lead and aches all over. My brain feels achy and sore. I feel much worse in the morning, and I cannot get out of bed; I feel better at night. I feel bad every day. I ache all over, as though someone had beaten me up. Exercise has been prescribed to me, but it makes me worse. Also, I am very sensitive to hot and cold. My sexual drive is low. I have a general feeling of anhedonia. As far back as I remember—in junior high school—I was always exhausted. I always complained about fatigue, not depression, because that has been the overwhelming problem. I feel the depression is secondary to the fatigue. In high school, I was a compulsive overeater, and I was bulimic for a few years, but it was never severe, and I was only about 10 pounds overweight. In those days, I would sleep 10 or 12 hours a night on the weekend and still feel exhausted; I could not get up for school on Monday. As an adolescent, I felt inferior. I could not make decisions, I did not want to go to camp or leave home for long periods of time—I felt so insecure. Recently, I had a sleep study done, which showed a short latency to stage REM sleep (49 minutes). I was diagnosed as having dysthymic disorder and began taking antidepressants. When I took tranylcypromine, it was the first time in my life that I felt like a normal person. I could play sports, I had a sex drive, I had energy, and I was able to think clearly, but the benefits lasted for barely 2 months. My response was equally short-lived to phenelzine, imipramine (Tofranil), selegiline (Eldepryl), and bupropion. I have not responded to SSRIs at all. I also wish to point out that I had never experienced high periods before I took antidepressants. My main problem has always been one of exhaustion. When I responded to medications, they worked very quickly (within a few days), and I felt great, but they all stopped working after a short time. The dose would be raised, and, again, I would feel better. Eventually, when I got to high doses, I either could not tolerate the high dose or the drug would no longer help. I have taken different combinations of drugs for 10 years, and I have not been able to feel well for more than 6 weeks at a time. Recently, I went to an immunologist. He said I have an abnormality in regulating antibody production and recommended γ-globulin shots. They did not help. When I first started working, I always felt tired and foggy headed, so it was difficult to be sharp while at work. At
times, I would close the door to my office and put my head down. Working has become increasingly
difficult for me. I had two great jobs, which I blew. As of last year, I had to go on disability. I am
desperate for relief, as my condition has drastically affected my life. Disability has been hard for me. I
am single and have no other financial resources. I am very despondent, as I feel that my life is passing
by without the hope of my ever really improving.

The foregoing clinical picture is compatible with a pseudounipolar or bipolar III disorder as
described previously. If so, mood stabilizer augmentation of the tranylcypromine would have
been a therapeutic choice to pursue. Some biologists and immunologists, as well as some
psychiatrists, believe that abnormal substances circulate in the bloodstream, supplying the
brains of such patients. Industrial toxins have also been suggested. Although awaiting more
definitive research on the etiology of chronic fatigue syndrome, the psychiatrist can
cautiously consider certain patients for thymoleptic trials. That decision can be bolstered by
the following considerations: The patient wakes up with fatigue and dread of facing the day;
fatigue is part of a more generalized psychomotor inertia or lack of initiative; fatigue is
associated with anhedonia, including sexual anhedonia; and fatigue coexists with anxious and
pessimistic ruminations. Although none of the foregoing considerations alone is
pathognomonic for depression, in aggregate, they point in that direction. The occurrence of
hypomaniac-like periods (as in the previous vignette) further supports the link between some
cases of chronic fatigue and mood disorder. Several recent neuroendocrine challenge studies
suggest that some chronic fatigue patients might have a strong anxiety substrate and could be
managed accordingly. This is not to say that chronic fatigue is largely a matter of missed
affective diagnoses with bipolar II and panic disorder features; yet, it would be a pity to miss
potentially treatable diagnoses. A family or past personal history of classic affective illness or
episodes should strongly weigh in this direction. Obviously definitive data are lacking on the
essential nature of chronic fatigue, and practitioners should be guided by their clinical
experience with therapeutic trials of nonsedating thymoleptic agents while they await new
research developments.

**Schizophrenia**

Despite some genetic overlap between schizophrenic and bipolar disorders, clinically, the two
groups of disorders are in the main separate. Young patients with bipolar disorder might seem
psychotic and disorganized and, thus, schizophrenic. Their thought processes are so rapid that
they may seem loose, but, unlike patients with schizophrenia, they display an expansive and
elated affect, which is often contagious. By contrast, the severely retarded bipolar depressive
person, whose affect may superficially seem flat, almost never exhibits major fragmentation
of thought. The clinician, therefore, should place greater emphasis on the pattern of
symptoms than on individual symptoms in the differential diagnosis of mood and
schizophrenic psychoses. No pathognomonic differentiating signs and symptoms exist.
Differential diagnosis should be based on the overall clinical picture, phenomenology, family
history, course, and associated features. Because the two groups of disorders entail different
combinations of pharmacological treatments on a long-term basis (mood stabilizers are
usually needed as the mainstay in bipolar disorder), the differential diagnosis is of major
clinical importance. Table 13.4–10 summarizes clinical experience in the area and lists the
most common pitfalls in diagnosis. In the past, many bipolar patients, especially those with
prominent manic features at onset, were labeled as having acute schizophrenia or
schizoaffective schizophrenia. In the past, such misdiagnoses (which typically led to long-
term treatment with conventional neuroleptic agents) were costly in terms of tardive
dyskinesia, vocational and social decline, and even suicide. For instance, some patients with
postspsychotic depressive disorder of schizophrenia have postmanic depressions that were
treated with classic neuroleptic monotherapy without the benefit of more definitive thymoleptic agents.

Table 13.4–10. Common Causes of Misdiagnosis of Mood Disorder as Schizophrenia

<table>
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<tr>
<th>Cause</th>
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<tr>
<td>Reliance on cross-sectional rather than longitudinal picture</td>
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<tr>
<td>Incomplete interepisodic recovery equated with schizophrenic defect</td>
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<tr>
<td>Equation of bizarreness with schizophrenic thought disorder</td>
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<tr>
<td>Ascribing irritable and cantankerous mood to paranoid delusions</td>
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<tr>
<td>Mistaking depressive anhedonia and depersonalization for schizophrenic emotional blunting</td>
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<tr>
<td>Flight of ideas perceived as loose associations</td>
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<tr>
<td>Lack of familiarity with the phenomenological approach in assessing affective delusions and hallucinations</td>
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<tr>
<td>Heavy weight given to incidental schneiderian symptoms</td>
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Modern treatments—even with atypical antipsychotics—that tend to keep many persons with schizophrenia out of the hospital do not always seem to prevent an overall downhill course in many cases. By contrast, the intermorbid periods in bipolar illness are relatively normal or even supernormal, and yet, over time, some social impairment may result from the accumulation of divorces, financial catastrophes, and ruined careers. (Although rapid-cycling disorders, which have sharply risen during the past two decades, cause considerable social impairment, mood symptoms are so prominent that differentiation from schizophrenia is generally not difficult; in addition, such patients usually display more classic bipolar phases before the rapid cycling.)

Postpsychotic depressions in persons with established schizophrenia are sometimes due to inadequate control of schizophrenic symptomology. In other patients, especially more intelligent young patients with schizophrenia, they reflect the experience of losing one’s ego and sanity. It would be more meaningful to give such patients a diagnosis of schizophrenia and a superimposed major depressive diagnosis and to treat the patient accordingly.

**Schizoaffective Disorder**

As the previously mentioned considerations suggest, depression in the setting of a schizophrenic disorder does not necessarily constitute a distinct nosological entity. The concept of schizoaffective (or cycloid) psychosis should be restricted to recurrent psychoses, with full affective and schizophrenic symptoms occurring nearly simultaneously during each episode. This diagnosis should not be considered for a mood psychosis in which mood-incongruent psychotic features (e.g., Schneiderian and Bleulerian symptoms) can be explained on the basis of one of the following: (1) affective psychosis superimposed on mental retardation, giving rise to extremely hyperactive and bizarre manic behavior; (2) affective psychosis complicated by concurrent brain disease, substance abuse, or substance withdrawal, known to give rise to numerous Schneiderian symptoms; or (3) mixed episodes of bipolar disorder (which are notorious for signs and symptoms of psychotic disorganization). Official diagnostic systems, such as DSM-5, use the category of schizoaffective disorder broadly. Thus, patients with clear-cut manic episodes receive a schizoaffective diagnosis if delusions or hallucinations occur in the interepisodic period in the absence of prominent affective symptoms. Many psychotic symptoms in mood disorders are often explanatory (albeit delusional), whereby the patient tries to make sense of the core experiences of the affective illness. In patients with recurrent episodes, delusional thinking can be carried over
into the interepisodic period. Such patients are thus delusional in the absence of prominent mood symptoms and technically might be considered schizoaffective.

However, affective illness is typically a lifelong process, and limiting its features to discrete episodes is artificial. In the past, neuroleptic agents were prescribed on an as-needed basis to reduce the strong affective charge of those interepisodic delusions, but they did not effectively eliminate the affect-laden experiences. Atypical antipsychotic agents introduced during the 1990s are more likely to be beneficial in this regard. Augmenting with continued thymoleptic treatment (resorting to ECT, if necessary) and an empathic psychotherapeutic approach may prove more rewarding in the long run.

A 29-year-old female college graduate, mother of two children and wife of a bank president, had experienced several manic and retarded depressive episodes that had responded to lithium carbonate. She was referred to me because she had developed the delusion that she had been involved in an international plot. Careful probing revealed that the delusion represented further elaboration, in a rather fantastic fashion, of a grandiose delusion that she had experienced during her last postpartum manic episode. She believed that she had played an important role in uncovering the plot, thereby becoming a national hero. Nobody knew about it, she contended, as the circumstances of the plot were top secret. She further believed that she had saved her country from the international scheme and suspected that she was singled out for persecution by the perpetrators of the plot. At one point, she had even entertained the idea that the plotters sent special radio communications to intercept and to interrupt her thoughts. As is typical in such cases, she was on a heavy dose of a lithium–antipsychotic combination. The consultation was requested because the primary mood symptoms were under control, and yet she had not given up her grandiose delusion. She flippantly remarked that “I must be crazy to believe in my involvement in an international plot,” but she could not help but believe in it. Over several months, seen typically in 60-minute sessions weekly, the patient had developed sufficient trust that her beliefs could be gently challenged.

She was, in effect, told that her self-professed role in the international scheme was highly implausible and that someone with her superior education and high social standing could not entertain a belief, to use her own words, “as crazy as that.” She eventually broke into tears, saying that everyone in her family was so accomplished and famous that to keep up with them she had to be involved in something grand; in effect, the international scheme, she said, was her only claim to fame: “Nobody ever gives me credit for raising two kids, and throwing parties for my husband’s business colleagues: My mother is a dean, my older brother holds high political office; my sister is a medical researcher with five discoveries to her credit [all true] and who am I? Nothing. Now, do you understand why I need to be a national hero?” As she alternated, over subsequent months, between such momentary flashes of insight and delusional denial, antipsychotic medication was gradually discontinued. Maintained on lithium, she now only makes passing reference to the grand scheme. She was encouraged to pursue her career goal toward a master’s degree in library science.

The vignette illustrates how phenomenological understanding, rational pharmacotherapy, and practical psychotherapeutic or vocational guidance can be fruitfully combined in the approach to patients with psychotic mood disorders. It also indicates that problems with insight are not necessarily state dependent in mood disorders. Cognitive disturbances have recently been described in all mood disorders, even when they are nonpsychotic. At a more fundamental level, the vignette suggests that clinical diagnoses cannot be based entirely on operational criteria; one’s opinion of a patient’s illness is not infrequently changed by its response to treatment.
REFERENCES


13.5 Mood Disorders: Intrapsychic and Interpersonal Aspects

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The symptom criteria listed in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) reliably define mood disorders, but they do not completely describe these syndromes or explain how patients experience them. Depressed patients suffer emotionally, cognitively, and physically. There are three key theoretical approaches that have been applied to mood disorders: psychoanalytic/psychodynamic, cognitive, and interpersonal. They vary in their frequency of use in clinical practice and in the amount of research that they have received.

Theory has uses and limitations. Theory can help to organize clinical and research thinking about depression and can pinpoint aspects of the syndrome. A theory can provide a narrative thread or focus to anchor a clinical formulation and to give coherence to a therapy. Indeed, some theoretical approach is necessary for clinicians to impose order on the overwhelming amount of clinical data with which patients present for the treatment. Theories may also allow predictions to be made about the treatment mechanisms and outcomes. The authors submit that an organizing theoretical framework is as essential to structure psychotherapy as grammar is to speech. Hence, understanding the theoretical backgrounds of psychotherapies is crucial for the psychotherapeutic clinician.

Theories should be considered approximations of the truth, needful of testing and subject to disconfirmation. Thomas Huxley in 1870 famously described “The great tragedy of Science—the slaying of a beautiful hypothesis by an ugly fact.” Dogma and ideology have done psychiatrists and other mental health professionals more harm than good, for example, in separating psychotherapy and pharmacotherapy into opposing camps—a rift from the 1950s that is only now healing. Inasmuch as the etiology of mood disorders is complex and no single theory comprehensively explains it, rigid adherence to any theory is unwarranted and potentially problematic. Clinicians should understand and use multiple theories, flexibly choosing the optimal theoretical perspective to apply to a given patient’s illness and then persevering in using that model for an appropriate course of treatment. They should then proceed following that theoretical approach rather than devolving into eclecticism. (The authors of this chapter recommend formal training in any treatment modality the clinician plans to undertake. Theoretical understanding does not suffice.) However, to develop clinical expertise in any therapy, it is essential to be able to understand patients’ problems through the lens of the theory underlying it.

Psychodynamic theory has the longest historical tradition. Both cognitive theory and psychodynamic theory largely focus on intrapsychic phenomena, whereas interpersonal theory, the newest and least formally developed, focuses more on interpersonal, extrapsychic reality. It is widely accepted that aspects of both cognitive and interpersonal theories derive from psychoanalysis. Each approach provides a potentially useful explanation of the plight of the depressed patient. Although the utility of therapies derived from cognitive theory (cognitive behavioral therapy [CBT]) and interpersonal theory (interpersonal psychotherapy [IPT]) has been better tested for depression than psychodynamic therapy to date, no theories of depression have been formally tested in all of their assumptions. They are best considered working clinical models.
PSYCHODYNAMIC ASPECTS OF MOOD DISORDERS

A contemporary psychoanalytic understanding of mood disorders includes a comprehensive focus on biological underpinnings, cognitive function, and interpersonal situation and style. What is unique to psychoanalysis is its attention to intrapsychic, unconscious pressures in its consideration of psychological symptoms, including mood disorders. In order to describe intrapsychic aspects of mood disorders, several basic psychoanalytic ideas about mental life first must be defined:

1. From a psychodynamic view, mental life exists on two levels: Both within the realm of consciousness and also within a less accessible realm, described as “the unconscious.” Psychic or emotional symptoms arise from aspects of mental life that are at least in part unconscious. This is true of mood disorders.

2. Psychoanalysts have found it useful to conceptualize the mind as comprising three basic theoretical psychic structures, the id, the ego, and the superego. In brief, the id is considered the aspect of the mind that subsumes the drive derivatives and desires. The ego serves as intermediary between the id and the external world. It contains many intrapsychic functions, including motor action, perception, self-esteem, the relationship to reality, and the ability to modulate the drives and to modulate anxiety. Defense mechanisms, which are unconscious intrapsychic mechanisms employed to modulate both the drives and anxiety, are ego functions. The superego is conceptualized to comprise the person’s value system. The superego can both punish and reward the person, depending upon whether or not his or her actions are consonant with his or her moral values.

3. Moods are pervasive ego states that color the entire ego with the same affect state. Unlike simple affective responses to events, they are not focused but general, either because the affect is too strong or because the ego is too weak to contain a focused response. Because moods tend to be generalized states, they typically involve some degree of denial of the opposite feelings. From a psychoanalytic vantage, moods carry an unconscious significance, notwithstanding their presumed biological and neurotransmitter underpinnings.

4. Since Sigmund Freud’s discovery of the importance of the unconscious in everyday mental life and of individuals’ capacity to shut off unwanted, painful, emotionally laden experiences using defense mechanisms, the current understanding of moods and symptoms has been enhanced by the recognition that these psychic phenomena represent a breakthrough of unconscious fantasy into consciousness. Persistent unconscious fantasies often underlie people’s psychological symptoms, dreams, personalities, and important life choices.

5. Freud initially described another central principle in the organization of mental life: That people unconsciously avoid “unpleasure” and that ideas that produce unpleasure are screened from consciousness by “repression,” or processes now called defenses. Clinically, the degree to which unpleasure is avoided varies from person to person, and Freud later modified his original theory about people avoiding unpleasure. In Beyond the Pleasure Principle, he attempted to describe intrapsychic mechanisms that could account for phenomena in which the pursuit of pleasure is given up for the more fundamental need to discharge intense emotional tensions to protect the individual. Thus, major depression is a condition in which the person is living beyond the pleasure principle.
Psychoanalytic descriptions of major depression

Psychoanalytic formulations highlight the phenomenology of aspects of major depression, helping to make the emotional backdrop of the illness more understandable. Although these theories provide a clinically rich set of ideas that can be useful in treating such patients, it should be emphasized that no theoretical positions are supported by systematic research. The field of psychoanalysis has been fairly resistant to research. Nor are these psychoanalytic formulations, despite their differences, mutually exclusive. Some of these formulations shall be outlined, and illustrative clinical examples shall be provided.

Response to Loss/Anger Turned Inward

The classic psychoanalytic understandings of depression were stated by Karl Abraham, Freud, and Sandor Rado and emphasized depressed patients’ reactions to object loss, in reality or in fantasy. In these formulations, the profound response to loss is believed to occur in part because the current loss invokes an earlier, childhood loss, also either of a fantasy or a reality nature. These authors noted depressed patients’ ambivalent or hostile object relations, along with object attachments characterized by excessive dependency, laced with an emphasis on need gratification in emotionally charged relationships. Major depression occurs only after the tie to the object is shattered. In *Mourning and Melancholia*, Freud highlighted the way in which depressed patients irrationally attack themselves. In his formulation, this occurs because aspects of an ambivalent object become internalized, or incorporated, into the patient’s sense of self, and hostility directed toward the object is instead directed at the self. This state of affairs serves to preserve the relationship with the other person (the object) in reality.

Stuart Asch described a variation in these dynamics in which some patients become depressed not because of object loss but due to maintaining a submissive tie to the object. This tie is maintained because the patient perceives separation to be an aggressive act with destructive consequences. Rage at having to play this part is directed toward the self, as the patient feels devalued because of the submission.

Joseph Sandler and Walter Joffe, also focusing on the phenomenon of loss leading to depression, called the Hampstead Index, a comprehensive clinical registry of childhood responses to abandonment and loss, for cases of childhood depression. They inferred that depression is a basic affective response to loss. They emphasized that more than just the other person is lost and that the child feels that he or she has also lost a sense of self in relationship to the lost object, or a previous set of feelings about the self. Thus, as Freud and Abraham also noted, Sandler and Joffe emphasize a symbiotic or narcissistic tie to the object. They saw individuals predisposed to depression as struggling against feelings of helplessness and injured self-esteem in childhood.

Ms. A, a 26-year-old woman, presented with severe major depression in the context of her boyfriend B’s expressing increasing anger at her and his saying that he wanted to move out of their home. An anxious person at baseline, Ms. A took to her bed for several weeks, closing the blinds so that no light could enter her room. She stopped eating, lost weight, and slept most of the time. She dropped out of school and took a leave of absence from work. She thought almost constantly of suicide, although she had not picked a method and her deep religious commitment made this an unacceptable choice. In her first session, she spoke about how worthless she felt and how she blamed herself for her boyfriend wanting to break up with her. She said she thought that she was too “pointless,” “anxious,” and “boring” for him and that her presence stifled him. She expressed no
anger toward B at the time of her presentation, saying that she “understood” why he was being like this. She also said she hoped that this was just a “bad phase” that he would get over, although he told her repeatedly that he was dating another woman. In psychotherapy it gradually emerged, however, that over the past month B had been breaking dishes and furniture in their home. He yelled at Ms. A almost constantly. This patient’s depression remitted with psychodynamic psychotherapy only as she became aware of her own murderous rage toward B, at which time she began to view herself in a less negative and denigrated manner.

**Guilt**

Melanie Klein postulated that depressed patients fear that they cannot protect an idealized, or good, internalized “other” from destructive, rageful impulses. Although emphasizing a different facet of major depression, this view coincides with Freud’s focus on the destruction of the object tie in major depression. As a result, the depressed patient’s characteristic guilt, inhibitions, and punitive superego develop. However, not all depressions are characterized by excessive guilt, and Klein’s description applies only to this subset of patients. Klein also highlighted the danger that depressed patients foresee in “triumphing” over parents or siblings via any life success: Success is experienced as aggressively humiliating to loved ones or as damaging to others. Klein theorized that idealization and devaluation are “manic defenses” against the guilt and sense of loss experienced in the resulting depression.

Ms. C, a 23-year-old woman, became acutely depressed when she was accepted to a prestigious graduate school. Ms. C had been working diligently toward this acceptance for the past 4 years. She reported being “briefly happy, for about 20 minutes” when she learned the good news but rapidly slipped into a hopeless state in which she recurrently pondered the pointlessness of her aspirations, cried constantly, and had to physically stop herself from taking a lethal overdose of her roommate’s insulin. In treatment, she focused on her older brother, who had regularly insulted her throughout the course of her life, and how “he’s not doing well.” She found herself very worried about him. She mentioned that she was not used to being the “successful” one of the two of them. In connection with her depression, it emerged that Ms. C’s brother had had a severe, life-threatening, and disfiguring pediatric illness that had required much family time and attention throughout their childhood. Ms. C had become “used to” his insulting manner toward her. In fact, it seemed that she required her brother’s abuse of her in order not to feel overwhelmed by survivor guilt about being the “healthy, normal” child. “He might insult me, but I look up to him. I adore him. Any attention he pays to me is like a drug,” she said. Ms. C’s acceptance to graduate school had challenged her defensive and essential compensatory image of herself as being less successful, or damaged, in comparison with her brother, thereby overwhelming her with guilt. Her depression remitted in psychodynamic psychotherapy as she better understood her identification with and fantasy submission to her brother.

**Impairment in Self-Esteem Regulation**

A general trait of patients with major depression is the loss of self-regard. Yet loss of self-regard can occur in the absence of depression. Edward Bibring disagreed with Klein’s formulation that emphasized the importance of a punitive superego and argued that conflicts about aggression and object loss were secondary determinants in depression. He viewed depression instead as resulting from a sense of helplessness, impaired self-esteem, and self-directed anger triggered by failures to live up to the narcissistic aspirations of any developmental phase.

Charles Brenner also de-emphasized the classic psychoanalytic focus on object loss, seeing a depressive propensity as equally likely to connect with organizing fantasies of narcissistic
injury, and particularly of castration. Brenner states that these fantasies are accompanied by reactive aggression against those blamed for the painful affects, with consequent guilt.

Mr. D, a 39-year-old successful and aggressive lawyer, had “never been depressed a day in my life” before developing a kidney stone that required a 5-day hospital stay full of medical interventions. He was well on discharge but developed major depression, with lethargy, decreased energy, hopelessness, and weight loss. He cried all the time. “I feel like a big, fat failure,” he announced. Handsome but insecure, Mr. D prided himself on his physical prowess and appearance and on his ability to attract the amorous attentions of “beautiful women.” “I’m not supposed to be sick,” he said, “Especially down there. It makes me feel old, ugly, and unattractive. Disgusting, in fact.” In describing his experiences in the hospital, he reported that the humiliation, or narcissistic blow to his self-esteem resulting from the illness and hospitalization, had so overwhelmed him (“I was hooked up to these disgusting tubes—even in my penis!” he wailed) that he had uncharacteristically not even complained about being placed into a four-bed hospital room with three homeless people who hadn’t showered. “I figured they were in control, so I didn’t even think about it,” he said. His symptoms remitted in psychoanalysis with therapeutic exploration of the way in which the hospitalization had in fantasy felt like a castration.

Many contemporary psychoanalysts amplify upon these models in their understanding of depression, while acknowledging the prominence of impaired self-esteem regulation. Edith Jacobson emphasized the development of self and object representations in depressed patients. She noted depressed patients’ disappointment with parental figures, resulting in devaluation and degradation of their images and of the self-representation, especially when a mature separation had not been achieved.

**Inadequacy of Early Caregivers**

Psychoanalysts have given a personal, intrapsychic face to the well-known epidemiological observation of the connection between parental (particularly maternal) depression and subsequent depression in children. Hans Kohut described depression as connected to experiences of profound emptiness in patients whose parents were unable to empathize with their early affective experiences. Such is the case, as many parents of depressed patients are themselves depressed. These patients crave compensatory relationships (“selfobject” relationships, mirroring experiences, and idealizing relationships), leaving them vulnerable to disappointment, as real relationships cannot live up to these compensatory fantasies.

Leo Stone highlighted depressed patients’ refusal to accept the separateness and autonomy of the object. Again, this view emphasizes the symbiotic tie to the object to compensate for an incomplete sense of self. Stone suggested that depressed patients unconsciously coerce objects; they are disappointed in them and prone to envy and rage because of an early history of “oral frustration.” Aggressive fantasies about disappointing and hurting loved ones give rise to the severe guilt with which these patients struggle.

Ms. E, a 21-year-old college student, presented with major depression and panic disorder since early adolescence. She reported hating herself, crying constantly, and feeling profoundly hopeless in part because of the chronicity of her illness. Even at the time of presentation, she noted her sensitivity to her mother’s moods. “My mother’s just always depressed, and it makes me so miserable, I just don’t know what to do,” she said. “I always want something from her, I don’t even know what, but I never get it. She always says the wrong thing, talks about how disturbed I am, stuff like that, makes me feel bad about myself.” In one session, E poignantly described her childhood: “I spent a lot of time with my mother, but she was always too tired, she never wanted to do anything or play with me. I remember building a house with blankets over the coffee table and peeking out,
Spying on her. She was always depressed and negative, like a negative sink in the room, making it empty and sad. I could never get her to do anything.” This patient experienced extreme guilt in her psychotherapy when she began to talk about her mother’s depression. “I feel so bad,” she sobbed. “It’s like I’m saying bad things about her. And I love her so much, and I know she loves me. I feel it’s so disloyal of me.” Her depression remitted in psychodynamic psychotherapy as she became more aware of and better able to tolerate her feelings of rage and disappointment with her mother.

Sidney Blatt, a psychoanalytic researcher, contrasts anaclitic depressed patients, anxiously attached individuals who struggle with excessive dependence on others, with introjective depressed patients, who are compulsively self-reliant. Blatt contends that anaclitic patients suffer more from feelings of loneliness, helplessness, and weakness; introjectives from a sense of worthlessness, self-criticism, and guilt.

**PSYCHOANALYTIC FORMULATIONS OF DYSTHYMIA**

Psychoanalysts have largely written about major depression, but some have also addressed dysthymia. Asch noted underlying masochistic pathology in dysthymic patients, a view that has been de-emphasized by contemporary dysthymia researchers, who have underlined that chronic depression, can appear phenomenologically like masochistic character structure, simply because of its chronicity. (In other words, masochism is a redundant concept in chronic depression.) Milton Horowitz emphasizes the “pleasure of revenge” in the patient’s defeating of all around him or her through failure, hopelessness, and negativity, and he regards this as more important than the experience of personal suffering for many such patients. David Milrod describes both the rewarding and the punitive aspects of superego function in response to narcissistic injury in patients with chronic dysthymia and self-pity.

Ms. F, a 20-year-old college student, came to psychotherapy complaining of chronic depression. She described herself as “dull, but difficult too.” While she enjoyed school, she had trouble finding things outside of school that she enjoyed doing. She was bored, lethargic, and unhappy most of the time. Although she had friends and a boyfriend—albeit a man much less desirable than she might otherwise have been expected to find—she resented their demands on her time, often because she found herself upset when she was with them. Her relationships with her boyfriend, some of her closer friends, and her mother were characterized by intermittent “crises,” events when Ms. F felt ignored, criticized, and abused by them, and she wound up locking herself in her room to cry, sometimes for days. As psychotherapy unfolded, it became clear that her boyfriend was very demanding of her time, yet rarely actually spoke to her. For example, he preferred to have her “around” while he worked on his computer for hours on end, but when he went out “to hang out” he preferred to spend time with his friends, without her. Ms. F handled this situation with a combination of resignation and resentment: She stayed with him while he worked, then often ignored him at parties that they both attended, in order to “get back at him.” In psychodynamic psychotherapy, her dysthymia and passive masochism resolved simultaneously, enabling her to stop feeling worthless in social situations and with her boyfriend and to become more assertive in all of her relationships.

**SYNTHESIS: DYNAMICS OF DEPRESSION**

Features common to many psychoanalytic theories of depression include feelings of exquisite narcissistic vulnerability stemming from a variety of sources, including early loss or experiences with parents perceived as traumatically unempathic, frustrating, or rejecting. A sense of helplessness or inadequacy in relation to these experiences, with accompanying fantasies of damage or castration, can contribute to this vulnerability. The resulting impairment in self-esteem regulation is common to all depressed patients, who are prone to a self-image of being unlovable, damaged, or inadequate.
Depressed patients perceive that they have either failed to live up to their ambitions or to their moral values in the ego ideal, the intrapsychic mechanism that triggers guilt in depression. Many psychoanalysts hypothesize that the resulting aggression toward a frustrating parent, or toward the self as damaged, contributes decisively to the propensity toward depression. In depressed patients, aggression is largely self-directed. Guilt (conscious or unconscious) or shame theoretically results from the patient’s perceived sense of failure, with a diminished sense of self. Difficulties in self-esteem regulation contribute to a self-representation of being “bad” or shamefully out of control, aggravating the original problem in a vicious cycle.

The sine qua non of depression in this conceptualization is aggression directed toward the self-representation, which proves uncontainable and spreads to a mood state. This may arise from a withdrawal of positive, or “libidinal,” supplies to the self-representation and replacement with aggression in the following ways:

1. By not living up to personal aspirations (giving rise to shame, rather than guilt);
2. By not living up to the ego ideal (precipitating guilt);
3. In an interpersonal depression, as described by Freud, in which a symbiotic bond to an ambivalent object tie is shattered. From a psychoanalytic perspective, this type of depression is associated with more primitive pathology, and these patients are more likely to be in a borderline or psychotic spectrum, because of the nature of the primitive, symbiotic interpersonal bond.

These different pathways trigger a common self-assessment of being worthless, bad, inadequate, or unlovable. The resulting hostility directed toward the self is a core feature of depression.

Retroflected hostility has been pinpointed in the historical psychoanalytic literature as also contributing to borderline and obsessional pathology. Indeed, many patients with these underlying character structures also experience major depression. From a psychoanalytic perspective, the essential feature of all depressions is the self-directed aggression, which becomes a mood state. Difficulty with self-esteem regulation, which is not an essential component of other syndromes, is always prominent in depression, coupled with aggression turned inward that exacerbates guilt and shame.

**PSYCHOANALYTIC FORMULATIONS OF MANIA**

From a psychoanalytic perspective, the clinical presentation of mania arises as a result of a global, massive regression that affects all three psychic structures: The id, the ego, and the superego. The regression leads to a primitive mental state in which the pleasure principle is reinstated. In *Group Psychology and Analysis of the Ego*, Freud described mania as a fusion of the ego with its superego. Less cryptically, psychoanalysts have highlighted a common organizing fantasy in manic patients of a fantasy incorporation, or mystical union, of the patient with someone of great power, often an aristocrat, or God, as in the story of St. Theresa’s mystical union with God. Such organizing fantasies, couched in both sexual and “oral” terms, magically impart a sense of omnipotence and specialness to the patient, highlighting one aspect to the common phenomenology of mania. Bertam Lewin noted that in mania early relationships with both parents that had become desexualized during the process of superego formation during latency become resexualized during the manic episode and that in fantasy the manic patient is identified with both partners (male and female) during the sexual act. The states of mania, and of hypomania, involve massive utilization of the defense
mechanism of denial, in which sad and negative aspects of reality are entirely ignored. One author hypothesized that the manic episode was precipitated by the need to control the memory and experience of intolerable pain. In this way, mania could be considered a defensive reaction, different from depression, in response to pain and distress.

Ms. G, a 42-year-old housewife and mother of a 4-year-old boy, developed symptoms of hypomania and later of frank mania without psychosis, when her only son was diagnosed with acute lymphocytic leukemia. A profoundly religious woman who had experienced 10 years of difficulty with conception, Ms. G was a devoted mother. She reported that she was usually rather “down.” Prior to her son’s illness, she used to joke that she had become pregnant with him by divine intervention. When her son was diagnosed and subsequently hospitalized, he required painful medical tests and emergency chemotherapy, which made him very ill. The doctors regularly barraged Ms. G with bad news about his prognosis during the first few weeks of his illness.

Ms. G was ever present with her son at the hospital, never sleeping, always caring for him, yet the pediatricians noted that as the child became more debilitated and the prognosis more grim, she seemed to bubble over with renewed cheerfulness, good humor, and high spirits. She could not seem to stop herself from cracking jokes to the hospital staff during her son’s painful procedures, and as the jokes became louder and more inappropriate, the staff grew more concerned. During her subsequent psychiatric consultation (requested by the pediatric staff), Ms. G reported that her current “happiness and optimism” were justified by her sense of “oneness” with Mary, the mother of God. “We are together now, she and I, and she has become a part of me. We have a special relationship,” she winked. Despite these statements, Ms. G was not psychotic, and said that she was “speaking metaphorically, of course, only as a good Catholic would.” Her mania resolved when her son achieved remission and was discharged from the hospital.

**COGNITIVE THEORY OF DEPRESSION**

Learning theory long has been a branch of behavioral psychology. Aaron Beck, finding that psychoanalytic theory did not sufficiently explain dreams of depressed patients, developed a theory of depression based on educating the patient about his or her negative thinking, or cognitions. Beck and colleagues then successfully tested CBT, a treatment built on this theory, in clinical trials. The cognitive model is based on the recognition that people are not objective; rather, an individual’s idiosyncratic perception of events affects his or her emotions and behaviors. Depressed individuals perceive reality in subjectively depressed ways. Elaborate discussions of cognitive theory exist, and cognitive explanations have been extended from their original depressive origins to a range of psychopathology. Brad Alford and Beck argue that cognitive theory provides a comprehensive and coherent paradigm for psychopathology.

Beck’s initial observations about major depression have a salience and simplicity worth repeating. He noted that depressed patients tend to have characteristically skewed and negative thoughts about (1) themselves, (2) their environment, and (3) the future, a cluster he termed the **cognitive triad**. Indeed, depressed individuals frequently report negative thinking about themselves: “I’m a loser,” “Everything I do goes wrong,” “I’m weak and defective.” The environment appears hostile and overwhelming: “Even if I felt capable—which I don’t—there’s no way I could cope with what I have to do”; “My friends will react badly if I try to speak up”; “She will reject me.” Finally, not only do things look grim in the present, but there is no prospect of relief in the future: “It’s never going to get any better.” These three aspects of negative perspective converge to provide a convincingly, despairingly bleak and mood congruent view of the world. This outlook helps to explain why depressed patients see no way out of their misery and contemplate suicide.
Cognitive theory has explored the form as well as the content of thinking characteristic of depressed patients. Not only are cognitions skewed to the negative and pessimistic, but particular types of distortions occur. Depressed individuals tend to engage in “all or nothing,” dichotomous thinking: If things aren’t entirely one way, then they must be the opposite. Depressed individuals make arbitrary (negative) inferences about events, selectively abstract negative details out of context, overgeneralize (concluding negative rules from single instances), magnify (the negative) and minimize (the positive), and take personally events that may not be directly about them. Depressed patients “catastrophize,” leaping from one imagined worst case scenario to the next in disastrous cascade:

He will take what I said as an insult, and will never speak to me again, and will tell all our friends. Then no one will like me, I’ll be all alone, and my social life will be ruined forever.

They selectively focus on negative evidence, failures, and setbacks that confirm their theories of defectiveness, while ignoring or discounting the successes that they have as “flukes.”

J, a 19-year-old college sophomore, made two mistakes on a test. Although his overall grade was high and the mistakes themselves appeared minor to the therapist, J took them as proof that he was defective and deficient. His perfect score on the next test, by contrast, he discounted as “luck … the teacher was being easy on me,” but not as any evidence of his personal competence. If, while depressed, you consider yourself a loser, then you pay most attention to outcomes that fit that schema.

Beck made the important point that the depressed outlook is not objective but irrational. “Automatic thoughts” of characteristically self-deprecatory and hopeless nature pop involuntarily into the patient’s head. Because these thoughts are mood congruent, depressed individuals find them believable and tend not to question them. The negative thinking characteristic of depressed patients is damaging in two respects. First, it is painful and depressing: Many patients are barraged with negative ideas about themselves and their situation, in effect a stream of insults. Second, these thoughts tend to inhibit action: If you know you are incompetent and going to fail, then you will also have thoughts like, “Why bother?” Depressive thinking patterns not only hurt, they paralyze individuals into inaction, which then leaves them more time to ruminate on their inactivity (“I’m not doing anything with my life”) and to suffer self-criticism. The deterioration of productive behavior due to negative thinking will then lead to more things going wrong in the patient’s life, providing more examples of the patient’s incompetence and reinforcing the negative thinking.

The case examples above provide good examples of self-critical thinking, which in cognitive theory would be understood as the irrational, automatic thoughts of a depressed patient: Ms. A felt “pointless” and “boring,” Mr. D “like a big, fat failure,” “old, ugly, and unattractive … disgusting”; Ms. F as “dull, but difficult too.”

Immediate and specific negative cognitions (“He doesn’t like me”) fit into larger, more basic and stable patterns of self-conception called “schemas” or core beliefs. For depressed patients, these tend to be global, negative, all-or-nothing assumptions based on early childhood experience: “If I do something imperfectly, it’s (and I’m) worthless”; “If I’m not in total control, I’m completely helpless.” Early cognitive theory presented such negative thinking as cause rather than effect of depression. Although cognitions are clearly an important aspect of depression, it seems naive at this point to expect that this is the single etiology of a complex and multidetermined syndrome that has both genetic and environmental components. Hence, over time cognitive theory has tended to back away from that etiological stance.
A general cognitive explanation of a major depressive episode is that a vulnerable individual, perhaps predisposed both by biology and by negative schemas based on early childhood, experiences a current life situation that evokes “automatic” thoughts. For example, a relatively minor setback at work might activate underlying schemas by eliciting the thoughts, “I’ve done a bad job,” and thereby “I’m a terrible worker,” “I’ve let the company and my co-workers down,” “My boss hates me,” and therefore “I’ll never succeed,” “I’m a failure.” Or a disagreement in a relationship might rouse ideas such as, “K doesn’t like me,” evoking and seemingly confirming the more general core beliefs: “I’m a terrible person,” “I’m a lousy parent,” and furthermore “No one could possibly love me.” The onset of these thoughts and accompanying depressive symptoms further compromises functioning, reinforcing the negative outlook. As mood darkens and the negative thoughts become ever more credible and pervasive, the patient gives up activities (“Why bother?”) and feels still more helpless and hopeless.

Cognitive therapy, the treatment that follows from this approach, includes a Socratic discussion and evaluation of the patient’s thoughts, weighing the evidence supporting and contradicting such thoughts. The patient actively tests hypotheses based on automatic thoughts (“I’ll fail at whatever I do”) by attempting various selected behaviors as homework. As the patient learns to recognize the irrational nature of depressive thinking, he or she can challenge rather than simply believe it and can begin to extinguish such thinking, replacing automatic irrational thoughts with rational responses. Outcome research repeatedly has shown that this approach is efficacious in treating mood disorders and other psychiatric syndromes.

**Dysthymic and Bipolar Disorders**

Cognitive theory has not been particularly altered for dysthymic disorder. Rather, chronicity of depression would simply seem to ingrain negative core beliefs more deeply. Cognitive Behavioral Analysis System of Psychotherapy (CBASP), an eclectic treatment that James McCullough developed specifically to treat chronic depression, postulates that chronically depressed patients fail to behave appropriately in interpersonal encounters. CBASP combines elements of cognitive, behavioral, psychodynamic, and interpersonal therapies in focusing on the patient’s behaviors and thinking in interpersonal encounters, including those with the therapist.

Cognitive behavioral treatments have been developed not only for unipolar depression but also as an adjunct to medication for bipolar disorder. Mania may be viewed as the mirror of depression, wherein overvalued positive ideas (“I’m special” or “I’m the greatest”) automatically arise, again distorting reality, but this time in the opposing direction. Thinking itself accelerates in mania. By and large, cognitive theory has had less to say about manic than depressed states, and adaptations of cognitive therapies for mania are more practical than theoretical. They focus on psychoeducation about the illness, behavioral stabilization such as maintaining a regular sleep schedule, and emphasize the importance of adherence to pharmacotherapy. Following these principles, Francisco Colom and Eduard Vieta have developed an empirically tested psychoeducational treatment of bipolar patients.

Aspects of cognitive theory have been tested for unipolar depression, with sometimes contradictory results. CBT, which directly addresses depressive negative cognitions and helps patients to weigh their evidence rather than simply believe them, has repeatedly demonstrated efficacy as a treatment of major depression and does improve negative cognitions. Yet other
antidepressant treatments relieve depression and improve cognitions without specifically addressing cognitions, and behavioral activation—a behavioral approach without the cognitive component—has been shown to be at least as efficacious as CBT. Efficacious treatments of depression may spread from a particular theorized target to have generalized benefits.

**Comparison to Psychodynamic Theory**

It will be seen that cognitive theory does not contradict and to some degree overlaps with psychoanalytic theory. The treatments emerging from these theories differ greatly, however, in large part due to their differing definitions of the role of the therapist, handling of the therapeutic relationship, and approach to the meaning of that relationship: in psychoanalytic terms, the transference. Both theories focus on intrapsychic processes and on self-critical thinking, but cognitive theory emphasizes the distinction between rational and irrational thinking and their connection to mood rather than to unconscious fantasy.

**INTERPERSONAL THEORY OF DEPRESSION**

Interpersonal theory dates back to the era after World War II, when it arose as a heretical response to the more intrapsychic emphasis of psychoanalysis. Psychoanalytic theory emphasized the importance of early life experience, and many therapists at that time saw the patient’s psychic structure as essentially formed by the end of adolescence. Psychiatrists such as Adolf Meyer, Harry Stack Sullivan, Erich Fromm, and Frieda Fromm-Reichmann challenged then current theory by emphasizing the influence of the real impact of current life events on their patients’ psychopathology, focusing on environmental and interpersonal encounters rather than underlying intrapsychic drives and structures.

Sullivan coined the term “interpersonal” as a rubric for considering current life experience. He scrutinized communications in the social field, a more “external” outlook than traditional psychoanalysis. The interpersonal theorists worked mainly with inpatients diagnosed with schizophrenia in a prepharmacological era. Although their work stirred great controversy at the time and a Sullivanian school distinct from the psychoanalysis of drives and ego psychology still exists, Sullivan was trained in psychoanalysis and did not entirely disagree with his forebears. Over time, the rift between Sullivanians and other psychoanalysts has narrowed.

The consideration of current interpersonal factors gained currency over succeeding decades, and it is now mainstream clinical thinking that current life events and interpersonal functioning affect and are affected by psychopathology. A school of interpersonal psychoanalysis—not particularly focused on mood disorders—arose. Psychoanalytically trained therapists like Silvano Arieti and Jules Bemporad emphasized interpersonal factors in the treatment of depressed patients. Jack Anchin and Donald Kiesler have reviewed other interpersonally based psychotherapies. None of these theories has received empirical testing.

Researchers did develop a host of related data about interpersonal issues associated with depression. For example, research showed that interpersonal support protects an individual against depression: Having a confidant to talk to reduces the risk of developing a depressive episode. Major life stressors, including the death of a significant other, struggles in important relationships, and upheavals such as a change in marital status, housing, job status, or physical health have been shown to increase the risk of depressive episodes in vulnerable
individuals. Moreover, the onset of depressive episodes leads to deterioration in relationships and social functioning.

John Bowlby postulated that people have an evolutionarily determined, instinctual drive to form emotional attachments. Animal evidence now supports this theory. This basic component of human nature ensures infant survival: Children need to have parents nearby or available for feeding and protection. As children develop, they begin to explore their environment, gradually moving out from the “secure base” of their attachment figure. Disruptions in this early caregiving connection may lead to vulnerability of attachment style. For example, loss of one’s mother in the first decade of life has been shown to be a risk factor for subsequent depression. Children with insecure childhood attachments may not learn to ask for help from others. When such vulnerable individuals face stressors or feel an absence or inadequacy of interpersonal support during times of stress, they may be helpless to respond effectively and prone to developing symptoms. Furthermore, individuals with insecure attachment styles may have difficulty in developing comfortable relationships on which they can rely for support in times of need.

In the 1970s, when Gerald L. Klerman, Myrna M. Weissman, and their colleagues were conducting a randomized controlled trial of outpatients with major depressive episodes, they recognized that many such patients received psychotherapy in community treatment. They sought accordingly to add a psychotherapy to their trial but realized that it was unclear then (as now) of what such community psychotherapy consisted. They then developed IPT as a manualized, time-limited treatment of outpatients with major depressive disorder based on interpersonal and attachment theories as well as empirical evidence of the psychosocial nature of depression. IPT is thus one specific therapeutic application of more general interpersonal theory. IPT demonstrated efficacy for major depression in this and in subsequent outcome trials.

In simplest terms, interpersonal theory as applied to IPT can be understood as a link between mood and events. For all people, upsetting external events evoke a sad or demoralized mood: In lay terms, they are “depressing.” For biologically or environmentally predisposed individuals, however, a sufficiently disturbing life event can trigger an episode of major depression. Examples of such life events are the death of a significant other (complicated bereavement), a problematic relationship (role dispute), or other major life change (role transition). Once a depressive episode starts, its symptoms compromise functioning, producing more negative life events in a vicious downward cycle. This formulation seems straightforward, even commonsensical, but depressed patients have a peculiar amnesia for external events and tend to blame themselves for how they feel or to see the depressed state as who they are. It can be helpful clinically to remind them that they are ill, not defective, and that outside events may have contributed to their distress.

IPT therapists do not propose this as an etiological theory of depression, but as a pragmatic one: The depressive mood episode can be linked either to a precipitating life event or to consequent life events that become the focus for the treatment. The IPT therapist defines major depression as a medical illness—a treatable medical problem that is not the patient’s fault—and links it to an interpersonal focus such as a role dispute. The therapeutic contract for the patient is to solve the interpersonal focus within a time-limited period. Solving the interpersonal problem is at once a realistic relief (e.g., improving a marriage), relieves depressive symptoms, and builds interpersonal skills that may hopefully protect against future interpersonal triggers and depressive episodes. Typical areas of interpersonal skill building
are issues such as self-assertion, confrontation, effective expression of anger, and the taking of social risks.

Clinicians armed with differing theories approach the same material in different ways. IPT seeks a life event or interpersonal situation as a plausible and pragmatic fiction on which to focus a time-limited treatment in which the patient can work on interpersonal skills. For example, the case of Ms. A might be conceptualized as major depression arising in the context of a role dispute with her boyfriend, B. Had she been treated in IPT, the focus might have been on recognition and appropriate expression of her own anger as part of learning to renegotiate that relationship. Alternatively, or additionally, clinical judgment might have defined the breakup of that relationship as a role transition that Ms. A needed to mourn and accept in order to move on to better relationships or activities. Ms. C’s difficulty in tolerating her acceptance to graduate school might similarly be considered a role transition, as might Mr. D’s bout of renal stones. Medical illnesses, even if transient, frequently provoke role transitions by shifting a patient’s perception of his life trajectory; Mr. D may have interpreted his hospitalization as evidence of his fading potency, aging, and mortality. Ms. E’s situation might conceivably be defined either as a role transition—adjusting to college life away from her mother—or as a role dispute with her mother.

Preliminary evidence supports the theory underlying IPT as a treatment. Patients in two IPT treatment trials were asked to report the degree to which they had resolved the interpersonal crisis (e.g., role transition) on which their treatment had focused. Subjects’ report of making changes in this interpersonal focal area correlated with symptomatic improvement during the trial.

Dysthymic Disorder

An adaptation of IPT has been developed for dysthymic disorder, but differences in the treatment are largely those of technique. Patients with chronic depression tend to be socially isolated (Ms. F above is slightly unusual in having a boyfriend, although her choice of boyfriend was in keeping with the disorder) and invariably have interpersonal difficulties. If the syndrome began early in life, as is often the case, then patients may never have developed important communication skills. They tend to be passive and unassertive, to experience self-assertion as “selfish” rather than a healthy and sometimes necessary negotiation of one’s own goals in life, and to view anger as a “bad” feeling rather than a useful interpersonal signal that someone is bothering them. Even if they have had such capabilities in the past, their interpersonal functioning will have eroded under the pounding discouragement of chronic depression. Chronicity breeds resignation and entrenches maladaptive interpersonal patterns.

Bipolar Disorder

In all of the theoretical approaches under discussion, mania has received less attention than unipolar depression. There is no real adaptation of interpersonal theory for mania. Clinically, it is apparent that manic patients lose social judgment and become overinvolved and labile in relationships with others. Ellen Frank and colleagues have adapted IPT for bipolar patients as an adjunctive treatment to pharmacotherapy by combining it with a behavioral strategy. Interpersonal social rhythms therapy (IPSRT) is a hybrid of IPT and social zeitgeber theory, which stresses the importance of maintaining diurnal structure through regular patterning of circadian events, or social rhythms. In particular, this involves ensuring a regular bedtime to prevent the loss of sleep that often triggers a manic episode. As with CBT for bipolar
disorder, this represents more of a clinically reasonable, pragmatic extension of an already established treatment than a theoretical evolution. This approach, described in a manual, has shown benefit as an adjunct to pharmacotherapy in a randomized controlled trial for bipolar patients.

**Future Directions**

Psychoanalytic, cognitive, and interpersonal theories all provide insights into mood disorders. None is received truth, none can be considered fully tested in empirical studies, and all are surely incomplete. Nor has this section covered all theories of mood disorder: Biological, behavioral, feminist, and many other theories have been proposed for depression. Psychoanalytic, cognitive, and interpersonal theories each capture important aspects of complex syndromes. In the hands of skilled clinicians, therapists and patients may find each approach useful in conceptualizing the patient’s status and organizing his or her treatment.

Future research may elaborate more comprehensive applications of these theories to bipolar disorder. And theory alone does not suffice to train a clinician: clinical experience and supervision, as well as personal therapy, help to expand clinical understanding and ability.

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13.6 Mood Disorders: Suicidal Behavior

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Suicidal behavior is one of the most alarming signs not only in psychiatry but also in everyday life, and it is among the most frequent sources of contact with medical services, particularly with psychiatric services. Suicidal behavior (completed suicide and suicide attempt) as well as suicidal ideation or planning are very rare in the absence of current major mental disorders; they are not the linear or direct consequences of them. Although suicidal behavior is very complex, multicausal phenomenon involving several medical–biologic, psychosocial, demographic, and cultural components, a history of untreated major mood disorders (particularly in the presence of previous suicide attempt) constitutes the most important risk factor. However, because the majority of patients with mood disorders never complete (and more than half of them never attempt) suicide, other familial–genetic disorders, personality, psychosocial, and demographic risk factors also play a significant contributory role. The exploration of the role of these factors help to provide a better understanding of what makes the minority of patients with mood disorders suicidal, while the majority of patients are not suicidal. In addition to suicidal behavior, major mood disorders (both unipolar major depression and bipolar disorder) are also associated with a considerable amount of illness-related health and economic problems, such as loss of productivity, secondary substance-use disorders, family breakdown, and increased somatic morbidity and mortality. Given the high lifetime prevalence of unipolar major depressive and bipolar disorders, they are among the most frequent as well the most potentially life-threatening psychiatric illnesses. Despite the great clinical and public health significance of major mood disorders, people with these disorders are still under-referred, under-diagnosed and under-treated. This is particularly true for those who die by suicide and for those who attempt suicide and receive medical attention. As the act of killing oneself is considered to be a major cause of years of life lost, its prevention is receiving more and more attention nowadays.

RELATIONSHIP BETWEEN MOOD DISORDERS AND SUICIDAL BEHAVIOR

Psychological autopsy studies from several different countries consistently show that around 90 percent of consecutive suicide victims have at least one but frequently more (mostly untreated) major psychiatric disorders at the time of their death, and the rate of major mood disorders is between one-half and two-thirds. Comorbid anxiety and personality disorders are also frequently present, but they are not the main diagnosis, as these patients experience suicidal behavior mainly in the case of a coexisting major depressive episode. Although the ratio of attempted to completed suicide in the general population is about 15–40:1, it is much lower (5–10:1) among patients with major mood disorders, suggesting that these patients use more lethal (or more violent) suicide methods. Patients with mood disorders, particularly bipolar patients, often present a low ratio of suicide attempts to completed suicides, which points to the relatively high lethality of suicide attempts in bipolar disorder. Such findings indicate that bipolar patients have a particularly high level of intent to die and a high lethality of the methods used. Among all individuals hospitalized due to severe suicide attempts in Finland from 1997 to 2003 (N = 23,321), mood disorders (N = 5,164) raised the risk of completed suicide by 72 percent and of suicide attempt by 59 percent during the mean follow-up time of 3.6 years. As in other studies, the risk was very high just immediately after discharge from hospital.
Completed suicide and suicide attempts are two different but greatly overlapping phenomena: around half of those who complete suicide have attempted suicide at least once previously, and the first attempt (even if the method used is nonviolent or nonlethal) significantly increases the risk of future completed suicide. This is partly because of the fact that those who repeatedly attempt suicide frequently switch their method from nonviolent to violent or from nonlethal to lethal. Between 10 and 18 percent of adults in the general population worldwide report lifetime suicidal ideation, and 3 to 5 percent have made at least one suicide attempt in their lifetime. Suicidal ideation, suicide attempt, and completed suicide are three different but greatly overlapping features. Prior suicide attempt and current major depression are the two strongest predictors of future suicide, and the vast majority of suicide attempters or completers come from a population of people with current suicidal ideation, particularly in the presence of an untreated major depressive episode.

The standardized mortality ratio of suicide death in (unipolar and bipolar) patients with major mood disorders compared to that in the general population has been reported to be 10- to 30-fold. While suicide is around the 10th most common cause of mortality in the general population in well-developed countries, it is among the most common leading causes of death among patients with unipolar major depression and bipolar disorder, and the life expectancy of these patients is decreased by about 10 to 12 years. Studies published many decades ago estimated that 15 to 19 percent of severe (mostly hospitalized) patients with unipolar and bipolar major depressive episodes would die by suicide. However, most recent studies—maybe reflecting the more widespread and effective treatments—have found that this figure is less than 10 percent, which is, of course, still very high. A study from the United States found that there was a severity-dependent hierarchy in suicide risk among patients with major depressive disorders. Whereas the lifetime risk of completed suicide in the general U.S. population was 0.5 percent, the same figures in nonsuicidal major depressive outpatients, major depressive inpatients hospitalized without specification of suicidality, and severe major depressives hospitalized for suicidality were 2.2, 4.0, and 8.6 percent, respectively. In a national long-term follow-up study on suicide risk in Denmark on all subjects born between 1955 and 1991 who had been treated in a psychiatric hospital in Denmark up to the year 2006, or as outpatients after 1995, it was found that the absolute lifetime risks of completed suicide in patients with diagnosis of bipolar disorders were 7.8 percent for males and 4.8 percent for females, while the same figures for patients with diagnosis of unipolar depression were 6.7 and 3.8 percent, respectively. It should be noted, however, that because the diagnostic switch between unipolar depression and bipolar disorder was not taken into account during this long-term follow-up study, the real lifetime risk of completed suicide should be higher in bipolar disorder and lower in unipolar disorder.

Other long-term follow-up studies also show that the rate of completed suicide is higher in bipolar disorder (types I and II combined) than in unipolar depression, and similarly, population-based epidemiological studies also found a substantially higher rate of suicide attempts in bipolar I and II disorders than in patients with unipolar major depressive disorder: more than half of bipolar patients and around one third of unipolar depressives report a lifetime history of one or more suicide attempts, and suicidal ideation, a major precursor of suicidal behavior in patients with mood disorders, is even more common. The majority of the studies show that out of the three different clinical manifestations of major mood disorders (unipolar depression, bipolar I disorder, and bipolar II disorder), bipolar patients in general, and bipolar II subjects in particular, carry the highest risk of both attempted and committed suicide. Considering only 10 studies, published between 1976 and 2004, in which unipolar, bipolar I, and bipolar II patients were analyzed separately, and summarizing the data, it was
found that the rate of previous suicide attempts was the lowest in unipolar major depression patients (13 percent), highest in bipolar II patients (33 percent), and intermediate in bipolar I patients (28 percent). Most recent studies found that completed and attempted suicide is more frequent in bipolar II patients than in bipolar I patients, but meta-analyses found this difference statistically insignificant. However, in everyday clinical practice, bipolar II patients are frequently overlooked. Clinicians often acknowledge the fact that the risk of suicide is higher among bipolar II patients as they often have a cyclothymic affective temperament, which predisposes them to suicide risk, and they often have rapid mood shifts, which are found in the clinical history of such patients.

The risk of completed and attempted suicide in bipolar disorder is more pronounced at younger ages, especially in the first few years after onset. However, bipolar patients with past suicide attempts have earlier age at onset than those without prior suicidality. Since the correct diagnosis of bipolar disorders usually comes at an average of 8 to 10 years after the onset of the illness, and delays in the correct diagnosis as well as delays in the initiation of mood stabilizers at illness onset confer an increased risk of suicidal behavior, these findings strongly suggest that early recognition of the bipolar nature of depressive disorders and adequate short-term and long-term treatment is crucial for preventing suicide.

The first suicide attempt significantly increases the risk of future suicide attempts or completed suicide, and about 20 percent of those who attempt suicide eventually will die by their own hand. However, up to half of suicide victims have made at least one prior suicide attempt, indicating that about 50 percent of suicide victims die by their first suicidal act. Therefore, to detect the risk of suicide in patients with mood disorders and to plan prevention strategies, as early as possible, even before the first suicidal act, is crucial in suicide prevention. This chapter summarizes the most relevant clinically detectable suicide risk and protective factors in mood disorders and briefly highlights the most effective preventive strategies. It will focus on completed suicide (an act of deliberately taking one’s life) and suicide attempt (a self-injurious act with intent to end one’s life), both of which are commonly referred to as “suicidal behavior,” but it will not cover deliberate self-harm (defined as an intentional injuring of one’s body without apparent suicidal intent).

**CLINICALLY DETECTABLE SUICIDE RISK AND PROTECTIVE FACTORS IN PATIENTS WITH MOOD DISORDERS**

Because suicide is a rare event in the community, its precise prediction in individual cases is very difficult but not impossible. However, suicidal behavior (completed suicide and suicide attempt) is quite frequent among patients with mood disorders who contact different levels of the health care some weeks or months before their death or attempt, which emphasizes the potentially key role of health care workers in suicide prevention. The scientific literature identifies several clinical, biological, psychosocial, and demographic risk and protective factors that have been found to be statistically significant with suicidal behavior.

Suicide risk factors are classified as short-term versus long-term, proximal versus distal, changeable versus unchangeable, psychiatric–medical versus sociodemographic, and clinical versus biological. As for biological risk factors, a decreased (dysregulated) central serotonergic system in suicide victims and suicide attempters (particularly in those with violent method), regardless of the psychiatric diagnosis, is a very strong correlate of suicidal behavior and is one of the most consistent neurobiological findings in the field of psychiatry. Some studies, however, suggest that alterations in other neurotransmitter (norepinephrine,
dopamine, GABA, and N-methyl-D-aspartate (NMDA) systems and in cholesterol as well as omega-6 and omega-3 metabolism might also be important in this respect. Studies consistently show that hyperactivity of the hypothalamic–pituitary–adrenal axis (as reflected in the abnormal dexamethasone suppression test), is a robust predictor of future completed suicide, primarily in patients with major depressive episodes. As decreased central serotonin metabolism is more strongly related to impulsive–aggressive personality characteristics than to any specific psychiatric disorder, these trait-related features increase the likelihood of suicidal behavior, particularly in the simultaneous presence of an acute episode of major psychiatric disorder and adverse psychosocial situations, including lack of social support. Despite the fact that current studies on the biology of suicidal behavior are very promising, in the everyday clinical practice (particularly in the case of urgent need of action), they have just very limited practical value. Therefore, clinically explorable risk and protective factors—as will be discussed below—are the most important aids in this complicated and highly responsible task.

Specific Clinical Characteristics of the Current Mood Episode

If patients with major mood disorders complete or attempt suicide, in the majority of the cases, they so during major depressive or mixed episodes but practically never during euphoric mania or euthymia (clinical recovery), indicating that suicidal behavior in patients with major mood disorders is both state and severity dependent. Severe major depressive episodes and the simultaneous presence of major depressive and manic syndrome (DSM-IV mixed affective episode and DSM-5 major depressive episode or manic episode “with mixed features”) are the most important time-related risk periods of suicidal behavior in patients with mood disorders. Both the DSM-IV mixed affective episode and DSM-5 mania or major depressive episode “with mixed features” are characterized not only by increased suicide risk but also by earlier age of onset, higher frequency of manic and depressive episodes, higher rate of rapid cycling course, as well as substance use and anxiety disorder comorbidity, all of which increase the risk of suicidal behavior.

According to both clinical and research observations, depression of suicide victims differs qualitatively from that of living depressed controls. Suicidal depressives often experience more severe forms of depression, with features highly related to suicide risk, such as insomnia, hopelessness, anxiety, agitation, weight or appetite loss, feelings of worthlessness or inappropriate guilt, and thoughts of death or suicidal ideation. Comorbidity with substance (including alcohol) use disorder(s) is also often observed in depressed suicide victims. Patients with mood disorders who exhibit volatile and erratic moods associated with dysphoria and agitation or who present the classic mixed states have a particularly higher risk of suicide. Predisposing factors interact with precipitating stressors, but deaths, separations, and other major losses, scandals, or imprisonment rarely precipitate suicide in the absence of a psychiatric disorder. Current mood states are critical determinants of suicidal risk in patients with mood disorders, particularly depressive and dysphoric-irritable mixed states (DSM-5 major depressive or manic episode with mixed features) that together are present in at least 75 percent of suicides in bipolar patients, whereas suicide is extremely rare in pure mania, hypomania, and after clinical recovery.

Subthreshold lifetime or current (hypo)manic symptoms during DSM-IV unipolar major depressive disorder (subthreshold bipolar depression and mixed depression that shows a great overlap with the clinical category of agitated depression) or the DSM-5 category of major depressive or manic episode with mixed features also increase the risk of suicidal behavior.
Analyzing the US National Comorbidity Survey-Replication database also showed that the history of lifetime suicide attempts was the highest in bipolar I disorder (66 percent), lower in bipolar II disorder (50 percent), and lowest in unipolar major depression without subthreshold bipolarity (30 percent). However, in patients with unipolar major depression with lifetime or current (intradepressive) subthreshold (hypo)manic symptoms (major depressive episode “with mixed features” in DSM-5), the rate of patients with prior a suicide attempt was intermediate between pure unipolar major depression and bipolar II disorder (41 percent). Studies also show that the psychotic nature of major mood episodes also increases the risk of suicide, particularly in patients with bipolar depression. In contrast to a major depressive episode, minor depression and pure dysthymic disorder (dysthymia without “comorbid” major depression) do not markedly increase the risk of suicide, but many patients with these milder forms of mood disorders develop major depressive episodes, and consequently an increased risk of suicide, during the long-term course.

**Comorbid Psychiatric, Personality, and Medical Disorders**

Patients with mood disorders with comorbid anxiety disorders, substance use disorders, cigarette smoking, personality disorders (mainly borderline-type), and serious, disabling, painful and fatal medical illness are also at increased risk of attempted and committed suicide. Young persons with bipolar disorder and ADHD have an increased likelihood of suicidal behavior compared with young patients who have only bipolar disorder. Besides the well-known role of chronic alcoholism, acute alcohol intake is also an important risk factor for attempted and completed suicide even in nonalcoholic depressives, as it could trigger the actual suicidal behavior and increases the lethality of suicidal acts. Strong evidence suggests that in addition to alcohol and substance use disorders, cigarette smoking is also positively related to suicidal behavior in the general population and—according to most studies—also in samples of patients with major mood disorders. Major depression, bipolar disorder, and schizophrenia are associated with higher rates of cigarette smoking than that of the general population, but smoking remains a significant suicide risk factor even after controlling for psychiatric morbidity. Smokers, in general, are more impulsive, and current smokers with major depressive disorder show a greater number of depressive symptoms and higher levels of suicidality (suicide attempts; suicidal ideations) during their depressive episode than those with major depressive disorder who have never smoked. Patients suffering from disabling, painful, and/or life-threatening medical disorders, including cancer, are also at elevated risk of suicide, particularly when depression is also present. The actual risk of suicide in patients with cancer varies with anatomical location, stage of the cancer, and with the result of cancer therapy. Despite the recent progress in cancer treatments, this diagnosis is still a major stressor for many patients, especially those with other psychiatric or psychosocial suicide risk factors.

**Prior Course of the Mood Disorder**

Clinically detectable suicide risk factors related to the prior course of the illness in patients with mood disorders are early onset of the unipolar or bipolar disorder, relatively early stage of the illness, first episode depression, predominantly depressed polarity during the prior course of the illness (which is typical for bipolar II disorder), rapid cycling bipolar disorder, and, of course, suicidal ideation or suicide attempt in the past: all of these have been repeatedly demonstrated to increase the risk of attempted or completed suicide in patients with mood disorders. Suicide risk appears to be particularly high primarily early in the course
of bipolar illness, and this also underlines the importance of precise diagnosis and effective treatment of specific mood disorders as early as possible.

**Specific Personality Features**

Impulsivity, aggressivity, pessimism, and few reasons for living, as personality traits, markedly increase the risk of all forms of suicidal behavior when combined with depression. There is a strong association between impulsiveness and bipolar disorder, and impulsivity becomes more pronounced during depressive or (hypo)manic episodes. Even modest manic symptoms during bipolar depressive episodes are associated with greater levels of impulsivity and higher rates of suicide attempts. Current findings also show that in contrast to hyperthymic temperament and cyclothymic, irritable or depressive affective temperaments, the first two are also characteristic for bipolar (mainly for bipolar II) disorder, which also increases the risk of suicidal behavior in patients with both bipolar and unipolar major depressive episodes. In addition, the role of cyclothymic temperament in suicidal behavior is supported by the finding that anger and hostility are most common in remitted bipolar and major depressive patients with cyclothymic affective temperament. The role of unstable affective temperament in suicidal behavior is also demonstrated by findings showing that cyclothymic temperament significantly predicts future bipolar transformation and suicide attempts in adult and juvenile depressives, and bipolar I, bipolar II, and unipolar major depressive disorder patients with cyclothymic temperament have a significantly higher rate of prior suicide attempts and lifetime or current suicidal ideation than noncyclothymic depressives. The persistent, frequent, and marked instability of mood, thinking, and behavior are the most characteristic features of cyclothymia, which is the attenuated manifestation of major bipolar mood disorders. However, marked affective temperaments, which can be detected in about 15 to 20 percent of the general population, become suicide risk factors only during major depressive episodes, as persons with marked affective temperament have a much higher chance of developing major mood disorders. Patients with cyclothymic and irritable affective temperaments who attempt suicide significantly more frequently report childhood physical and/or sexual abuse, suggesting that besides impulsivity, cyclothymic or irritable temperaments are further mediating variables between these early negative life events and adult suicidal behavior. Pessimistic personality features, cognitive rigidity, ruminative thinking, maladaptive coping strategies, and disturbed neurocognitive functions like impaired decision making, as could be detected also by specific neurocognitive tests, are also characteristics of most suicidal depressives. The interaction between personality features and illness characteristics in the suicidal process is best formulated in the “stress-diathesis model,” which proposes that suicidal behavior is determined not only by the stressor (acute major psychiatric illness or acute major personal crisis) but also by a diathesis or predisposition (impulsive, aggressive, pessimistic personality traits).

**Previous Suicide Attempt**

Previous suicide attempts, particularly in the case of violent or more lethal methods, are the most powerful single predictor of future attempts and fatal suicide both in patients with major mood disorders or with other psychiatric diagnoses. One third of unipolar and about half of bipolar depressives attempt suicide at least once during their lifetime, and suicidal behavior shows high consistency across major depressive episodes. In the majority of cases, suicidal depressives become suicidal again in the next depressive episode. Bipolar patients, particularly bipolar II patients, use more violent and more lethal suicide methods than unipolar depressives, respectively, and is more common in males. Nonviolent or low-lethality
suicide attempts do not mean low suicide risk, as those who repeatedly attempt suicide commonly change their method from nonviolent to violent, but the opposite pattern is rare. Bipolar depressives with a history of suicide attempts have a more severe symptomatology in general; they report more hopelessness, self-blame, guilt, current suicidal ideation; and more frequently show aggressive–impulsive personality traits than nonsuicidal bipolar depressives do. Therefore, higher rates of suicidal behavior (mainly completed suicide) in patients with bipolar disorder than in unipolar major depression may be partly due to a specific effect of bipolar disorder, resulting in more dangerous or more lethal suicidal behaviors.

**Family History of Suicidal Behavior**

Family, twin, and adoption studies show that a family history of suicidal behavior and/or major mood disorders in first- and second-degree relatives are among the strongest risk factors for both attempted and completed suicide in psychiatric patients in general, and in patients with major mood disorder in particular. The heritability index of completed suicide is approximately 40 percent, and it is even higher among depression-related suicides. However, the familial component of suicidal behavior seems to be partly independent of specific psychiatric disorders, as relatives of suicidal persons are more than 10 times more likely than relatives of comparison subjects to attempt or complete suicide after controlling for psychopathology. Similarly, a recent longitudinal study found that the children of parents with mood disorders who attempted suicide were five times more likely to attempt, even after controlling some other offspring risk factors for suicidal behavior, such as previous suicide attempt and history of mood disorder (both assessed at baseline) or mood disorder at the time point before the suicide attempt. Bipolar and unipolar major depressive patients who have a family history of suicidal behavior and who were exposed to childhood physical and/or sexual abuse are at greater risk of suicidal behavior. Impulsivity and irritable temperament seem to be the link between childhood abuse and suicidal behavior, particularly in the case of pure or mixed major depressive episodes. Research data, including twin and adoption studies, show that the familial aggregation of suicidal behavior has several components: genetic background of major psychiatric disorders, genetic–familial nature of impulsive–aggressive personality traits irrespective from psychiatric disorder, and in some cases copycat mechanisms. However, it should be noted that the “suggestive” effect of a suicidal family member becomes active mainly when a major depressive or other severe mental disorder develops.

**Negative Life Events and Adverse Life Situations**

Although negative life events do not lead to suicidal acts in the general population, they could trigger suicidal behavior in vulnerable persons, particularly in high-risk groups, such as those with major depression. Adverse, unwanted, or stressful life events play an important role in the suicidal process as predisposing (childhood events, including physical and sexual abuse) and precipitating (adulthood events) factors. Although negative life events do not inevitably lead to suicidal behavior in healthy persons or even in the high-risk groups such as psychiatric (particularly mood disorder) patients, they may actually trigger the suicidal process, particularly if other risk factors or adverse situations are also present. One third of patients with unipolar major depression or bipolar disorder report a history of childhood physical and/or sexual abuse or neglect, and depressed patients with such a history have an earlier age of onset of bipolar illness, greater psychiatric comorbidity, and increased rates of suicide attempts. These adverse childhood events may lead to developmental and
neuroendocrinological scars that render the subject vulnerable for suicidal behavior in a crisis situation during adulthood, including severe major depression or bipolar disorder.

Affect mastery, or the capacity to regulate affect, is gradually acquired after birth—it is not present early on. Only with time and with reasonable parenting do children attain the capacity to regulate themselves and to keep themselves in reasonable emotional composure. The various developmental stages bring different emotional stresses to children. They must learn to deal with separations, frustrations, or other emotionally challenging circumstances, hence the importance of good early attachment experiences is unambiguous. The parent who is frightened, insecure, or vindictive, prevents the child from making a “secure attachment.” Insecure attachment with affective dysregulation, which is now identified in various central nervous system activities as well as in the hypothalamic–pituitary–adrenal (HPA)-axis activity, is considered a suicide risk as well.

About half of all completed suicides in both bipolar and unipolar mood disorders are associated with recent severe, acute negative life events, or adverse life situations, such the death of a relative or close friend, isolation, living alone, separation or divorce, and being unmarried. However, the stressors are commonly dependent on the victims’ own behavior, particularly in the case of bipolar I or bipolar II disorder. Hypomanic episodes, but mainly manic episodes, can easily lead to financial extravagance, aggressive–impulsive behavior, or episodic promiscuity, thus generating several interpersonal conflicts, marital breakdown, and new negative life events, all of which have a negative impact on the further course of the illness and on the family atmosphere of the patients as well, which may ultimately trigger a new depressive episode and suicidal behavior. Other relevant stressful events identified as suicidal risk factors include interpersonal or occupational difficulties; personal or economic losses; retirement; bereavement; social isolation; feeling stigmatized, as also commonly seen in patients with mood disorders; and limited access to support or health care or social services. Permanent adverse life situations (e.g., unemployment and social isolation) as well as acute psychosocial stressors (e.g., loss events and financial breakdowns) in adult patients with unipolar or bipolar disorders are useful indicators of suicidality in the clinical practice, primarily if other risk factors are also present. It should be noted, however, that unemployment is frequently the consequence of a major mood disorder, particularly in cases of comorbid substance use disorder. The risk of suicide is very high in the first few days of hospitalization and a few days and weeks after discharge from an inpatient psychiatric departments particularly in the case of unplanned discharge, in patients with a short hospital stay, with a high number of previous hospitalizations, and, of course, in the case of lack of follow-up care. Doctors should be alert when a patient discharged from an inpatient or outpatient psychiatric department seeks help for any psychological or even medical problems.

**Demographic Factors**

Although Caucasians, males, older persons, and urban residents, as well as minority groups (e.g., immigrants, ethnic minorities, specific professions, prisoners, lesbian, gay, bisexual, and transgender persons) are more and less overrepresented among completed suicides, females and young persons more commonly attempt suicide. Suicide mortality is elevated among those in a certain profession—especially veterans, health care professionals, and agricultural workers. However, the role of these demographic factors in suicidal behavior is less pronounced among patients with mood disorders; therefore, these do not have a clinically significant powerful predictive value in the case of patients with unipolar major depression or bipolar disorder, and they have just weak importance in the prediction of suicidal behavior in
individual cases. However, due to the interaction of genetic biological and psychosocial risk factors, close relatives of suicide victims are at a particularly elevated risk of suicidal behavior, and these persons always need some kind of professional help ideally immediately after the suicide of their relatives. Suicidal behavior shows a typical seasonal variation: spring and early summer is the peak, and winter is the low of completed suicides on both hemispheres, and this seasonal pattern is more pronounced among depression-related suicides, among males, and among those who use a violent suicide method.

**Clinical Utility of Suicide Risk Factors**

As suicidal behavior is very rare in the absence of a current major psychiatric disorder, a mental state examination is an integral part of the assessment. The suicide risk factors in mood disorders are shown in Table 13.6–1. This table organizes the risk factors from the point of view of the clinical examination when clinicians collect information about the present clinical manifestations as well as about the past history of patients with mood disorders. However, these risk factors have different clinical relevance and diverse predictive utility; illness-related factors are more alarming and more powerful than personality-related risk factors. Suicide risk factors have an additive effect; the more risk factors present, the higher the suicide risk. For proper prevention, clinical assessment of suicide risk should pay attention to warning signs. The American Association of Suicidology proposed to remember the acronym “Is Path Warm”:

- **I** Ideation—threatened or communicated
- **S** Substance abuse—excessive or increased
- **P** Purposeless—no reasons for living; anhedonia
- **A** Anxiety, agitation and insomnia
- **T** Trapped—feeling no way out; perceived burdensomeness
- **H** Hopelessness
- **W** Withdrawal—from friends, family, society
- **A** Anger (uncontrolled)—rage, seeking revenge
- **R** Recklessness—risky acts, unthinking
- **M** Mood changes (dramatic)

Clinicians should be aware of communications about suicide; very often, patients talk about suicide, death, and/or having no reason to live. Most suicidal individuals give definite warnings of their suicidal intentions, but significant others are either unaware of the significance of these warnings or do not know how to respond to them. However, suicidal intent is sometimes denied or minimized. Clinicians should always remember to ask about suicide; questioning patients about suicide thoughts and plans is always indicated and crucial for proper prevention. Talking about suicide does not increase the risk. During suicidal crisis, patients may withdraw from friends and/or social activities, and they may also lose interest in hobbies, work, school, and so on. Suicidal individuals may also prepare for death by writing out a will (unexpectedly) and making final arrangements, giving away prized possessions, clearing up business matters pertaining to survivors, or accumulating drugs or poisons for taking his or her life, and so on. Because these warning signs, which are highly indicative for current suicidal danger, are reported mostly by the relatives of patients, keeping contact with family members or with significant others is also important. Several suicidal intent scales have been developed that could be useful in special circumstances, but they are routinely used mostly in clinical research.
Suicide Protective Factors in Patients with Mood Disorders

In contrast to the numerous suicide risk factors, only a few circumstances are known to have a protective effect against suicidality, and suicidal behavior is always the result of the complex interplay between risk and protective factors. Good family and social support, pregnancy and postpartum period, having a large number of children, holding strong religious beliefs (regardless of the nature of religion), regular physical activity, and restricting lethal suicide methods whenever possible, (e.g., to reduce domestic and car exhaust gas toxicity, barriers at train stations and bridges), as well as introducing stricter laws on drug and gun control seem to have some protective effect. Recent studies have found that optimistic personality features as well as hyperthymic temperament may be also a protective factor and that there is a strong relationship between psychological resilience and hyperthymic temperament both in depressive and healthy individuals. However, one of the most
extensively studied and changeable suicide protective factors in major mood disorders is acute and long-term treatment, both pharmacological and nonpharmacological.

Suicidal behavior, as a final act, is always the result of a dynamic interplay between risk and protective factors. However, in individual cases, suicide risk factors have a more practical relevance, and the presence of one or more suicide risk factors is more important than the lack of protective ones. In the majority of cases, more than one suicide risk factors are present simultaneously, and their effect is cumulative: the higher the number of risk factors, the higher the suicide risk. They are usually closely related to each other. For example, elderly major depressives frequently have multiple medical disorders, and they commonly experience loss events and isolation; major depression easily leads to secondary alcoholism, loss of job, family breakdown, financial problems, and so on. Considering the clinically relevant suicide risk factors in patients with mood disorders, in the majority of cases, suicidal behavior is predictable, but, of course, not guaranteed. Severe major depression with agitation, anxiety, insomnia, or hopelessness, particularly in combination with prior suicide attempt and, of course, with current suicidal ideation, are the most important signs for identifying acute or hyperacute suicide risk that requires prompt action.

**ANTIDEPRESSANT-ASSOCIATED SUICIDAL BEHAVIOR: THE ROLE OF UNDERLYING BIPOLARITY**

Given that suicidality is the most visible outcome of untreated or inadequately treated depressive illness, the U.S. Food and Drug Administration (FDA) warning of emergent suicidality in children and adolescents based on the antidepressant arm of placebo-controlled randomized trials has created understandable concern in clinical practice. The issues involved are of broader public health importance for all patients, not just for youngster patients. In 2004, the FDA advised that antidepressants could sometimes be related to suicidal behavior, which in their database examined mainly pertains to children and adolescents. Newer meta-analyses have confirmed the FDA’s position for a slightly increased risk of suicidality (suicidal ideation and attempts but not completed suicide) in juvenile patients in randomized controlled antidepressant trials on unipolar major depression. As in other branches of medicine, psychiatrists must always be vigilant of the rare risk of iatrogenesis when prescribing potent agents like antidepressants to patients with depressive disorders where the risk of suicidality is inherent and quite common.

The most challenging paradox of contemporary psychiatry is that antidepressants prevent suicidal behavior among severely ill, frequently suicidal “real-life” unipolar major depressives, but they can induce such behavior rarely in less severe, actually nonsuicidal unipolar major depressives in randomized controlled clinical trials, particularly in the youngest age cohorts. The main cause of the many disbeliefs about antidepressants and suicide is that some people do not realize that these two opposite effects are not in the same magnitude. As antidepressants prevent depression-related suicidal behavior in the vast majority of cases, they could increase the risk only in a small, vulnerable subpopulation; therefore, in the everyday clinical practice, the suicide preventive effect of antidepressants highly overshadows this unwanted iatrogeny. There is no doubt that suicide mortality is much higher among untreated depressives than among antidepressant-treated depressives. The rarely occurring suicidal behavior in patients taking antidepressants is mostly the consequence of the lack of antidepressant effect (antidepressant-associated suicidality) but is rarely the result of suicide-inducing potential of antidepressants (antidepressant-induced suicidality), as antidepressants can sometimes worsen depression. Unrecognized bipolar
depressives (mainly bipolar II depressives in the daily clinical practice) and mixed “unipolar” depressive patients with intradepressive (hypo)manic symptoms (DSM-5 major depressive episode “with mixed features”) in the randomized controlled trials (RCTs) on antidepressant monotherapy in unipolar major depression are considered “unipolar” major depressives, which means that these patients receive antidepressants and—if needed—co-administered anxiolytics, but not mood stabilizers. Antidepressant monotherapy without the concomitant use of mood stabilizers or atypical antipsychotics in threshold and subthreshold bipolar depressives—who have typically early illness onset and young current age—can result in high rates of antidepressant resistance and can sometimes worsen the cross-sectional picture of depression, particularly in adolescents and young adults, not only by causing (hypo)manic switch but also by inducing or aggravating depressive mixed state or agitation, also called “activation syndrome,” which is the major substrate of suicidal behavior. However, 30 to 40 percent of diagnosed unipolar patients with major depressive disorders have clinically significant lifetime or current subthreshold hypomanic symptoms (subthreshold bipolar depression and mixed depression or major depressive episode “with mixed features,” respectively) as well as other basic clinical features, such as a family history of bipolar disorder, early onset, and bipolar conversion, which are characteristic and external validators for bipolar disorder. This means that more than one third of DSM-5 diagnosed unipolar major depressives are in fact subthreshold or mixed bipolar depressives, and in addition to the antidepressant resistance, primarily these patients are the subjects of bipolar conversion as well as ultimately antidepressant-associated worsening of depression and related suicidality. In contrast to “officially” diagnosed bipolar I and bipolar II depressives as well as actively suicidal or psychotic depressives, subthreshold bipolar and unipolar major depressives with mixed features are not excluded from the RCTs on “unipolar” major depression. The slightly elevated (but in absolute sense very low) risk of suicidal behavior (attempts but not completed suicides) among younger patients taking antidepressant drugs compared to those taking a placebo in randomized controlled antidepressant trials in DSM-III and DSM-I diagnosed unipolar major depressive disorders might be the consequence of the depression-worsening effect of antidepressant monotherapy in subthreshold and mixed bipolar depressed patients who were included into these trials and falsely diagnosed as suffering from unipolar depression and receiving antidepressants but not mood stabilizers. The depression-worsening effect of antidepressant monotherapy in threshold and subthreshold bipolar depression is more pronounced in the everyday clinical practice where not only most major depressives with subthreshold bipolarity but also many bipolar II patients are diagnosed and treated as unipolar depressives. Among antidepressant-treated patients, the rate of prior suicide attempts is much higher in the case of unrecognized versus recognized bipolarity, and antidepressant-induced “activation syndrome” or agitation is also more common in bipolar than in unipolar depression. The recognition of the role of “pseudounipolar” depressive mixed states in suicidal behavior has clear implications for suicide prevention. The correct identification of the “covert” bipolar nature of the given depressive episode, as reflected in mixed or agitated clinical presentation, is crucial for selecting the most appropriate treatment.

As a consequence of the FDA Black Box Warning in 2004, the decreased use of antidepressants in children and adolescents seen in some countries has been accompanied by a concurrent increase in suicide rates in those age groups, whereas in middle-aged and older persons, the utilization of antidepressants increased continuously, and suicide rates further decreased. These findings indicate that the Black Box Warning, contrary to its original intention, resulted in an increasing number of young depressives not receiving antidepressants and an increase in the suicide mortality of this age group. This increase, which occurred among young depressed persons without antidepressant treatment, also shows
that in everyday clinical practice, the suicide preventive effect of antidepressants highly overshadows the rare and unwanted suicide-inducing effect. The precise and early diagnosis of bipolar disorder, even in first-episode depressives, and the formal recognition of bipolar depressive mixed states in the official diagnostic system (mixed features specifier across all mood syndromes in the DSM-5) will help to red flag those pseudounipolar mixed depressives for whom antidepressant monotherapy is contraindicated and for whom mood stabilizers and/or atypical antipsychotics are indicated on clinical grounds.

PREVENTION OF SUICIDE IN PATIENTS WITH MOOD DISORDERS

Prevention of suicide in patients with depressive disorders is not only a great challenge for everyone who cares for or has contact with them but could also be among the most reliable indicators of the efficacy as well. As much of the putative psychosocial and demographic suicide risk factors are not modifiable in the frame of individual health care, consequently, suicide preventive efforts of psychiatrists and other medical professionals should focus on the treatable and amendable contributory psychiatric disorders involved in such behavior. The role of the health care system in suicide prevention varies as a function of the setting (e.g., psychiatric settings vs. primary care practice), with specialized suicide prevention centers (where they exist) playing a most important role. Because suicidal behavior is a very complex phenomenon, even in patients with mood disorders, its prevention should be also complex, and the majority of suicide attempts and completed suicides in patients with mood disorders are preventable. As suicidal behavior in patients with mood disorders is very rare in the absence of a major depressive or mixed affective episode, reducing the time spent in these high-risk states is essential for their suicide prevention. While successful acute treatment can only prevent suicide connected with the given mood episode, given the highly recurrent nature of major mood disorders, it is adequate long-term therapy that can provide effective protection for a longer period of time.

In the case of acute suicide danger, the patient needs close observation and urgent hospitalization, even against of his or her own wish. Crisis intervention, whenever needed, is also helpful. After an open discussion with the patient and relatives, involuntary admission is rarely needed. It should be explained that hospitalization will be as short as possible and that it is best for the patient. In cases when acute hospitalization is not indicated, close observation by family members and removing possible means of suicide (i.e., guns, drugs, pesticides, and car keys) is advised, as is consultation with a local outpatient psychiatrist in the GP and other non-psychiatric practice. As anxiety, psychomotor agitation, and insomnia markedly increase acute suicide risk, prompt pharmacological treatment of these symptoms is always needed, and these treatments provide immediate results. In the most severe suicidal (sometimes stuporous or catatonic) depressives, electroconvulsive therapy (ECT) is the most useful treatment strategy.

Suicide Prevention in the Frame of Psychiatry

Suicide and suicide attempts are not only among the most tragic events of human life, but they are also the most hard end points or most visible treatment outcomes in patients with psychiatric and particularly mood disorders. In addition, unfortunately many psychiatrists will lose a patient to suicide, which can cause severe distress for the doctors as well as the entire treating team. Although the elimination of acute suicide danger by all possible means is a common task for everyone, it is especially important that health care professionals diagnose those who are at risk so that they can be managed effectively.
Suicide prevention in patients with mood disorders is much more than detecting and managing the actual suicide risk. Targeting only those persons who are at acute suicide risk is frequently ineffective because it is often too late to make a successful intervention at this late stage. As suicidal behavior does not usually occur in the very early stages of depression and other major mental illnesses, this offers some time for making a correct diagnosis and effective acute and long-term treatment even before the first suicidal act.

Large-scale, retrospective, and prospective open-naturalistic and controlled long-term clinical studies, including severely ill, comorbid, frequently suicidal depressives (usually inpatients), have shown that appropriate acute and long-term pharmacotherapy (antidepressants in unipolar depression and mood stabilizers in bipolar disorder) markedly reduces suicide morbidity and mortality—and probable other forms of aggressive, violent behaviors—even in this high-risk population. Bipolar patients on mood stabilizers with or without antidepressants or antipsychotics, and unipolar depressives on antidepressants, show a 70 to 80 percent (range 56 to 93 percent) risk reduction of completed and attempted suicide compared to those without pharmacological treatment. Although long-term treatment with lithium and antiepileptic mood stabilizers results in a similar reduction in suicide mortality, lithium may have some superiority in preventing suicide. Register-based observational cohort studies also show that former inpatients with unipolar major depression who continued treatment with antidepressants, and former inpatients with bipolar disorder who continuously took mood stabilizers (lithium or antiepileptic mood stabilizers), had a markedly decreased rate of completed suicide compared with those who stopped taking antidepressants or mood stabilizers.

This marked antisuicidal potential of lithium seems to be more than the simple result of its episode-prophylactic effect, as it has been shown that during the long-term lithium prophylaxis of recurrent bipolar or unipolar affective disorder patients with at least one prior suicide attempt, a significant reduction in the number of suicide attempts was found not only in the excellent responders but also in moderate responders and in nonresponders. The clinical importance of this finding is that in the case of lithium nonresponse, when the patient has one or more suicide risk factor, instead of switching lithium to another mood stabilizer, the clinician should retain lithium (even on a lower dose) and combine it with another mood stabilizer. The well-documented strong antisuicidal effect of lithium in patients with bipolar and unipolar major mood disorder has also been supported by results derived from the general population: investigating the lithium levels in tap water and drinking water in Texas, Japan, Austria, and Greece, lithium levels were significantly and negatively associated with suicide rates. The evidence that suicide rates among depressed patients have progressively and significantly lowered through the first half “pretreatment era” (1900 to 1939), “ECT era” (1940 to 1959), and “antidepressant era” (1960 to 1992) also supports the suicide-preventive effect of antidepressants in depressed patients. As comorbid anxiety, agitation, and insomnia increase the short-term suicide risk for depressed patients, anxiolytics, atypical antipsychotics, and sleep-promoting drugs—mostly for short-term use—are also part of the therapeutic arsenal. Most recent findings show that ketamine, a glutamate antagonist, is a promising drug for rapidly reducing current suicide risk. Overall, the data reviewed here justify the claim that the increased use of antidepressants (and mood stabilizers) in the last two to three decades was an important contributor in reduced suicidal mortality in Canada, Australia, and most European countries.

Pharmacotherapy, however, is a necessary but not sufficient method of reducing suicidal behavior in depressed patients, and psychosocial interventions are always needed.
Psychoeducation and supportive psychotherapy are also always needed. There is some evidence that concurrent depression-focused psychotherapies, in combination with pharmacotherapy, also improve the compliance of patients and increase the effectiveness of pharmacotherapy and may therefore contribute to suicide prevention for patients with severe unipolar or bipolar disorders. The interaction between pharmacotherapy and psychosocial interventions is quite complex. It has been reported, for example, that successful episode-preventive medication with mood stabilizers in bipolar patients counteracted dysfunctional cognitions (including lowered self-esteem), and adjunctive cognitive therapy could help to optimize the long-term course of bipolar illness.

However, psychotherapy for depression alone is not enough for preventing depression-related suicide. A systematic review and meta-analysis show that there is little evidence for the assumption that suicidality in depressed patients can be reduced with psychotherapy for depression despite decreasing depressive symptomatology, indicating that in suicidal depressives psychotherapy and psychosocial interventions should be always combined with appropriate acute (and if necessary long-term) pharmacotherapy. Concurrent depression-focused psychotherapies, in combination with pharmacotherapy, also improve the compliance of patients and increase the effectiveness of pharmacotherapy, and may therefore contribute to suicide prevention for patients with severe recurrent unipolar or bipolar disorders. Both hopelessness–pessimism and aggressiveness–impulsiveness may be amenable to cognitive-behavioral therapy and pharmacotherapy (e.g., selective serotonin reuptake inhibitor (SSRI) antidepressants, lithium, and other mood stabilizers). As a significant part of depressives stop their medication in the first few weeks or months, aftercare of recently discharged depressive patients is essential for improving compliance and maintaining efficacy. The role of psychosocial interventions in suicide prevention is also supported by the World Health Organization (WHO) organized study of 1867 suicide attempters (many of whom should have current major depression) seen at emergency departments. A brief individual psychoeducational and psychosocial intervention before discharge and regular contact thereafter (eight telephone, postcard, or personal contacts during the 18-month follow-up) resulted in significantly fewer completed suicides (0.2 percent) in the intervention group ($n = 872$) than in the treatment as usual group ($n = 827$, 2.2 percent).

**Suicide Prevention in the Primary Care**

Despite the fact that more than two thirds of suicide victims contact different levels of health care (mostly GPs and psychiatrists) during last few weeks or months before their death, the rate of recognition of depression and adequate pharmacotherapy among depressed suicide victims is around 20 to 25 percent, which is disturbingly low. While the current prevalence of major mood disorders in the primary care practice is around 8 to 12 percent, many depressed patients are not recognized by their GPs. However, more recent studies reported much higher rates of recognition and treatment of depression in primary care practice (62 to 85 percent), and 33 to 50 percent of them were treated with antidepressants. Physician factors related to poor recognition of depression include lack of experience, insufficient or suboptimal knowledge about symptoms, treatment and good prognosis in treated depression, prejudices about mental illness, lack of postgraduate psychiatric training, insufficient interview skills, lack of cooperation with psychiatrists, and a low level of empathy. Although suicidal behavior is a relatively rare event in primary care, given that depression is quite frequent in GP practice and is very common among completed suicides, major depression, particularly in combination with past or current suicidal behavior, it should be taken very seriously even in primary care. Compared to nonsuicidal patients, suicide victims visit their GPs much more
frequently in the last 4 weeks of their life. Many physicians and even mental health care professionals avoid discussing suicide directly and frankly with patients for fear of provoking suicidal behavior or, more likely, because of personal discomfort. However, asking questions about suicidal ideation and past suicide attempts does not trigger suicide. This is particularly true if such a discussion is accompanied by some sentences explaining that depressive disorders can be successfully treated and that suicidal intent will vanish after (or even before) the recovery from depression. Asking simple questions (e.g., “What do you think about the future?” “Do you feel that life is not worth living?”) can easily facilitate further, more deep and honest discussion on the topic of suicide. This is beneficial, as many patients think they are alone or unique in their suicidal ideas. Leaflets, posters, and fliers left in the waiting room as well as providing appropriate websites indicating the symptoms, dangers, and treatable nature of depression and preventable nature of suicide are also beneficial.

Postgraduate training on better recognition and management of depressive disorders among psychiatrists and particularly in primary care appears to prevent suicide. The first example for the significant role of GPs in suicide prevention comes from the Swedish Gotland Study. The study demonstrated that after a short intensive postgraduate training for GPs on the island of Gotland on the diagnosis and treatment of depression, suicide rates and the number of depression-related hospital admissions declined significantly and antidepressant prescription increased markedly a few years after the training. The rate of depressive suicides among all suicides decreased significantly after the training, indicating that the decline in suicide mortality after the education resulted directly from a robust decrease in depressive suicides, and suggesting that this result might not be caused by random fluctuation or by other unknown factors. However, the decline in depressive suicides after the GP training had mostly been the result of a decline in female depressive suicides. Few suicidal males were known to the local medical services, although many of them were known to the police and social welfare services. The main reasons for this are that male depression is frequently masked by abusive, aggressive behavior, and males seek professional help less frequently than females. The favorable effects of the GP training faded after a few years, and repeated education again led to another decrease in suicides, again, mainly in females. Indeed, recent international data have supported the findings of the pioneering Gotland Study, also showing the importance of GPs as the front line in diagnosing and treating depression and in reducing suicide mortality. The community-intervention suicide prevention project in Hungary between 2000 and 2005 also showed that education of GPs and other health-care professionals as well as the public is an effective method of reducing suicide mortality. Similarly, a randomized-controlled study from Australia demonstrated that suicidal behavior during the 2-year follow-up period was lower for older persons treated by educated GPs as compared to control GPs. However, primary care education in isolation does not have any significant long-term effect on suicide mortality, and primarily complex, permanent, and multilevel educational and organizational interventions are useful. The multilevel community program should be based on the involvement and the strong collaboration with psychiatrists, GPs, gatekeepers, and media. The effect of these multilevel community suicide prevention programs has been demonstrated recently by the German Nuremberg Alliance Against Depression Study and the International European Alliance Against Depression Project, a multifaceted community-based action program against depression and suicide. Better management of depression requires not only improved recognition and treatment skills from the doctors but also good compliance from the patients, as nonadherence to antidepressant therapy is one of the most common causes of treatment failure. GPs should work in close and permanent collaboration with the local mental health services. Outpatient psychiatric consultation is also helpful in the cases of differential diagnostic problems, treatment
resistance, and comorbid substance use disorder regardless of whether the patient is suicidal or not. If long-term prophylactic pharmacotherapy is needed (bipolar disorder, recurrent unipolar major depression), then the GP may direct the patient to a psychiatrist for optimizing the therapy. Although depressive disorders represent an important target for suicide prevention in old age, there should be increased attention also for psychosocial and somatic-medical risk factors in this age range.

Regular aftercare with fixed appointments is highly recommended, particularly for those patients with previous suicide attempts. Psychological support should be available for each suicidal depressed patient. This is important because the actual clinical picture immediately after suicide attempt is often misleading, due to the cathartic effect of self-aggression, resulting in a short-lived but sometimes marked improvement in the depression. This can also serve as one of the explanations why some health care workers misinterpret suicide attempts as manipulative acts.

Health care professionals, of course, are unable to prevent all suicides, including those occurring in the context of patients with mood disorders. Nevertheless, the current theoretical knowledge and the available treatment and preventive strategies are sufficient to prevent many, probably most of them. The most important methods of suicide prevention in patients with mood disorders are shown in Table 13.6–2.

Table 13.6–2. Suicide Prevention Strategies in Patients Mood Disorders

<table>
<thead>
<tr>
<th>A. Eliminating acute suicide danger (physical inhibition, emergency hospitalization, sedation, anxiolysis, crisis-intervention)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Improving the early diagnosis and treatment of mood disorders with particular regard to the soft (subthreshold) clinical manifestations of bipolar disorder</td>
</tr>
<tr>
<td>1. Education of health care workers, patients, relatives and gatekeepers (clergymen, policemen, teachers, social workers, peer-helpers, etc.)</td>
</tr>
<tr>
<td>2. Adequate acute and long-term treatment aftercare (pharmacotherapy, nonpharmacological interventions such as psychoeducation, psychotherapy, cognitive therapy, family counseling and family therapy, regular long-term care, regular contact, etc.)</td>
</tr>
<tr>
<td>C. Improving the patients’ compliance (psychoeducation, psychotherapy, cognitive therapy, etc.)</td>
</tr>
<tr>
<td>D. Educating the public via printed and electronic media, including the Internet</td>
</tr>
<tr>
<td>1. Educating about the symptoms, dangers, and treatable nature of mood disorders and the preventable nature of suicidal behavior</td>
</tr>
<tr>
<td>2. Reducing the stigma against mood disorders and suicide</td>
</tr>
<tr>
<td>3. Providing information on how and where to get help in the case of mood disorder and suicide crisis</td>
</tr>
</tbody>
</table>

However, as health and social care workers can only help those who contact them, public education media campaigns on symptoms, dangers, treatability, and referral pathways are vitally important. As psychosocial and community factors also play an important role in suicide, it is not only health care workers that are responsible for its prevention. All members of the society have their own task, major or minor, and entailing more or less responsibility, in addressing this issue. However, prevention of mood disorder–related suicidal behavior is primarily the duty of psychiatric and primary health care. On an aggregate level, however, organization and societal changes (e.g., the improvement in a primary health care system, empowerment strategies in the workplace, and community or the alleviation of unpredictability and stressful transitions in a society) seem to reduce increased suicide figures. To reduce suicide mortality the following must be done: improve the well-being of
people in general (including decreasing unemployment and providing more support for health and social services); restrict lethal suicide methods whenever possible (e.g., reduce domestic and car exhaust gas toxicity and introduce stricter laws on gun control); and finally, initiate more restrictive alcohol and drug policies, which also reduces suicide mortality. These are the responsibilities of the health care system and all of society.

REFERENCES


Nordentoft M, Mortensen PB, Pedersen C. Absolute risk of suicide after first hospital contact in mental disorder. *Arch Gen Psychiatry*. 2011;68:1058.


INTRODUCTION

Mood disorders comprise two separate chapters in the DSM-5: “Depressive disorders” and “Bipolar and Related Disorders.” Among the major changes, mixed episode as a diagnostic entity was eliminated and a course specifier “with mixed features” has been added for both major depressive episodes and manic/hypomanic episodes. Interestingly, this allows an individual with an major depressive episode with three or more (hypo)manic symptoms and no prior manic/hypomanic episodes to remain within the major depressive disorder domain, rather than be classified as a forme fruste of bipolar disorder. Other changes within the depressive disorders chapter are the inclusion of disruptive mood dysregulation disorder (DMDD) and premenstrual dysphoric disorder as new diagnoses, and the replacement of chronic depression and dysthymia with a single diagnostic entity—persistent depressive disorder (PDD). The essential feature of PDD is depressed mood and at least two depressed symptoms present for 2 years or more (1 year for children or adolescents). There is still the possibility that major depressive episodes may occur intermittently (double depression).

Abnormally and persistently increased goal directed activity or energy has been added to the stem criterion for a manic/hypomanic episode. Further, manic/hypomanic episodes emerging during antidepressant treatment are considered to be indicative of bipolar disorder, provided that the symptoms persisted beyond the physiological effects of treatment. The “not otherwise specified” (NOS) category has been replaced with “other specified depressive disorder,” “other specified bipolar and related disorder,” and “unspecified bipolar and related disorder.”

Unfortunately, there are limited systematic treatment data for new disorders such as disruptive mood dysregulation disorder and other specified depressive or bipolar disorder or unspecified bipolar disorder. Therefore, the main focus of this chapter will be on the treatment of major depressive disorder and bipolar disorder.

TREATMENT OF MAJOR DEPRESSIVE DISORDER

Major depressive disorder is typically a disorder of recurrent depressive episodes rather than a single episode. Several treatment options are available for managing patients with major depressive disorder and the list of treatments continues to expand, although the progress in identifying search for novel strategies has been slow. This section will provide an outline of foundations of the management of major depressive disorder and provide guidance to clinicians on selection of first-line antidepressants, and the next steps if first-line treatments fail. The reader is referred to other chapters in this book for the management of major depressive disorder during pregnancy and postpartum period, and the management of major depressive disorder in children and adolescents and elderly.
FOUNDATIONS OF MANAGEMENT

Address Acute and Maintenance Treatment

Effective management of the major depressive disorder requires a focus on both acute and maintenance aspects of the disorder from the outset (see Table 13.7–1). While some authors differentiate continuation and maintenance phases after the acute treatment phase, there is limited evidence to support this differentiation. The primary goal in the acute phase is to achieve remission—a state that comes close to being symptom free (typically remission represents a score of ≤7 on the Hamilton Rating Scale for Depression (HAM-D) or ≤10 on the Montgomery-Asberg Depression Rating Scale [MADRS]). Since failure to achieve remission is associated with a higher risk of recurrence, this has replaced the previously accepted treatment aim of response, defined as a reduction of ≥50 percent on one of the above scales.

Table 13.7–1. Phases of Antidepressant Treatment

<table>
<thead>
<tr>
<th>Treatment Phase</th>
<th>Duration</th>
<th>Goals</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute and continuation</td>
<td>8–12 weeks</td>
<td>Achieve symptomatic remission</td>
<td>Establish therapeutic alliance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor side effects</td>
<td>Provide psychoeducation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Restore function</td>
<td>Select optimal antidepressant treatment(s)</td>
</tr>
<tr>
<td>Maintenance</td>
<td>6–24 months or longer</td>
<td>Return to full function and quality of life</td>
<td>Supportive and measurement-based care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevention of recurrence</td>
<td>Monitor progress</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continue psychoeducation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rehabilitate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Manage comorbidities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monitor for recurrence</td>
</tr>
</tbody>
</table>

Included in the psychiatric assessment, it is important to assess anxiety symptoms, substance use, suicidality, psychotic features, bipolarity, and other psychiatric comorbidities, as well as conduct a careful assessment of physical health, psychosocial, functional factors, and concurrent prescription medications. Details of prior treatment response are also valuable in guiding future treatment decisions.

During the acute phase of treatment, it is also important to monitor comorbid conditions and tailor the treatment appropriately to individual needs. Reports on psychiatric comorbidity indicate that anxiety disorders (60 percent), substance use disorders (25 percent), and impulse control disorders (30 percent) are highly prevalent among patients with lifetime major depressive disorder diagnosis. There is also a bidirectional relationship between major depressive disorder and physical health. Individuals with prior depressive episodes have high risk of medical disorders including heart disease and diabetes, while patients with medical disorders, including cardiovascular and stroke disease, chronic pain, obesity, diabetes, epilepsy and other central nervous system (CNS) disorders, and cancer have two to fourfold increases in risk of major depressive disorder.

Although symptomatic improvement/remission has been the traditional goal for the treatment of depression, it is increasingly recognized that improvement in function (e.g., return to work or other meaningful activities) and overall quality of life are most valued by patients. It is
important to listen to the apprehensions and expectations of patients and provide education about depression and treatment options. Many patients will also have searched the Internet for information and will welcome a chance to discuss the materials they have downloaded. These discussions are likely to recur during ongoing supportive care and it is important to establish good rapport at the initial visit.

Since many depressed patients have medical comorbidities, requiring a range of pharmacotherapies, and frequently receive more than one antidepressant medication, it is essential to consider the risk of drug–drug interactions. Most antidepressant-related interactions are associated with cytochrome (CYP) P450 or P-glycoprotein effects. Examples include the potent inhibitory effects of fluoxetine and paroxetine on CYP2D6 that can elevate serum levels of co-administered drugs including beta-blockers. Paroxetine and sertraline are also potent inhibitors of P-glycoprotein that may elevate levels of digoxin, calcium channel blockers, and some chemotherapy drugs. Web-based drug interaction checkers are readily available.

Regular follow-up appointments are important, particularly in the first 2 to 3 months. The first follow-up visit should generally be 2 weeks after initiating treatment, although high-risk patients with suicide intent or psychotic features should be seen sooner and more frequently. Each visit should include an assessment of symptom change, side effects, and function, as well as an evaluation of psychosocial stressors and supports. There is evidence to suggest that patients who do not obtain at least a 20 percent reduction on a standard symptom rating scale, such as the HAM-D by 2 weeks, have a worse outcome compared to those who do show early symptom reduction. In practical terms, this supports a dose adjustment or confirmation of treatment adherence after 2 to 4 weeks visit.

Although some patients may achieve remission early in the course of treatment (2 weeks or less), the majority of those who do remit will do so after 6 to 8 weeks. Typical rates of remission are between 30 to 40 percent with most antidepressants and response rates are generally in the 50 to 65 percent range, for patients who are not considered treatment resistant.

Consider Measurement-Based Care

Traditionally, the use of clinician-rated scales to evaluate outcomes in the treatment of major depressive disorder has been restricted to clinical trials and other research protocols. More recently, brief clinician-administered and patient self-report measures have been introduced into routine clinical practice (measurement-based care). The advantages of administering a rating scale include longitudinal monitoring and the opportunity to refer to previous evaluations in clinical discussions about areas of improvement or deterioration. However, some clinicians are still reluctant to quantify symptom severity during their time with a patient and feel this detracts from the therapeutic relationship.

Several clinical instruments are readily available and completion times range from 5 to 20 minutes depending on the scale length. Abbreviated versions such as the HAMD-7 item scale are also available. The Patient Health Questionnaire (PHQ-9) is a self-report scale containing the nine items listed in DSM-5, rated according to their frequency of occurrence. An alternative is the Quick Inventory for Depression Symptomatology (QIDS), which is available in both observer-rated and self-report forms. Two easy to administer scales that evaluate functional outcomes are the Sheehan Disability Scale (SDS) and the Lam
Employment Absence and Productivity Scale (LEAPS). An emerging trend involves the use of smart phones or other personal devices to provide remote data capture of objective measures such as sleep–wake patterns, body temperature, or physical activity.

Evaluate Adherence

Adherence is a pivotal component of any therapy. Unfortunately, many patients neglect to take their medication on a frequent basis, missing doses for days or weeks, or discontinuing altogether. This increases the risk of relapse or recurrence. “Forgetting” to take medication as prescribed is more likely to occur as patients begin to feel better and about 50 percent admit to decreased adherence by 3 months. On the positive side, there is evidence that adherence improves in the weeks leading up to and just after a follow-up appointment. Although not currently a routine practice, plasma monitoring of antidepressant blood levels provides an additional method to assess adherence. There is also evidence that a brief telephone contact to monitor symptoms and side effects early in the course of treatment improves adherence and ultimately outcome.

ANTIDEPRESSANT TREATMENT STRATEGIES

Recognize First-, Second-, and Third-Line Approaches

Selecting an antidepressant should reflect a balance between physician judgment and patient preference, taking into account symptom profile, past history of treatment response and tolerability, potential for drug-drug interactions, and in many instances, cost. First-line antidepressants include SSRIs, SNRIs, other second generation, and novel antidepressants. These agents have comparable efficacy but superior tolerability to the first-generation MAOI and tricyclic antidepressant (TCA) agents, which are considered third-line treatments for major depressive disorder. Second-line options include novel antidepressants and adjunctive treatments. Although there are very few direct comparisons of effectiveness/efficacy and tolerability among antidepressants, two major studies contribute most information on treatment outcomes. Combining knowledge from these trials with course specifiers for individual patient episodes of depression can help to refine treatment selection.

Comparative Antidepressant Studies. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) is the largest published effectiveness trial to evaluate sequential monotherapies and adjunctive antidepressant treatment strategies. It includes medications from each of the above drug classes over four sequential stages in approximately 3,000 patients starting with citalopram in Phase I, with remission as the primary outcome measure. Based on the QIDS scale, 33 percent of those in Phase I achieved remission and 47 percent achieved response. Those who did not achieve remission were eligible to enter the second phase of treatment. In this phase, one arm involved a comparison of switching to another SSRi (sertraline); an SNRI (venlafaxine); bupropion, or CBT. The second arm of Phase II evaluated adjunctive treatment with bupropion, buspirone, or CBT. Despite the large initial sample size, the number of subjects evaluated in the third and fourth phases was substantially smaller and it is difficult to draw conclusions about the relative effectiveness of TCA, MAOI, and other adjunctive strategies. Overall, STAR*D highlighted the relatively low rate of remission (approximately 30 percent) following an adequate trial of citalopram. In addition, the study did not support conventional thinking that switching to a different drug class (e.g., from SSRI to SNRI) following failure with an SSRI was superior to switching within the same class. There was also no difference in outcomes between switching and adjunctive
treatment strategies. While the time to achieve remission was longer in those who received CBT, the overall rates of remission did not differ significantly from pharmacotherapy strategies. STAR*D also highlighted the marked reduction in remission rates after two consecutive trials, and the high rates of dropout after each phase.

Among meta-analyses, the most influential study involved a multiple comparisons network meta-analysis of 12 second-generation antidepressants from 117 published trials that collectively included almost 26,000 participants. To incorporate all trials, the authors accepted different severity rating measures (HAM-D, MADRS, and Clinical Global Impression) with “response” as the primary efficacy outcome. The percentage of patients dropping out was a proxy for intolerability. Escitalopram, mirtazapine, sertraline, and venlafaxine were ranked as the top four antidepressants for efficacy, although escitalopram and sertraline were preferred when tolerability and efficacy rankings were combined. While sample size was a major strength in this study, methodological differences across trials may have influenced conclusions. Other meta-analyses suggest comparable efficacy between bupropion and SSRIs, as well as superiority for escitalopram compared to other SSRIs. However, many have argued that differences among first-line antidepressants are minimal.

**Course Specifiers for Depressive Episodes.** Course specifiers for depressive episodes may also provide some guidance for treatment selection. In the case of anxious distress (tense, restless, fearful, etc.), it would be preferable to select an antidepressant with established efficacy in the treatment of generalized anxiety disorder (GAD). There is also evidence that patients who display melancholic features (specifically anhedonia and lack of reactivity) may have a different response to current first-line antidepressants (e.g., SNRI and SSRI) compared to those with nonmelancholic features. Patients with atypical features (preservation of mood reactivity, hypersomnia, hyperphagia, weight gain, and a heightened sensitivity to interpersonal rejection) were historically thought to respond better to MAOIs, but it appears that current first-line antidepressants are all equally effective for patients with atypical features. Two specifiers that are most likely to influence treatment selection are with seasonal pattern, where light therapy is recommended at least as an adjunctive treatment, and with mood congruent or mood incongruent delusions, where either an antidepressant/antipsychotic combination therapy or ECT is recommended.

An additional specifier in DSM-5 is major depressive disorder with mixed features. This requires at least two of the hypo(hypomania) criteria (e.g., grandiosity, expansive mood, and pressured speech) but without meeting full criteria for (hypo)mania. Currently, it is unclear whether patients within this subtype will remain as patients with major depressive disorder or cross over to meet criteria for bipolar disorder. Lurasidone is an appropriate first-line therapy currently for such patients given the evidence from a recent clinical trial that showed improvement in both depressive and hypomanic symptoms in patients with major depressive disorder with mixed features.

**Select a First-Line Antidepressant.** Early in the course of treatment, most clinicians would select a first-line agent from SSRI, SNRI, other second-generation or novel drug classes. While overall efficacy is likely similar among these agents, differences in their receptor pharmacology and the adverse event profile may aid the clinician in treatment selection. For instance, the SSRI antidepressants share blockade of the serotonin (5HT) transporter as their common mechanism of action, but they differ in their actions on additional receptors. Differences among SNRI antidepressants are even more distinct. Venlafaxine, duloxetine, and desvenlafaxine preferentially block the 5HT transporter, while levomilnacipran
predominantly blocks the norepinephrine (NE) transporter. These differences in transporter and receptor affinities make some antidepressants more activating (e.g., bupropion) and others more sedating (e.g., mirtazapine). These differences may allow clinicians to tailor the selection of antidepressants for individual patients to increase acceptability, regardless of the fact that the efficacy may be similar.

Another major consideration when choosing an antidepressant is the side effect profile of the drug and patient sensitivity to side effects. Gastrointestinal and sexual side effects are particularly common with SSRIs, while patients with pre-existing hypertension may be more prone to further elevation in blood pressure with an SNRI such as venlafaxine. Prolongation of QTc interval has also been noted at higher doses with various antidepressants, including citalopram. The relative frequencies of side effects associated with SSRIs and SNRIs are listed in Table 13.7–2. Clinicians need to be vigilant for the emergence of hypo(manic) symptoms during treatment with antidepressants, particularly in patients with a family history of bipolar disorder and in those who display reverse vegetative symptoms as a part of a major depressive episode. It is prudent to offer information about hypo(manic) symptoms to such patients and advise them to make an early appointment for assessment if they experience these symptoms. The risk of antidepressant-induced mood elevations in patients who meet criteria for a major depressive episode with mixed features in the context of major depressive disorder is likely higher, and hence such patients also need to be educated and monitored closely.

An increase in reported suicidal ideation in adolescents and young adults during antidepressant clinical trials resulted in “black box warnings” about prescribing SSRIs and other antidepressants to this age group. However, the relationship between increased suicidal ideation and completed suicide remains controversial (see Table 13.6–2). Other rare but serious adverse effects of antidepressants include the 5HT syndrome, increased upper gastrointestinal bleeding (particularly when antidepressants and nonsteroidal anti-inflammatory agents are coprescribed); hyponatremia has also been of concern, especially in elderly depressed patients, and there is a reduction in seizure threshold with most antidepressants, particularly bupropion.

Some second-generation antidepressants with unique mechanisms of action also have noradrenergic effects. Bupropion is both an antidepressant (Wellbutrin) and a medication for smoking cessation (Zyban) with predominantly noradrenergic and dopaminergic effects. It is an activating antidepressant; hence, it is frequently prescribed in combination with a more sedating 5HT enhancing antidepressant. Mirtazapine promotes release of both 5HT and NE through blockade of α2-noradrenergic receptors. It has a sedating profile and is often prescribed to depressed patients with severe insomnia. Mirtazapine is also associated with weight gain. Trazodone is another antidepressant with dual effects on 5HT and NE receptors. Because of its highly sedating properties, it is more often prescribed at subtherapeutic antidepressant doses (50 to 100 mg) as a hypnotic. Nefazodone has a similar mode of action to trazodone with additional NE transporter blocking effects. Despite a favorable efficacy profile, reports of life-threatening hepatotoxicity have resulted in the virtual discontinuation of its use. Moclobemide is a reversible MAO-AI that may be prescribed to treat major depressive disorder without dietary precautions, although it is not available in the United States. For a list of additional side effects, see Table 13.7–2).
Table 13.7–2. Prevalence of Side Effects among Selective Serotonin-Reuptake Inhibitors and Serotonin- and Norepinephrine-Reuptake Inhibitors

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Recommended Dose Range (mg)</th>
<th>Side Effect Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>20–40</td>
<td>Nausea, dry mouth, sweating</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10–20</td>
<td>Male sexual dysfunction and nausea</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20–60</td>
<td>Nausea, dry mouth, somnolence, nervousness, anxiety, insomnia, tremor, anorexia</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>100–300</td>
<td>Dry mouth, headaches, somnolence, agitation, insomnia, sweating, tremor, anorexia, dizziness, constipation</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20–60</td>
<td>Nausea, diarrhea, dry mouth, headaches, somnolence, insomnia, sweating, asthenia, male sexual dysfunction, dizziness</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50–200</td>
<td>Nausea, diarrhea, dry mouth, headaches, somnolence, insomnia, fatigue, tremor, male sexual dysfunction, dizziness</td>
</tr>
<tr>
<td><strong>SNRI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75–375</td>
<td>Headaches, somnolence, dry mouth, dizziness, nervousness, insomnia, sweating, male sexual dysfunction</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>50–100</td>
<td>Dry mouth, dizziness, nausea, sweating</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30–120</td>
<td>Nausea, dry mouth, constipation, insomnia, male sexual dysfunction</td>
</tr>
<tr>
<td>Levomilnacipran</td>
<td>20–80</td>
<td>Nausea, dry mouth, headaches, male sexual dysfunction</td>
</tr>
</tbody>
</table>

**Other Second-Generation and Novel Antidepressants**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Recommended Dose Range (mg)</th>
<th>Side Effect Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agomelatine*</td>
<td>25–50</td>
<td>None</td>
</tr>
<tr>
<td>Bupropion</td>
<td>150–450</td>
<td>Insomnia, dry mouth, nausea</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>15–60</td>
<td>Dry mouth, constipation, increased appetite, weight gain</td>
</tr>
<tr>
<td>Moclobemide*</td>
<td>300–600</td>
<td>None</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>10–40</td>
<td>Diarrhea, nausea, headaches</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>10–20</td>
<td>Nausea</td>
</tr>
</tbody>
</table>

**Novel Antidepressants.** In addition to the SSRI, SNRI and other “second generation” antidepressants, a number of new antidepressants with additional modes of action are available in many countries to treat depression. Vilazodone is an SSRI with additional 5HT-1A partial agonist effects. This mimics the effect of combining a 5HT-1A partial agonist, such as buspirone, with an SSRI. Favorable aspects of the drug include low rates of sexual side effects, lack of cardiac arrhythmias, and minimal weight gain. Vortioxetine is also a 5HT transporter blocker, with additional receptor effects including 5HT3 and 5HT7 antagonism, as well as 5HT1A and 5HT1B agonism. During the clinical trial development program, measures of cognition including executive function, verbal learning, memory, and processing speed were evaluated and found to be significantly improved. Agomelatine is available in Europe, South America, and many other countries as an antidepressant, but is not available in North America. The mode of action of this antidepressant involves agonism of melatonin-1 and melatonin-2 receptors, combined with 5HT-2C antagonism. There are no direct effects on the 5HT system, although 5HT-2C antagonism facilitates release of dopamine in the
prefrontal cortex and may account for its favorable effect on anhedonia and minimal sexual side effects.

**Inadequate Response to First-Line Treatments: Next Steps**

When a patient has received at least 4 to 6 weeks of treatment with a first-line antidepressant and shown no improvement despite a dose increase, the following options should be considered: (i) further dose increase, particularly when the medication appears to be well tolerated; (ii) switching to a different antidepressant within the same or a different class; and (iii) adjunctive therapy with an established agent such as an atypical antipsychotic, lithium, triiodothyronine or a second antidepressant with a different neurotransmitter action (e.g., bupropion added to an SSRI).

**Consider Optimizing before Switching.** Usually the first step is dose optimization, particularly when the drug is well tolerated at a relatively low therapeutic dose or if past treatment history suggests tolerance for high doses of other medications. Extending the initial trial beyond 4 to 6 weeks is indicated if there is an incremental but slow improvement during the first 4 weeks.

Potential advantages of switching from one monotherapy to another are cost, single side effect profile, and simpler dosing regimen. These factors are likely to be associated with improved adherence, when compared to adjunctive treatment regimens. Two clinician-monitored methods for switching monotherapies are typically used. The first requires a complete tapering of the initial drug before starting the second drug. This is known as the “V-method.” The second “X-method” involves a gradual tapering of the initial drug, while the second drug is introduced, resulting in a cross over process. This method minimizes discontinuation-emergent symptoms, and is preferred when there are similar pharmacodynamic drug profiles (e.g., switching from one SSRI to another or from an SSRI to an SNRI); however, it should not be used when the potential for a hazardous drug–drug interaction exists (e.g., switching from an MAOI drug to a TCA or SSRI).

**Apply Adjunctive Strategies.** In clinical practice, the majority of adjunctive treatments are administered sequentially, with the second agent being added only after the first has been ineffective or partially effective. This second-line approach was used at several stages in the STAR*D trial. In a few studies, concurrent combined treatments have been initiated from the outset with inconclusive results. Until there are specific indications for this approach, sequential adjunctive treatments are generally preferred.

Several agents, not primarily indicated for the treatment of depression, including lithium, triiodothyronine (T3), and atypical antipsychotics, are frequently used adjunctively with existing antidepressants. Most studies of lithium involve augmentation of TCAs and the daily dose varied widely (250 to 1,200 mg); nevertheless, two recent meta-analyses support the efficacy of lithium. There is also limited support for the use of T3 at a dose of 25 to 50 μg/day as an augmentation strategy. At the third level of STAR*D, lithium and T3 both produced modest increases in remission. Buspirone, a partial postsynaptic 5-HT1A agonist, was also evaluated in the STAR*D trial and was comparable in effectiveness to bupropion in some but not all outcome measures in the augmentation of citalopram.

There is a large body of evidence to support the adjunctive use of atypical antipsychotics in the treatment of major depressive disorder and also in treatment-resistant depression (TRD).
Although they share a common dopamine D2 antagonist action, atypical antipsychotics differ in their affinities for D2 and other receptors. This supports switching from one atypical agent to another in the absence of a favorable response or if adverse effects of the first atypical are intolerable. Based on a series of studies, the combination of olanzapine and fluoxetine demonstrated superiority over either agent alone for TRD. The only SSRI involved in these trials was fluoxetine, but it is likely that olanzapine (5 to 10 mg) would also be effective when combined with other antidepressants. Quetiapine (150 to 300 mg) is the only atypical agent to demonstrate antidepressant efficacy as monotherapy in the treatment of major depressive disorder and is also effective when combined with a range of antidepressants in previously treatment-resistant patients. Augmentation with risperidone was efficacious in two double-blind, placebo-controlled trials. Aripiprazole (5 to 15 mg) has been shown to be an effective adjunctive therapy in major depressive disorder, where response and remission rates were double the rates in those who received “add-on” placebo. Interestingly, patients who either worsened or failed to improve with a first antidepressant treatment still showed significant benefit with adjunctive aripiprazole. Adjunctive treatment with ziprasidone in a TRD trial was not significantly better than continuation of the SSRI (sertraline), supporting the view that atypical antipsychotic adjunct efficacy is not a class effect but depends on the individual receptor profiles of each agent. Although atypical antipsychotics provide a valuable additional treatment option for TRD, their potential to cause serious side effects, including weight gain, dyslipidemia, hyperglycemia, extrapyramidal symptoms and QTc interval prolongation, is of concern, particularly when long-term treatment is anticipated. An unanswered question is how long to continue any adjunctive agent particularly when the additional therapy carries a hazardous side effect burden (e.g., weight gain or hyperlipidemia).

Other strategies to consider when patients have failed to respond to the above strategies include the addition of psychotherapy, with most evidence supporting CBT or modified versions such as cognitive behavioral analysis systems psychotherapy. ECT is very effective in antidepressant treatment refractory patients with response rates as high as 70 percent. ECT also remains an established treatment of certain groups of depressed patients, particularly those with acute suicidal ideation or with mood congruent or incongruent delusions. Other neurostimulation approaches including repetitive transcranial magnetic stimulation (rTMS) and vagal nerve stimulation may also be considered as adjunctive treatments.

**Consider Third-Line Antidepressants**

Both tricyclic and MAOI antidepressants are restricted in their use today because of tolerability and safety concerns. Amitriptyline, the most evaluated TCA, has mixed reuptake inhibition effects on both 5HT and NE transporters with additional cholinergic, histaminergic, serotonergic, and noradrenergic receptor actions. These multiple effects are responsible for the wide range of side effects including sedation, weight gain, urinary retention, and cardiac conduction defects. Nortriptyline is a metabolite of amitriptyline that is often used to treat late-life depression and has a less extreme side effect profile. Imipramine, desipramine, and clomipramine are also TCAs that are typically reserved for third-line use, although clomipramine is indicated for the treatment of OCD and not major depressive disorder in the United States. In all cases, plasma monitoring may be helpful in determining appropriate doses.

Tranylcypromine, phenelzine, and isocarboxazid are irreversible inhibitors of both MAO-A and MAO-B. While this mode of action provides a broad-spectrum inhibition of monoamine
reuptake and a favorable antidepressant effect, it also increases the risk of orthostatic hypotension, and in the presence of tyramine-rich foods may produce a life-threatening hypertensive crisis. This necessitates a low tyramine diet during MAOI treatment. Hence, these agents are generally reserved for otherwise treatment-resistant patients. Selegiline is an irreversible inhibitor of MAO-B that has been used as an adjunct therapy for Parkinson disease and is available in both oral and transdermal patch delivery systems to treat major depressive disorder. Its use is generally restricted to TRD patients.

**Recognize Experimental Antidepressant Options**

Evidence has emerged that ketamine, given intravenously, provides a rapid but transient antidepressant response, even in formerly treatment-resistant depressed patients. Similar preliminary results have been reported for nitrous oxide. Both novel treatments support the growing interest in glutamate and NMDA receptors in the pathophysiology of depression. Similarly, evidence that proinflammatory cytokines such as interleukin 1 (IL-1) and IL-6 are frequently elevated in depression has stimulated interest in the potential role of anti-inflammatory agents as antidepressants. Celecoxib, minocycline, and infliximab are examples of anti-inflammatory agents with potential antidepressant properties. So far these remain experimental treatments, as does deep brain stimulation (DBS) to targeted brain areas.

**MAINTAINING REMISSION**

**Address Risk Factors for Relapse and Recurrence**

The primary aim of maintenance treatment is to prevent the occurrence of a new episode (recurrence). It is appropriate for patients with major depressive disorder who have experienced recurrent episodes or PDD but not following a single-episode major depressive disorder. Maintenance medication is more effective than placebo in virtually all studies to date. Given the high rate of relapse for individuals who have had three or more episodes, they should receive prolonged maintenance therapy.

Patients who consistently relapse following antidepressant discontinuation, those with recurrent psychotic episodes, persistent residual symptoms, or a strong family history of mood disorders should be considered as candidates for prolonged maintenance therapy. In any case, clinicians and patients need to decide collaboratively whether to initiate maintenance treatment or to maintain contact and rapidly reinstate treatment if there are emergent symptoms. If a new episode develops when the patient is free of treatment, then early intervention shortens the length of the new episode. There are virtually no data to suggest when to discontinue maintenance medication, although a study examining the impact of discontinuing venlafaxine after either 1 year or 2 years of maintenance treatment supported the benefits of longer-term treatment. When the decision to discontinue treatment is made, careful monitoring is required, particularly for the first 6 months as this is a high-risk period for recurrence.

**TREATMENT OF BIPOLAR DISORDERS**

The discovery of the utility of atypical antipsychotics and some anticonvulsants such as valproate and lamotrigine for bipolar disorder in the 1990s heralded a new era in the pharmacological treatment of bipolar disorder. The availability of several newer treatments for the management of bipolar disorder has presented clinicians with options to tailor the
treatment to suit individual patient needs based on the efficacy, adverse events, and patient preferences. The past two decades have also witnessed significant progress in understanding the adjunctive role of psychological treatments in managing bipolar disorder.

This section will address the foundations of the management of bipolar disorder and specific treatment options for the management of mania, bipolar depression, and prophylaxis of bipolar disorder. Clinical recommendations are provided for the management of each phase of bipolar disorder with guidance on first-, second-, and third-line choices, but it is important to acknowledge that these recommendations are mainly applicable for bipolar I disorder. This section also covers briefly the management of bipolar II disorder as well as the management of comorbidity in bipolar patients. The reader is advised to refer to other sections in the book for managing bipolar disorder during pregnancy and postpartum period as well as in children and adolescents and older adults.

FOUNDATIONS OF MANAGEMENT

Diagnose and Intervene Early

Although mania is the defining feature of bipolar I disorder, depressive episodes and subsyndromal depressive symptoms are more common in bipolar I disorder. Indeed, prospective cohort studies suggest that patients with bipolar I disorder spend more time (a ratio of 3:1) experiencing depressive episodes/symptoms than manic episodes/symptoms. Depressive symptoms are even more problematic for bipolar II patients as they spend 37 times more days experiencing depressive symptoms than hypomanic symptoms.

Given this, patients with bipolar disorder are more likely to seek help when they are depressed and often do not volunteer information about previous manic/hypomanic episodes. Hence, clinicians must be vigilant to the possibility of bipolar disorder in every patient presenting with depressive symptoms. Studies suggest that about two-thirds of patients with bipolar disorder are misdiagnosed initially, and major depressive disorder is the most common misdiagnosis. While screening instruments such as the Mood Disorders Questionnaire are useful, they do not replace a thorough clinical assessment that systematically probes for previous history of manic/hypomanic symptoms. Clinicians should have a high index of suspicion for a diagnosis of bipolar disorder in patients presenting with a history of substance abuse (e.g., cocaine or alcohol), family history of bipolar disorder, or reverse vegetative symptoms (e.g., anergia, hypersomnia, and hyperphagia) and/or psychotic features as a part of depressive episode.

Early intervention has the potential to improve outcomes in bipolar disorder. Indeed, studies in first episode mania patients suggest that those that remain episode free after their first manic episode show improvements (reversal of cognitive deficits) in cognitive functioning and minimal decline in age-related gray matter volumes.

Conduct Systems Review, Baseline Investigations, and Implement Safety Monitoring for Psychotropic Medication

In addition to obtaining a comprehensive psychiatric history to diagnose bipolar disorder, clinicians are advised to conduct a systems review of medical history with particular attention to personal and family history of cardiovascular, endocrine, and metabolic disorders as the incidence of medical comorbidities is higher in bipolar patients compared with general
population. Many psychotropic medications have a tendency to cause weight gain and some cause metabolic syndrome and therefore, it is important to conduct some baseline laboratory investigations and obtain weight and waist circumference either before when possible or within few days of the initiation of specific pharmacotherapy (see Fig. 13.7–1. for details) for bipolar disorder. Patients that require treatment with some psychotropic medications such as lithium or valproate need additional specific lab investigations prior to initiating treatment. During the follow-up visits, clinicians are advised to routinely monitor for medication-induced adverse events at each scheduled clinical follow-up and institute appropriate strategies to address them. Patients should have weight, appropriate laboratory investigations, and serum levels of lithium or valproate measured at regular intervals as outlined in Fig. 13.7–1.

**Treat the Disorder and Not Just Acute Episodes**

Pharmacotherapy is the cornerstone of the management of bipolar disorder. When initiating treatment of acute episodes, while stabilization of acute episodes is the immediate goal, it is essential for clinicians to bear in mind that bipolar disorder is a recurrent illness, and hence prevention of further mood episodes is an equally important consideration in treatment selection. Therefore, when choosing a medication to treat an acute episode, those that have proven efficacy in treating not only the index episode but also in preventing the recurrence of both manic and depressive episodes should be considered first before selecting the medications that have efficacy for only acute episodes. There is growing consensus that mood episode recurrences are “toxic” to the brain and are associated with cumulative reductions in brain volumes, lower brain-derived neurotrophic factor (BDNF) levels, cognitive impairment, and poorer response to pharmacotherapy, and thus prevention of recurrence of mood episodes is paramount in the management of bipolar disorder. Consensus is growing that prophylaxis should be offered for all patients with bipolar I disorder including for those after the first manic episode as prospective naturalistic cohort studies suggest that 60 to 75 percent of first episode manic patients experience a recurrence within 4 years. Adjunctive psychological treatments such as psychoeducation promote treatment adherence and reduce the risk of relapse of mood episodes in bipolar patients, and hence should be initiated as soon as the patient is amenable to such strategies.

**Treat Acute Episodes to Full Remission**

Acute manic, hypomanic, and depressive episodes must be treated to full and sustained remission. This is because several studies now suggest that residual subsyndromal mood symptoms not only significantly affect quality of life and functioning but also strongly predict relapse of subsequent full-blown mood episodes. Patients who recovered from an index mood episode with residual mood symptoms experience a new episode 3.4 times faster than those that recovered from an index episode with no residual symptoms. Median time to recurrence of a mood episode is five times faster in those with residual symptoms compared with those with full recovery from an index episode.
Assess for and Treat Comorbidities

Psychiatric and physical comorbidities are common in bipolar disorder. While the estimates of the prevalence vary, at least 75 percent of patients with bipolar disorder have at least one lifetime comorbid psychiatric disorder. Alcohol or substance use disorders are present in at least 40 percent of patients, and some type of anxiety disorder is present in 50 to 75 percent of patients. There is evidence that patients with alcohol and substance use disorders or
anxiety disorder comorbidities take longer time to recover from an index episode and are more likely to relapse compared with those without these comorbidities. Hence, the optimal management of bipolar disorder should include not only treatment of mood symptoms/episodes associated with this condition but also assessing for comorbidities and instituting appropriate pharmacological/psychological management strategies to address comorbidities in order to improve outcomes. During the maintenance treatment, clinicians should routinely monitor for onset of new psychiatric, substance or alcohol use comorbidities, and manage them as clinically indicated.

**Address Cognitive Impairment**

Patients with bipolar disorder often complain of cognitive difficulties. A thorough clinical assessment should be conducted in such patients to address contributory factors such as comorbid substance use, psychotropic medications-induced confusion or sedation, lithium-induced hypothyroidism, or valproate-induced hyperammonemia, etc. for cognitive difficulties. Evidence has accumulated over the past 15 years to suggest that cognitive dysfunction can be an inherent part of bipolar disorder for a substantial proportion of patients with bipolar disorder. Impairments are seen in several domains including in processing speed, verbal learning, working memory, and executive function and such impairments are present not only during acute mood episodes but also even during euthymic periods. The effect sizes for magnitude of impairment during euthymia are in the range of 0.6 to 0.8. Cognitive impairments particularly in the domains of verbal learning and executive function correlate with functional impairments. There is increasing interest in examining the efficacy of pharmacological treatments and cognitive remediation to address cognitive dysfunction. While evidence for efficacy is limited, there are no risks to attempting cognitive and functional remediation in such patients.

**Monitor for Treatment Adherence**

While the rates of treatment nonadherence vary depending upon how it is defined, there is evidence that up to 60 percent of patients with bipolar disorder are nonadherent or poorly adherent to pharmacotherapy. The consequences of poor adherence to pharmacotherapy include illness destabilization with increased relapse/recurrence of mood episodes, high suicide risk, increased hospitalization, disability, and poor functioning. Several factors such as poor insight/denial of illness, concerns about or experience of side effects of medications, inadequate efficacy of medications, younger age, low level of education, cognitive impairment all contribute to poor treatment adherence. It is important for clinicians to be cognizant of demographic variables and explore illness-related factors, attitudes toward illness and treatment-related factors that predict poor adherence and address them routinely at clinical follow-up visits. There is evidence that psychoeducation improves treatment adherence. More recently, customized treatment adherence programs have been developed that include modules on psychoeducation, substance abuse, medication routines, and communication with providers, and these programs can be tailored to address the specific reasons for the treatment of nonadherence in individual patients.

**Monitor for the Emergence of Mood Symptoms and Suicide Risk**

There is evidence that bipolar patients with subsyndromal mood symptoms are more likely to relapse into a full-blown mood episode compared with those without such symptoms. Therefore, it is prudent for clinicians to routinely screen for emergent subsyndromal
symptoms at each clinical visit. Clinicians may find Young Mania Rating Scale (YMRS) and MADRS particularly helpful in systematically assessing and quantifying subsyndromal symptoms. The reasons for the emergence of such symptoms such as poor treatment adherence, comorbidity, or partial efficacy of ongoing treatments should be identified when possible and addressed with psychoeducation or changes to pharmacotherapy as appropriate in order to rapidly resolve such symptoms. Subsyndromal depressive symptoms can also be treated with psychological strategies such as with interpersonal and social rhythm therapy (IPSRT) or CBT.

Clinicians should also routinely monitor for the emergence of suicidal ideation not only when treating acute episodes but also during the maintenance treatment. This is because suicidal ideation is common in patients with bipolar disorder and that between 25 to 50 percent of patients with bipolar disorder make a suicide attempt at least once during their lifetime. The rates of lifetime risk of suicide deaths in bipolar patients range from 8 to 19 percent with more recent studies in less severely ill populations suggesting lower rates. Regardless, the standardized mortality ratios for suicide in bipolar patients range from 10 to 30, which means that bipolar patients are 10 to 30 times more likely to die of suicide compared with the general population. A recent International Society for Bipolar Disorders (ISBD) Task Force identified several risk factors for suicide attempts and suicide deaths (see Table 13.7–3) in bipolar disorder.

Clinicians should be more vigilant for suicidal ideation in those with increasing number of risk factors. The risk of suicide attempt and suicide death is higher early in the course of the illness, during acute mood episodes or hospitalization, and within 4 to 12 weeks of discharge from the hospital. When suicidal ideation is endorsed, clinicians must take appropriate steps immediately to ensure the safety of the patient and these may include hospitalization, preventing/reducing access to methods of suicide (e.g., medication overdose), establishing therapeutic alliance, and involving family members/friends when possible in care, and addressing the illness related and psychosocial factors that led to the emergence of suicidal ideation.

**PHARMACOLOGICAL TREATMENTS**

This section briefly reviews the evidence for the treatment options for various phases of bipolar disorder and provides clinical recommendations.

**ACUTE MANIA: TREATMENT OPTIONS**

**Lithium**

There is robust evidence for efficacy of lithium in treating acute mania. When adequately dosed, therapeutic effect of lithium becomes apparent within 7 days as the separation from placebo was seen on as early as day 7 in clinical trials. While the response rates to lithium varied between the trials, on average, about 50 percent of patients met criteria for response to lithium in these 3 week trials.

Lithium is typically started at 900 mg/day and serum levels measured after 5 days of consecutive therapy, 12 hours after the last dose. Serum levels between 0.8 and 1.2 mEq/L are likely required to treat acute mania effectively, although lower levels may be appropriate in elderly. Lithium levels of ≥1.5 mEq/L can lead to symptoms of lithium toxicity and this
should be treated as a medical emergency. Patients should be educated and clinically monitored for signs of lithium toxicity that may include gastrointestinal (vomiting and diarrhea), neurological (coarse tremor, agitation, dysarthria, drowsiness, lethargy, ataxia) renal (polyuria and polydipsia), and cardiovascular (syncope, dizziness, arrhythmias) symptoms.

**Anticonvulsants**

**Carbamazepine.** Carbamazepine is as effective as lithium and neuroleptics in treating acute mania. Carbamazepine extended release (ER) is also effective with response rates between 40 and 60 percent that are similar to the aggregate response rates of 52 percent observed with carbamazepine in older studies.

Carbamazepine is typically started at 100 to 200 mg bid and the dose gradually titrated upward to achieve therapeutic effect. Most patients will need between 600 and 800 mg/day. Therapeutic effect is observed typically within 1 week to 10 days. There is no evidence to suggest a relationship between serum carbamazepine levels and acute therapeutic efficacy in mania.

**Oxcarbazepine.** While oxcarbazepine may be better tolerated than carbamazepine, the data for its efficacy in treating acute mania is conflicting. While four small controlled studies in adult manic patients support the efficacy, a recent larger clinical trial in children and adolescents with mania that compared oxcarbazepine with placebo found no differences in improvement in manic symptoms between the two groups. Given the lack of larger placebo--controlled trials in adults with modern methodology and a negative trial in children and adolescents with acute mania, further studies are clearly needed to determine the efficacy of oxcarbazepine for acute mania. This statement is consistent with a recent Cochrane review which concluded that there is currently insufficient evidence for efficacy of oxcarbazepine in treating acute mood episodes in bipolar disorder.

**Divalproex/Valproate.** Divalproex consists of sodium valproate and valproic acid in a 1:1 molar ratio. The landmark trial by Bowden and colleagues (1994) that compared the efficacy of divalproex with placebo and lithium led to the approval of divalproex for the treatment of acute mania. Divalproex is as effective as lithium in adult manic patients. Two out of three studies that compared divalproex with olanzapine showed similar efficacy at 3 weeks. Divalproex has similar efficacy to quetiapine in treating acute mania in adolescents.

Table 13.7–3. Factors Associated with Suicide Attempts and Suicide Deaths in Bipolar Disorder

<table>
<thead>
<tr>
<th>Variables</th>
<th>Increased Likelihood of Suicide Attempts in Bipolar Disorder</th>
<th>Increased Likelihood of Suicide in Bipolar Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Female</td>
<td>Male, females have higher SMR, no clear effect</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Younger, older age—higher lethality attempts</td>
<td>Older age—higher ratio of deaths/attempts</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>Minorities—specific to youth only</td>
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</tr>
</tbody>
</table>
Table 13.7 continued. Factors Associated with Suicide Attempts and Suicide Deaths in Bipolar Disorder

<table>
<thead>
<tr>
<th>Variables</th>
<th>Increased Likelihood of Suicide Attempts in Bipolar Disorder</th>
<th>Increased Likelihood of Suicide in Bipolar Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapeutic effect of divalproex</strong></td>
<td>Is apparent by day 7, although studies with divalproex oral loading (20 mg/kg/day or 30 mg/kg/day on days 1 and 2 followed by 20 mg/kg/day) suggest</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>Single, divorced, single parents</td>
<td></td>
</tr>
<tr>
<td>Religious affiliation</td>
<td>Discordant results</td>
<td></td>
</tr>
<tr>
<td><strong>Characteristics of Bipolar Disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of illness onset</td>
<td>Younger age</td>
<td></td>
</tr>
<tr>
<td>Duration of illness</td>
<td>Discordant results</td>
<td></td>
</tr>
<tr>
<td>Polarity of 1st episode</td>
<td>Depression, Mixed symptoms, Mania—more violent attempts</td>
<td></td>
</tr>
<tr>
<td>Predominant polarity</td>
<td>Depressive</td>
<td></td>
</tr>
<tr>
<td>Polarity of current episode</td>
<td>Depressive episodes, Mixed states</td>
<td></td>
</tr>
<tr>
<td>Other mood episode characteristics</td>
<td>Mixed features, Greater number and severity of episodes/rapid cycling, Anxiety, Atypical features, Suicidal ideation</td>
<td>Hopelessness, Psychomotor agitation</td>
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<td>Psychosis at any time</td>
<td>Discordant results</td>
<td>No effect</td>
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<tr>
<td>Bipolar disorder subtype</td>
<td>No clear effect</td>
<td>No clear effect</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
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<td></td>
</tr>
<tr>
<td>Psychiatric comorbidity</td>
<td>Substance use disorder, Cigarette smoking, Coffee intake, Anxiety disorder, Obesity or high BMI, Eating disorder</td>
<td>Substance use disorder—no clear effect, Anxiety disorder</td>
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<tr>
<td>Personality disorders and characteristics</td>
<td>Personality disorders—including borderline or cluster bipolar disorder in particular, Aggression or irritability, Impulsivity (discordant results)</td>
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</tr>
<tr>
<td>Other Clinical Variables</td>
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<td></td>
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<tr>
<td>First-degree family history</td>
<td>Mood disorders, Bipolar disorder, Suicide</td>
<td>Mood disorders, Bipolar disorder, Suicide</td>
</tr>
<tr>
<td>Prior suicide attempts</td>
<td>Presence</td>
<td>Present</td>
</tr>
<tr>
<td>Early life trauma</td>
<td>Childhood abuse, Higher early life stress</td>
<td></td>
</tr>
<tr>
<td>Psychosocial precipitants</td>
<td>Interpersonal problems, Occupational problems, Bereavement</td>
<td>Present within a week prior to death</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>Presence</td>
<td></td>
</tr>
</tbody>
</table>
more rapid onset of action with effect apparent by day 5 or sooner. Post hoc analyses of data from these trials suggest that divalproex has a broader spectrum of efficacy with effect in manic patients with and without concurrent depressive symptoms, psychotic symptoms, rapid cycling, and regardless of number of prior mood episodes.

There is a linear relationship between serum valproate levels and therapeutic efficacy for acute mania with higher serum levels yielding greater efficacy. The evidence suggests that optimal efficacy may not be obtained when serum levels are below 94 µg/mL. Hence, clinicians should titrate the dose of valproate to achieve serum valproate levels to this target range. If tolerability is not a concern, the doses could be further increased if necessary as some patients may require higher levels for optimal efficacy.

**Other Anticonvulsants.** Lamotrigine, gabapentin, topiramate, and licarbazepine are not effective in treating acute mania as none separated from placebo in controlled clinical trials in improving manic symptoms. Lamotrigine or topiramate adjunctive therapies are also ineffective in treating acute mania.

Other anticonvulsants such as tiagabine, pregabalin, levetiracetam, felbamate, and zonisamide have not been assessed in controlled trials for acute mania.

**Conventional / First-Generation Antipsychotics**

Haloperidol is the most widely investigated first-generation antipsychotic for acute mania. Several modern placebo-controlled trials of atypical antipsychotics such as risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole used haloperidol as an active comparator. In all these studies, haloperidol was more effective than placebo confirming the efficacy of haloperidol in treating acute mania.

The efficacy of haloperidol was apparent at early as day 2 in some trials. The doses of haloperidol used in these trials ranged from 2 mg to 15 mg per day, although in the ziprasidone trial up to 30 mg/day of haloperidol was allowed. These studies demonstrated that haloperidol was as effective as risperidone, olanzapine, and aripiprazole and more effective than quetiapine and ziprasidone. The extrapyramidal symptoms are common with haloperidol, and patients with bipolar disorder are more prone to movement disorders such as tardive dyskinesia. Furthermore, more patients treated with haloperidol experienced depression in some of these trials compared with placebo or atypical antipsychotics.

It is believed that the efficacy of haloperidol for acute mania is related to its ability to reduce dopamine transmission through the blockade of dopamine D2 receptors. Since all conventional antipsychotics reduce dopamine transmission through their effects on D2 receptors, they all are likely effective in treating acute mania. Chlorpromazine has been compared with lithium and found to have similar efficacy overall, although it appears to be more effective in “highly active” manic patients, which is likely related to its sedating effects while lithium has better efficacy in treating core manic symptoms. Loxapine-inhaled formulation was recently assessed for efficacy in treating agitation in acute manic patients and found to be effective, but its utility in treating core manic symptoms has not been assessed in placebo-controlled trials.

Haloperidol in combination with lithium or valproate is more effective than lithium or valproate monotherapy. Similarly, contrary to what clinicians might believe, valproate add-on
to haloperidol / perphenazine is more effective than monotherapy with haloperidol / perphenazine.

**Atypical Antipsychotics**

**Monotherapy.** Several atypical antipsychotics are currently in use for the treatment of psychosis. Of these, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, and asenapine have proven efficacy and hence approved for the treatment of acute mania in several countries. Table 13.7–4 provides a summary of the efficacy of atypical antipsychotics and the dose ranges commonly used in clinical practice. Clozapine and lurasidone are likely effective but no placebo-controlled trials have assessed their efficacy for acute mania to date. Cariprazine, a new atypical antipsychotic candidate with D2 and D3 partial agonist properties, is effective and was recently approved by the FDA for the treatment of mania.

The only study that compared two atypical antipsychotics head-to-head found no difference in efficacy between risperidone and olanzapine for acute mania. While other atypical antipsychotics have not been compared directly in double blind, controlled trials, there is no reason to believe that there are any clinically meaningful significant differences in efficacy between various atypical antipsychotics, given the broad similarity in effect sizes and placebo-corrected response rates.

**Table 13.7–4. Atypical Antipsychotics for Bipolar Disorder: Efficacy Summary and Dose Ranges**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range (mg)</th>
<th>Acute Mania</th>
<th>Acute Bipolar Depression</th>
<th>Mood Episodes</th>
<th>Mania</th>
<th>Depression</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>5–20</td>
<td>Yes</td>
<td>?Yes¹ (see comments)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes²</td>
<td>Improvement was seen mostly in sleep, appetite and inner tension but not in core depressive symptoms</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1–6</td>
<td>Yes</td>
<td>No data</td>
<td>Yes¹</td>
<td>Yes²</td>
<td>No</td>
<td>Magnitude of benefit for depression less than for mania</td>
</tr>
</tbody>
</table>

¹Prophylactic efficacy was demonstrated with Risperdal Consta but no studies with oral risperidone
Table 13.7–4 continued. Atypical Antipsychotics for Bipolar Disorder: Efficacy Summary and Dose Ranges

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range (mg)</th>
<th>Acute Mania</th>
<th>Acute Bipolar Depression</th>
<th>Mood Episodes</th>
<th>Mania</th>
<th>Depression</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>300–800</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>'For bipolar depression, 300 mg/day is as effective as 600 mg/day (see text for guidance) Appears to have equal efficacy in preventing both mania and depression</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>80–160</td>
<td>Yes</td>
<td>No</td>
<td>'Yes'</td>
<td>'Yes'</td>
<td>No</td>
<td>'Prophylactic demonstrated for adjunctive therapy but no data for monotherapy</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>15–30</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>'Less effective than olanzapine in preventing mood episodes</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>6–12</td>
<td>Yes</td>
<td>No data</td>
<td>'Yes'</td>
<td>Yes</td>
<td>No</td>
<td>Numerically fewer patients in the asenapine group had relapse of manic and depressive episodes but the differences were not significant</td>
</tr>
<tr>
<td>Asenapine</td>
<td>10–20</td>
<td>Yes</td>
<td>No data</td>
<td>Yes</td>
<td>?Yes</td>
<td>?Yes</td>
<td>Effective in depressed patients with mixed features</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>40–120</td>
<td>No data</td>
<td>Yes</td>
<td>Studies underway</td>
<td>Studies underway</td>
<td>Studies underway</td>
<td>For bipolar depression, 1.5–3 mg/day is recommended, while for mania, up to 12 mg/day is appropriate</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>3–12</td>
<td>'Yes'</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td></td>
</tr>
</tbody>
</table>
If a medication is effective rapidly, it can shorten the duration of the manic episode and the hospital length of stay. When atypical antipsychotics are dosed adequately, some improvement in manic symptoms is apparent typically within the first week with all atypical antipsychotics. While there is a perception that sedating atypical antipsychotic drugs may have more rapid onset of action, this is not borne out in clinical trials. For instance, although aripiprazole and ziprasidone are less sedating, their therapeutic effects in mania were apparent at first post-baseline measurements of day 4 and day 2, respectively in clinical trials.

Depressive symptoms are common in acute manic patients and several trials with atypical antipsychotics have included some patients with DSM-IV mixed episodes. Post hoc analyses from these trials suggest that olanzapine, asenapine, aripiprazole, and ziprasidone are effective in treating manic symptoms in patients with mixed episodes/dysphoric mania. Further, a meta-analysis suggests that atypical antipsychotics as a group are effective in treating acute mixed episodes and the effect size for their efficacy in treating mixed episodes is in the medium range that is similar to their magnitude of effect in manic patients. As to comorbid depressive symptoms, they improved with atypical antipsychotics in most studies but significant separation from placebo occurred only in few studies in favor of atypical antipsychotics (e.g., risperidone and quetiapine). Based on this, it is reasonable to conclude that atypical antipsychotics unlike conventional first-generation antipsychotics at the very least do not worsen or induce depressive symptoms in manic patients. DSM-5 has eliminated the mixed episodes category and introduced mixed features as a course specifier for manic as well as depressive episodes. While no clinical trials of atypical antipsychotic have been conducted to date in manic patients with mixed features as a course specifier, many patients who meet these criteria would have been included in previous trials. Indeed, a recent post hoc analysis of asenapine trials using DSM-5 mixed features specifier criteria supports the efficacy of asenapine in this population. It is likely that other atypical antipsychotics are also effective.

Combination/Add-On Therapy. There is evidence that as many as 80 percent of manic patients in clinical settings are treated with a combination of a mood stabilizer and an antipsychotic. In some cases, both medications are started at the same time (combination therapy) while in other cases, one medication is started and the other is added after a few days (add-on therapy).

In clinical trials of add-on therapy, although patients met entry criteria for mania severity, refractoriness to existing therapy was not established prospectively in many studies. Hence, it is unknown, if the add-on studies truly assessed the efficacy in refractory manic patients.

Regardless, there is evidence that response rates are greater when manic patients are treated with a combination/add-on of risperidone, olanzapine, quetiapine, aripiprazole, or asenapine with lithium or valproate compared with lithium or valproate monotherapy. On average, 20 percent more manic patients will respond with combination/add-on therapy compared with lithium or valproate monotherapy. While different combinations treatments are not directly compared, based on differences in response rates observed between monotherapy and combination therapies in various studies, there does not appear to be any clinically meaningful differences between different combinations of atypical antipsychotic and lithium or valproate. The only exception is ziprasidone adjunctive therapy that was not superior to lithium or valproate monotherapy in the only clinical trial that assessed this strategy.
There is preliminary evidence that adding an atypical antipsychotic to carbamazepine does not confer additional efficacy. For instance, risperidone or olanzapine combined with carbamazepine is no more effective than carbamazepine monotherapy. This is likely because carbamazepine through induction of hepatic microsomal enzymes reduces serum levels of antipsychotics and thus affects their efficacy.

Some clinicians believe that antipsychotic monotherapy is as effective as the combination strategy. There is preliminary evidence to suggest that this is clearly not the case. For instance, a large double-blind trial suggested that lithium given in combination with quetiapine XR was more effective than quetiapine XR monotherapy. Similarly, valproate in combination with haloperidol/perphenazine was more effective than monotherapy with an antipsychotic.

It is, however, important to note that greater efficacy of combination therapy comes with a trade-off in terms of adverse events as combination therapy is often associated with more adverse events than monotherapy.

**Miscellaneous Agents**

Tamoxifen, a drug used in the treatment of breast cancer, is a protein kinase c (PKC) inhibitor. There is evidence that treatment with lithium and valproate alters PKC signaling pathway and more specifically reduces specific isoforms of this enzyme. There is evidence from four small double-blind, placebo-controlled trials (2 monotherapy and 2 adjunctive therapies) that tamoxifen is effective in treating acute mania. However, clinicians must be aware that tamoxifen use in patients with breast cancer is associated with two to sevenfold increase in endometrial carcinoma. Further, there is no longer term safety data for tamoxifen in bipolar patients.

Verapamil was reported to be effective in two small earlier controlled trials and some open trials but a larger double-blind, placebo-controlled trials found no evidence for efficacy of verapamil in treating acute mania. Two very small trials suggest that nimodipine may be useful in treating manic symptoms, but larger trials are needed before any conclusions about its efficacy can be drawn. Calcitonin was reported to be effective in treating acute manic symptoms in a trial conducted in 80s, but a more recent double-blind trial that compared calcitonin nasal spray versus saline nasal spray in refractory manic patients found no difference between the two groups.

**CLINICAL RECOMMENDATIONS FOR THE MANAGEMENT OF ACUTE MANIA**

**General Principles of Management**

Manic episodes can be a part of bipolar I disorder or secondary to an underlying medical condition, neurological condition, head injury, substance use disorder (e.g., cocaine or amphetamines), or induced by drugs such as steroids. When possible, verbal de-escalation techniques should be tried to calm the manic patient and obtain a thorough psychiatric and medical history. Manic patients are often uncooperative and lack insight; collateral information is vital in such cases. Patients should be assessed for the risk of aggressive behavior, severity of mania, presence of psychotic features, and insight, all of which inform the clinician about the treatment setting for further management. Patients with severe mania
and aggressive behavior with little insight will require hospitalization, while those with mild-
to-moderate mania may be treated in an out-patient setting if adequate family support is
available and if the patient has some insight.

A thorough review of medication history should be conducted. If a patient had been taking
antidepressant medication, this should be discontinued. Similarly, other medications that
might be potentially contributing to manic symptoms such as stimulants or steroids should be
discontinued. A physical examination and appropriate baseline medical investigations should
be conducted before definitive pharmacological treatment is instituted, although this may not
be possible in some cases. If the patient has a history of substance use, this should be
addressed simultaneously while mania is being treated. Psychoeducation should commence
as soon as the patient is behaviorally stabilized and is amenable.

Management in an Emergency Setting

Patients presenting with a manic episode in an emergency setting are often agitated, irritable,
uncooperative, and lack insight. In some cases, they may be verbally or physically aggressive
and may escalate to becoming assaultive and violent. Hence, ensuring the safety of the
acutely manic patient and those around is a high priority. It is important to move the patient
to a low stimulus and comfortable environment as soon as possible.

The severity of agitation and aggressive behavior and patient’s willingness to accept
treatment dictate whether medications can be given orally or in an injectable form. Oral
medications are less likely to disrupt the therapeutic alliance and hence are preferable but
have the disadvantage of slower onset of action. Further, although oral administration of
benzodiazepines such as lorazepam, first-generation antipsychotics such as haloperidol and
lozapine, and second-generation antipsychotics (risperidone, olanzapine, quetiapine,
aripiprazole, ziprasidone, asenapine) is a common clinical practice in the emergency setting
to control agitation and aggressive behavior, they are not widely studied in controlled clinical
trials for efficacy in treating agitation and aggressive behavior in mania. Nevertheless,
clinicians often employ this strategy in many parts of the world. While haloperidol and
several second-generation antipsychotics have proven efficacy in treating acute mania, there
is little evidence to suggest that lorazepam is effective in treating core manic symptoms
although this may be useful in calming the patient. Hence lorazepam monotherapy for
controlling agitation in mania is not recommended but this can be given in conjunction
with an antipsychotic and in particular a first-generation antipsychotic such as haloperidol to
reduce the risk of extrapyramidal symptoms and to enhance the calming effect.

While lithium and carbamazepine are effective in treating acute mania, they have not been
studied for their efficacy in treating acute agitation and aggressive behavior in acute mania,
and hence are not recommended as monotherapy for treating agitation in an emergency
setting. Valproate oral loading dose has a similar faster onset of action as the antipsychotics
in treating acute mania but has not been studied for controlling agitation. For patients who
have a tendency to “cheek” the medication, orally disintegrating tablets (ODT) or liquid form
of antipsychotics is preferable. However, there is no convincing evidence to support that
these forms of administration have a faster onset of action in comparison to conventional
tablet forms.

Two novel forms of oral administration of antipsychotics have shown rapid efficacy in
controlling agitation. In a recent clinical trial, sublingual asenapine was shown to rapidly
control agitation within 2 hours in psychiatric patients that included manic patients with a number needed to treat (NNT) of 3. Sublingual asenapine bypasses the first-pass metabolism provided that the patient does not drink or eat for 10 minutes after the administration and this may explain the rapid effect. Similarly, loxapine aerosol delivered through inhalation with staccato system is also rapidly effective in controlling agitation in manic patients with an NNT of 3 achieved within 30 minutes. Loxapine inhalation (ADASUVE, 10 mg) is approved by the FDA in the United States as well as by the European Medicines Agency (EMA) for the treatment of agitation in mania. Since ADASUVE can cause bronchospasm that can potentially lead to respiratory distress and arrest, it is approved under the Risk Evaluation and Mitigation Strategy (REMS) Program to mitigate the risk of bronchospasm. This basically means that ADASUVE can be administered only in an enrolled health-care facility. Given the risk of bronchospasm, it is contraindicated in patients with a history of respiratory conditions such as asthma, chronic obstructive pulmonary disease (COPD), or other lung diseases associated with bronchospasm.

When a rapid control of agitation is required to ensure safety and if a patient is unwilling to take the medication orally, intramuscular (IM) administration of an antipsychotic should be considered. Haloperidol and second-generation antipsychotic medications such as olanzapine, aripiprazole, and ziprasidone IM formulations are rapidly effective within 2 hours in controlling agitation with an NNT of 3. Clinicians, however, must recognize that IM administration of medication against patients’ wishes can be a very negative experience for the patient and may interfere with establishment of therapeutic alliance. Hence, if IM formulations are used to manage agitation and aggressive behavior, patients should be switched to oral medications as soon as the patient is willing to take the medication.

**Treatment Selection for Acute Mania**

If a manic patient was given an atypical antipsychotic with proven efficacy for mania to control agitation in the emergency setting and if this was well tolerated and improved agitation, this should be continued and the doses adjusted as clinically appropriate to treat acute mania. However, if a first-generation antipsychotic such as haloperidol, or loxapine or chlorpromazine was used to control agitation, patients should be switched to a first-line antimanic agent as soon as possible. Although the first-generation antipsychotic are likely as effective in treating acute mania, they are not recommended as first-line antimanic agents by most experts because first-generation antipsychotics such as haloperidol have a tendency to induce depressive symptoms and increase the risk of depressive episodes in bipolar patients.

**First-Line Treatments**

Lithium, valproate, and several atypical antipsychotics are all considered first-line agents for treating acute mania (see Table 13.7–5) as they all are effective and that the response rates are broadly similar. Although multiple treatment meta-analyses suggest that risperidone may be more effective, it is likely that this was mostly driven by a risperidone clinical trial conducted in India that enrolled more severely ill manic patients, hence the greater effect size. Thus, it is unlikely, that there are any clinically meaningful significant differences in efficacy between these agents, and hence, monotherapy with any of these agents would be considered an appropriate first-line option for acute mania.
Table 13.7–5. Recommendations for Pharmacological Treatment of Acute Mania

| First line | Monotherapy: Lithium, divalproex, divalproex ER, olanzapine, risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, asenapine, paliperidone ER, carbiprazine Combination therapy with lithium or divalproex: Risperidone, quetiapine, olanzapine, aripiprazole, asenapine |
| Second line | Monotherapy: Carbamazepine, carbamazepine ER; ECT, haloperidol Combination therapy: lithium + divalproex |
| Third line | Monotherapy: chlorpromazine, clozapine, tamoxifen Combination therapy: lithium or divalproex + haloperidol, lithium + carbamazepine, adjunctive tamoxifen |
| Not recommended | Combination therapy: risperidone + carbamazepine, olanzapine + carbamazepine |

Some guidelines such as Canadian Network for Mood and Anxiety Treatments (CANMAT) that were published in collaboration with the ISBD recommend combination of an atypical antipsychotic with lithium or valproate also as a first-line option. This is because combination therapy in general results in approximately 15 to 20 percent more patients responding compared with monotherapy. As with monotherapy, there does not appear to be any clinically meaningful significant differences in efficacy between various proven combinations for acute mania. It is, however, important for clinicians to remember that combination therapy is likely associated with more adverse events.

Which First-Line Treatment? Given that several monotherapy and combination therapy first-line options are available for treating acute mania, clinicians have to make a choice as to which monotherapy or combination therapy should be used to treat a given patient with acute mania.

Since there are no efficacy differences between various first-line monotherapies and between different first-line combination therapies, physicians should consider clinical presentation, previous history of response/nonresponse, adverse events, and patient preference in deciding which monotherapy or combination to use to treat mania in a given patient. Patients are more likely to respond to combination therapy compared with monotherapy but this comes with additional adverse event liability. Therefore, clinicians must carefully weigh the risks and benefits of monotherapy versus combination therapy for each patient before making a decision on the most appropriate strategy.

If a decision is made to use monotherapy, patients presenting with acute agitation and aggressive behavior are commonly started on an atypical antipsychotic given their effectiveness in behavioral control and more rapid onset of action compared with mood stabilizers such as lithium. Lithium is the preferred agent in patients with “classical euphoric grandiose” type of mania whereas those with dysphoric/irritable mania, mixed features, comorbid alcohol or substance abuse or brain trauma may respond better to valproate. Similarly, patients with multiple previous mood episodes tend to respond poorly to lithium while this does not predict poor response to valproate. Atypical antipsychotics, and in particular, olanzapine, asenapine, aripiprazole and ziprasidone appear to be equally effective for patients with classical mania as well as those with mixed episodes/mixed features. While clinicians tend to believe that presence of psychotic features may require treatment with an antipsychotic, the evidence from clinical trials suggest lithium, valproate and atypical
antipsychotics are equally effective in treating mania in patients with and without psychosis. However, clinical trial data notwithstanding, if a manic patient who is on lithium or valproate continues to exhibit psychotic symptoms, clinicians should consider adding an antipsychotic. Given that there are clear differences in adverse event profile between various antimanic agents, this is also a very important consideration in treatment selection. For instance, olanzapine is not appropriate for manic patients who are overweight or obese or have a personal or family history of diabetes. Similarly, for patients with kidney disease with compromised kidney function, lithium is not appropriate.

Since there are no efficacy differences between combinations of different atypical antipsychotics (except ziprasidone) with lithium or valproate, the decision with regard to which combination to use for a given patient is also determined by taking into consideration previous history of response, adverse event profile of medications, clinical presentation and preference of the patient.

What If a Patient Does Not Respond to a First-Line Treatment? Since several first-line monotherapy and combination treatment options are available, if one first-line treatment is ineffective, it is appropriate to switch the patient to another first-line treatment. Most manic patients who respond to therapy will show some improvement in manic symptoms within the first 2 weeks. If no improvement is observed during this time period, a switch to a different first-line treatment should be considered. For instance, if a patient is not responding to an atypical antipsychotic monotherapy a switch to lithium or valproate or vice versa might be appropriate. A switch to a different monotherapy or combination could also be considered for tolerability reasons. In real-world clinical practice, it is unusual to encounter a patient who does not respond to one of the several first-line treatment options that are currently available to treat acute mania.

Second-Line Treatments

These should be considered mainly for those patients who have not responded to several first-line therapies.

Haloperidol is an effective treatment of acute mania. However, haloperidol has a tendency to induce depressive symptoms/switch patients into depression. Therefore, despite excellent efficacy for acute mania, haloperidol is recommended only as a second-line option.

Carbamazepine is also as effective in treating acute mania as other first-line antimanic agents but tolerability is a significant concern with carbamazepine. Further, carbamazepine induces hepatic microsomal enzymes, which results in induction of its own metabolism as well as the metabolism of other drugs, and this complicates the management of bipolar disorder.

The efficacy of lithium and valproate combination for acute mania is not examined in large double-blind, placebo-controlled trials. Nonetheless, given that both lithium and valproate are effective in monotherapy, it is likely that combination may provide some benefit for patients who are refractory to monotherapy with either agent or a combination of either agent with an atypical antipsychotic.
Third-Line Treatments

If a patient is a non-responder to all first-line and second-line treatments, third-line options should be considered. These include first-generation antipsychotics such as chlorpromazine, or an atypical antipsychotic clozapine or tamoxifen.

Treatments Not Recommended

Given the efficacy of valproate and carbamazepine for acute mania, clinicians tend to believe that other anticonvulsants are also effective in treating acute mania. However, there is evidence that gabapentin, topiramate, and lamotrigine are ineffective for acute mania and hence should not be used. Similarly, it is not advisable to combine atypical antipsychotics such as risperidone or olanzapine with carbamazepine as no additional benefit in efficacy can be achieved with this strategy.

ECT IN ACUTE MANIA

Although there is a paucity of well-designed studies assessing the efficacy of ECT for acute mania, it is believed that ECT is highly effective for acute mania based on the data from retrospective and prospective studies. ECT may be used as a first-line option in first trimester of pregnancy or in patients with delirious mania where rapid response is required. In other situations, given the cognitive adverse event profile, ECT should be used primarily in only those manic patients who have failed several first and possibly second-line treatments.

ACUTE BIPOLAR DEPRESSION: TREATMENT OPTIONS

There is a significant unmet need for the treatments of acute bipolar depression as few drugs have proven efficacy.

Lithium

The evidence for efficacy of lithium monotherapy in treating acute bipolar depression is sparse. Earlier small trials that used cross-over designs with short duration of lithium and placebo periods reported that response rates were significantly higher during lithium periods compared with placebo periods. The mean response rate to lithium in these studies was 76 percent. About half of the patients experienced relapse of depression when lithium was substituted with placebo.

However, the efficacy of lithium was not confirmed in a more recent large double-blind, placebo-controlled parallel design study as lithium was not different from placebo in improving depressive symptoms in bipolar I and bipolar II patients. The mean serum lithium levels in this study were 0.61 mEq/L, and therefore, it is possible that higher levels might have led to greater efficacy. In one study that compared lithium versus lithium plus paroxetine showed that the latter was more effective than lithium alone in patients with low serum lithium levels but in those that had serum lithium levels ≥0.8 mEq/L, there was no difference in efficacy, lending some support to the notion that higher serum lithium levels are required for lithium to be effective for treating acute bipolar depression.

Studies that compared antidepressant/other agent adjunctive therapy to mood stabilizer with mood stabilizer monotherapy (that included patients on lithium) in general found no
differences in efficacy between the two groups. Based on this, it has been suggested that mood stabilizer (lithium) monotherapy is effective. Lithium has been reported to have antisuicidal effect and furthermore, lithium is effective in preventing relapse of depressive episodes.

**Anticonvulsants**

**Divalproex / Valproate.** Similar to lithium, the data for efficacy of divalproex in acute bipolar depression is also sparse. Divalproex was superior to placebo in 3 out of 4 small placebo-controlled trials. A meta-analysis of these trials suggests that divalproex is effective and that approximately 40 percent of patients will respond and meet criteria for remission. It is currently unknown if there is a relationship between serum valproate levels and therapeutic efficacy for improving depressive symptoms.

**Lamotrigine.** Five double-blind, placebo-controlled studies with reasonable sample sizes of 7 to 10 weeks duration failed to demonstrate the efficacy of lamotrigine for treating acute bipolar depression. Since the lamotrigine dose needs to be titrated up gradually due to concerns about risk of serious skin rash with rapid up-titration, it is possible that 7 to 10 week study durations were not sufficient to demonstrate the efficacy given that the target dose of 200 mg was not reached until the beginning of week 5 or 6 in these clinical trials.

A pooled analysis of response rates from these trials suggests that lamotrigine is effective in treating acute bipolar depression but the magnitude of effect is small. However, the therapeutic effect was larger in those that had more severe depression.

There is evidence that lamotrigine addition provides therapeutic benefit in bipolar depressed patients who fail to respond to lithium monotherapy.

**Other Anticonvulsants.** There is only limited data for carbamazepine as its efficacy was assessed in only 3 small placebo-controlled trials that had a total of 40 bipolar depressed patients. The mean response rates to carbamazepine were 68 percent; relapse occurred in 50 percent of these patients with placebo substitution.

Gabapentin and levetiracetam are found to be ineffective in small controlled trials. No placebo-controlled data exist for other anticonvulsants.

**Atypical Antipsychotics**

While all atypical antipsychotics are effective in treating mania, only few of these have proven efficacy in treating bipolar depression. Among these, quetiapine has the best evidence for efficacy. Clinical trials, however, assessed only two fixed doses (300 mg/day and 600 mg/day) and there is no significant difference in efficacy between these two doses. Thus, for vast majority of bipolar depressed patients, 300 mg/day of quetiapine is sufficient to improve depressive symptoms. Although the efficacy of lower doses of quetiapine has not been studied in acute bipolar depression in clinical trials, experience from clinical practice suggests that some bipolar depressed patients do respond to lower doses.

Olanzapine was more effective than placebo in clinical trials of bipolar depression but the magnitude of benefit is small. Olanzapine plus fluoxetine combination is clearly effective,
and is approved by the FDA for the treatment of acute bipolar depression. Although not tested, it is likely that other SSRIs given in conjunction with olanzapine are also effective.

Lurasidone monotherapy and adjunctive therapy to lithium or valproate are also effective in treating acute bipolar depression and were recently approved by the FDA for this indication. Cariprazine, a D2 and D3 receptor partial agonist, at 1.5 mg/day was superior to placebo in one of the two double-blind trials in improving depression in acute bipolar depression. Drop-out rates were higher in the 3 mg/day group that may explain why 3mg dose was not significantly more effective than placebo.

Aripiprazole is not effective in treating acute bipolar depression as it was not superior to placebo in improving depressive symptoms in clinical trials. Although the studies allowed flexible doses between 5 to 30 mg/day, the mean doses in these studies were around 16 mg/day, which may have been too high. More patients in the aripiprazole group dropped out from these clinical trials. Thus, it is conceivable that tolerability related to higher doses may have impacted the efficacy. Indeed, in studies of patients with refractory unipolar depression, aripiprazole given in smaller doses has been effective in augmenting the efficacy of antidepressant medications. Ziprasidone monotherapy and adjunctive therapy are not effective in treating acute bipolar depression.

**Antidepressants**

There is continuing controversy about the role of antidepressants in treating acute bipolar depression. Most experts agree that monotherapy with antidepressant medications is not appropriate for bipolar I depression because of the concerns of manic/hypomanic switch and possible destabilization of the course of bipolar disorder. This advice is consistent with the recent data from a Swedish Registry study which demonstrated that manic switch is about 2.8 times greater in bipolar patients treated with antidepressant monotherapy compared with those taking antidepressants in conjunction with mood stabilizers. There is consensus that the risk of manic/hypomanic switch is higher with TCAs, older MAOIs, and possibly with SNRI antidepressants such as venlafaxine.

While adjunctive antidepressant therapy is widely used by clinicians to treat acute bipolar depression, the evidence for such strategy from clinical trials is conflicting. Fluoxetine adjunctive therapy to olanzapine is effective but paroxetine, citalopram, bupropion and agomelatine adjunctive therapy failed to provide benefit.

However, two out of three meta-analyses support the efficacy of antidepressants. Further, another recent meta-analysis that calculated the NNT for the various treatments of bipolar depression reported an NNT of 5.75 for antidepressants that is in the same range as the NNT of 5.62 for quetiapine and 5.24 for lurasidone. However, these meta-analyses included studies of both antidepressant monotherapy and combination therapy. This limits the applicability of findings from these meta-analyses to real-world practice as most experts do not recommend antidepressant monotherapy for treating acute bipolar I depression. A more recent meta-analysis that specifically examined the efficacy of modern non-SNRI antidepressant adjunctive therapy supports efficacy but the magnitude of benefit is small. There is little evidence to suggest that non-SNRI antidepressant adjunct therapy when used for the short-term treatment of bipolar depression increases the risk of manic/hypomanic switch or cycling in bipolar disorder.
**Adjunctive Therapy with Dopamine Agonists / Psychostimulants**

There is conflicting evidence for the efficacy of modafinil / armodafinil adjunctive therapy. While a modafinil and a phase 2 study of armodafinil were positive, only one out of three phase 3 studies of armodafinil adjunctive therapy supported its efficacy for bipolar depression. Armodafinil was well tolerated in these trials with no increase in manic switches.

Pramipexole adjunctive therapy has been shown to be useful in two small trials of patients with refractory acute bipolar depression, although only one of these had included patients with bipolar I depression.

**Omega-3-Fatty Acid Adjunctive Therapy**

Although there is evidence for the efficacy of adjunctive omega-3-fatty acid therapy in major depression, few studies assessed its efficacy in acute bipolar depression. The results of these studies are conflicting, but a meta-analysis of the data from these trials suggests efficacy. The evidence suggests that potential therapeutic benefits are likely to be derived from eicosapentaenoic acid (EPA) preparation. The omega-3-fatty acid preparations are in general well tolerated; a few patients report gastrointestinal symptoms such as diarrhea and bloating.

**Nutritional Supplements as Adjuncts**

N-acetylcysteine (NAC) is a glutathione precursor and hence is expected to have protective effects against oxidative stress. There is preliminary evidence that NAC, given at 2 g/day, may provide some benefit in treating depressive symptoms as one out of two studies that assessed the efficacy of adjunctive NAC versus placebo reported improvement in depressive symptoms in patients with bipolar disorder that included patients with bipolar I, bipolar II, and bipolar NOS. There were no significant tolerability issues with NAC.

**Glutamatergic Modulators**

A few small studies, some of which included treatment-resistant bipolar depressed patients, support the efficacy of the noncompetitive NMDA antagonist ketamine. When infused in subanesthetic doses of 0.5 mg/kg over 40 minutes as an adjunctive therapy, ketamine has been reported to rapidly improve depressive symptoms in patients with TRD. A recent systematic review concluded that a single ketamine infusion was associated with higher rates of response and remission at days 1, 3, and 7. The efficacy appears to be greater in those with unipolar depression than in those with bipolar depression. Ketamine may have antisuicidal effects. There is preliminary evidence that the benefits with ketamine could be maintained with further infusions or IM or oral or sublingual or intranasal administration of ketamine. However, administration of riluzole, another glutamatergic modulator, was not more effective than placebo in maintaining the antidepressant effects of ketamine. Ketamine infusion is associated with transient psychotomimetic effects as well as sedation, dizziness, lightheadedness, incoordination, blurry vision, and feeling “strange or unreal.”

Limited open-label data suggest that riluzole at doses of 50 to 200 mg may be useful in treating bipolar depressive symptoms.
**Somatic Treatments**

**Electroconvulsive Therapy.** There is consensus among the experts that ECT is one of the most effective treatments for acute bipolar depression. Response rates to ECT are in the range of 50 to 70 percent in refractory major depressive disorder and bipolar depression. A recent meta-analysis concluded that there is no difference in efficacy of ECT between major depressive disorder and bipolar depression. There is some evidence that patients with bipolar depression respond faster and require fewer treatments to improve compared with those with unipolar depression. It is not surprising that a recent study found that ECT is more effective than algorithm-based pharmacological treatments in patients with bipolar depression who have failed at least two previous pharmacological treatments. Most patients with bipolar depression require six to eight treatments to respond.

Maintenance pharmacotherapy is necessary for the vast majority of patients to prevent relapse of depressive and manic episodes. This should be commenced, when possible, prior to completion of the ECT course. While ECT is very effective, cognitive side effects can be often problematic. Therefore, clinicians need to pay particular attention to various ECT stimulation parameters such as electrode placement, pulse width, and electrical dose in order to minimize cognitive side effects.

**Magnetic Seizure Therapy.** Magnetic seizure therapy (MST) is relatively new technique that involves inducing seizure through magnetic stimulation of brain. There is preliminary uncontrolled evidence that MST is effective in treating depression. However, few patients with bipolar depression were included in these reports. Further, while MST appears to be effective, head-to-head comparison with ECT suggests that response and remission rates are better with ECT compared with MST. It is conceivable that further refinements in stimulation parameters of MST might lead to better efficacy. As expected, MST is associated with much safer cognitive side effect profile as memory, language, and practice seem to be relatively unaffected by MST.

**Transcranial Magnetic Stimulation.** The data with regard to efficacy of rTMS in acute bipolar depression is limited, although there is extensive literature supporting its efficacy in treating major depressive disorder. A recent meta-analysis which included data on 181 patients with different sub-types of bipolar disorder and different stimulation parameters concluded that overall, there is support for efficacy of rTMS in treating bipolar depression with a NNT of 6. However, given the small number of studies and differences in methodology, but clearly further controlled trials are needed to fully understand its role in treating bipolar depression.

**CLINICAL RECOMMENDATIONS FOR THE MANAGEMENT OF ACUTE BIPOLAR DEPRESSION**

**General Principles of Management**

Treatment goals in a patient with bipolar depression include treating depression to full remission without destabilizing the course of bipolar disorder while ensuring the safety of the patient. The risk of suicide is higher during acute depressive episodes and also in depressed patients with mixed features. Therefore, clinicians must carefully assess for suicide risk and appropriate steps must be taken to ensure the safety of the patient. The severity of depression, presence of mixed features or psychotic features, substance abuse or other psychiatric
comorbidities, and the severity of suicidal ideation should guide the clinician with regard to the most appropriate treatment setting for managing depression in each patient.

Adjunctive psychological treatments such as CBT, IPSRT, and family-focused therapy (FFT) are beneficial in reducing time to recovery, improving treatment adherence and recovery rates, and reducing subsyndromal symptoms in bipolar depressed patients and, therefore, form an important part of the optimal management of bipolar depression.

**Treatment Selection for Acute Bipolar Depression**

Many patients with bipolar disorder experience breakthrough depressive episodes. This may be because patients had been taking inadequate doses of maintenance medication, or partially or nonadherent to medications or the maintenance medications were ineffective in preventing the depressive recurrence or relapse. A thorough clinical assessment that gathers information about the course of bipolar disorder (e.g., number of previous manic and depressive episodes, their duration, and severity), the treatment history (current and previous medications, what worked and what did not work, tolerability issues), and adherence to treatment should help the clinician in determining the most appropriate treatment of a given patient.

**First-Line Treatments**

The evidence for the efficacy of many commonly used medications for treating depression in bipolar disorder is less robust and often conflicting. Therefore, it is not surprising that there is no general consensus among experts about the most appropriate first-line treatment options for bipolar depression. The CANMAT/ISBD group that published the most recent treatment guidelines took into account several factors such as efficacy from controlled trials, meta-analyses, clinical experience, safety of medication, and long-term efficacy in arriving at the first-line treatment recommendations for acute bipolar depression. A modified list of CANMAT recommendations for bipolar depression is provided in Table 13.7–6.

**Which First-Line Treatment?** If a patient had been taking one of the first-line treatments, optimizing the current treatment is the most appropriate first step before other interventions are considered. Similarly, a first-line treatment should be commenced in patients who are drug free or not taking first-line medications. While there is no clear research evidence to guide clinicians between various first-line monotherapy options, previous treatment history, illness course, symptom profile of depression, side effect profile of medications, and patient preferences are all important considerations in determining treatment choices among the first-line therapies. Lithium is more appropriate for patients with a history of classical manic episodes, an illness course that has mania, depression, and euthymia pattern, and a family history of bipolar disorder. Bipolar I patients with frequent depressions and infrequent mild manias are suitable for lamotrigine monotherapy while quetiapine is a better option for those with frequent depressions as well as manic episodes. Those with reverse vegetative symptoms such as hypersonomnia and hyperphagia may be reluctant to take quetiapine because of its sedating and appetite stimulating properties, although there is no reason to believe that it is less effective for this population. Lamotrigine dose needs to be escalated gradually due to concerns of skin rash with rapid dose escalation, and hence although it is effective in severely depressed patients, it may not be the most appropriate option given that it takes a few weeks to reach effective therapeutic dose. ECT or olanzapine plus an SSRI combination may be a better option for patients with depression with psychotic features. Lurasidone is relatively weight neutral and is preferred by patients who are reluctant to take medications that can
cause weight gain. While the pharmacological profile of this agent suggests that it may prevent mood episodes, given the lack of data, it may be prudent to consider combining lurasidone with lithium or valproate.

Table 13.7–6. Recommendations for Pharmacological Treatment of Acute Bipolar I Depression

| First line | Monotherapy: Lithium, lamotrigine, quetiapine, quetiapine XR, Lurasidone  
| Combination therapy: lithium or divalproex + lurasidone, lithium or divalproex + SSRI, lithium or divalproex + bupropion, olanzapine + SSRI, lithium + lamotrigine |
| Second line | Monotherapy: Divalproex, Cariprazine, Carbamazepine, Olanzapine, ECT
| Combination therapy: adjunctive SSRI to an atypical antipsychotic, adjunctive modafinil, adjunctive pramipexole, adjunctive EPA |
| Third line | Combination therapy: lithium + carbamazepine, adjunctive NAC, adjunctive rTMS |
| Not recommended | Combination therapy: Adjunctive ziprasidone, adjunctive levetiracetam |

What If a Patient Does Not Respond to a First-Line Treatment? If optimization of monotherapy with a first-line is agent is ineffective, a switch to another first-line monotherapy therapy (e.g., a switch from lithium to quetiapine or vice versa) or combination therapy (e.g., lamotrigine plus lithium or lurasidone plus lithium) is appropriate. Addition of an SSRI or bupropion could be considered for bipolar depressed patients who were unresponsive to optimization of lithium or valproate monotherapy, especially if there is a previous history of response to adjunctive antidepressant therapy. However, antidepressants are not appropriate for patients with a history of rapid cycling or those with mixed features. If antidepressants are used for treating acute bipolar depression, an attempt should be made to taper and discontinue them within 8 weeks of remission of depression. Given the scarcity of evidence for efficacy of second-line treatments, all first-line treatments should be tried before considering second-line treatment options.

Second-Line Treatments

ECT should be considered for patients who have failed several first-line treatments. ECT may be considered earlier for bipolar depressed patients with psychotic features, those at high risk of suicide, elderly, and those with rapidly deteriorating physical status due to poor oral intake because of depression.

Valproate monotherapy is appropriate for bipolar depressed patients who had tolerability issues with other first-line monotherapy options. While no data exists, it may also be useful for bipolar depressed with mixed features. Similarly, cariprazine or carbamazepine monotherapy is appropriate for patients who were unresponsive or had tolerability issues to lithium, valproate, and other first-line treatments. Adjunctive pramipexole or modafinil may be beneficial in refractory patients who have significant anergia, anhedonia, and hypersomnia. Antidepressant adjunctive therapy to other atypical antipsychotics such as aripiprazole or quetiapine may be helpful for some patients. Adjunctive EPA between 1 and 4 g/day is appropriate for refractory patients or those with tolerability issues.
Third-Line Treatments

These options are only appropriate for patients who failed all first- and second-line options because some third-line treatments such as adjunctive venlafaxine and MAOIs carry significant risks of potentially destabilizing the course of bipolar disorder. If these strategies are employed, clinicians need to educate patients and their family members about the potential risks of manic switch and illness destabilization.

Treatments Not Recommended

Monotherapy with aripiprazole and ziprasidone is not recommended. However, these agents are effective in treating and preventing mania. Hence, adding a first-line agent or SSRI to these medications is an acceptable option.

MAINTENANCE THERAPY/PROPHYLAXIS: TREATMENT OPTIONS

Lithium

Lithium is still considered the “gold standard” by many experts for the maintenance treatment of bipolar disorder. Lithium is effective in preventing mood episodes not only in bipolar I patients who had responded to lithium during acute episodes (enriched for lithium response) but also in those who had been treated with a different psychotropic medication for acute mood episodes (not enriched for lithium response). Lithium is effective in preventing both manic and depressive episodes, although the magnitude of benefit may be slightly lower for depression than it is for preventing mania. While earlier studies suggested that around 70 percent of patients with bipolar disorder remained episode free with lithium, more recent studies suggest that the response rates are probably below 50 percent. This may be due to several reasons including the cohort effect, and the fact that these studies recruited patients who were responders to other psychotropic medication during acute episodes.

There is evidence that lithium plus valproate combination is more effective than valproate alone in preventing relapse of mood episodes. In bipolar patients who are refractory to therapy with lithium or carbamazepine, combination appears to be helpful in reducing the risk of relapse of mood episodes.

It is recommended that lithium is given as a single daily dose as there is some evidence that multiple daily doses of lithium are more commonly associated with greater incidence of renal side effects and pathological changes in kidneys. Further, treatment adherence is likely better with single daily dose.

There is evidence from post hoc analyses of recent studies that serum lithium levels below 0.6 mEq/L are less effective. Therefore, for prophylaxis, serum lithium levels should be maintained between 0.6 and 1.2 mEq/L. There is inconsistent evidence with regard to whether serum levels above 0.6 mEq/L lead to greater efficacy. Higher lithium levels, however, are associated with greater incidence of adverse events. Lithium levels should be measured after the target dose has been achieved, in the steady state (approximately 5 days after the last dose change), about 12 hours after the last dose. Serum levels should be repeated until two consecutive levels within the therapeutic range are obtained for the same dose.
Patients receiving maintenance lithium therapy should be monitored as per modified ISBD safety monitoring guidelines (see Fig. 13.7–1) or more frequently if clinically indicated.

Patients on maintenance treatment of lithium should be educated about symptoms of lithium toxicity and the preventive measures. Risk factors for lithium toxicity include renal diseases, dehydration, drug interactions, elderly and those with organic brain syndromes. Lithium toxicity is a medical emergency, and if not treated can result in irreversible organ damage and death.

If lithium is to be discontinued for any clinical reason in bipolar patients whose serum lithium levels had been in therapeutic range, it should be tapered and discontinued over a period of a several weeks. This is because there is evidence that time to 50 percent risk of recurrence of mood episodes is four times shorter with abrupt discontinuation (1 to 14 days) compared with gradual (15 to 30 days) discontinuation of lithium.

Anticonvulsants

Carbamazepine. There is limited data for the efficacy of carbamazepine from placebo-controlled trials. However, most, although not all, controlled studies that compared carbamazepine with lithium showed similar efficacy. While no study showed that carbamazepine was more effective than lithium, there is some evidence that carbamazepine may be more effective than lithium in patients with “non-classical bipolar disorder” (i.e., patients with bipolar II disorder/bipolar NOS or with mood-incongruent delusions or with anxiety disorders or substance use comorbidity or mixed states).

The clinical trials have not specifically examined the relationship between serum carbamazepine levels and therapeutic efficacy in maintenance treatment. Hence, it is currently unknown what levels might offer optimal prophylactic efficacy. In clinical practice, serum carbamazepine levels are typically maintained between 4 and 12 µg/L, the same range used for treating patients with epilepsy.

Carbamazepine induces hepatic microsomal enzymes that metabolize carbamazepine. As a result, within the first few weeks of commencing carbamazepine, the clearance of carbamazepine increases by approximately twofold; hence, dosage adjustments are necessary in order to keep serum carbamazepine levels within the clinically accepted range. Carbamazepine causes leukopenia in 10 to 20 percent of patients, and it occurs commonly within the first 3 months of commencing treatment and resolves with discontinuation of carbamazepine. Agranulocytosis and aplastic anemia are rare but have a more rapid onset and occur in an unpredictable pattern. Therefore, periodic clinical monitoring is not likely to be of much help. Clinicians need to be vigilant to this possibility when hematological symptoms emerge clinically.

There are no controlled data to support the efficacy of oxcarbazepine in the maintenance treatment of bipolar disorder.

Valproate. In contrast to lithium that has robust data for its efficacy in maintenance treatment, only a single large double-blind, controlled trial assessed the efficacy of valproate in maintenance treatment of bipolar disorder. In this trial, valproate was not superior to placebo on the primary measure of time to any mood episode. This study was considered a failed trial for a variety of reasons including the fact that lithium was also not superior to
Valproate, interestingly, was superior to placebo on some secondary measures including time to discontinuation for a recurrent mood episode or depressive episode. In the subgroup of patients who were treated with valproate during the open-label phase, valproate was superior to placebo in time to any mood episode. Further, patients randomized to valproate were significantly less likely to drop out for a mood episode and less likely to be prematurely terminated for any reason. Thus, in aggregate, these data suggest that valproate may be beneficial for preventing mood episodes in patients who respond to valproate during acute episodes.

A randomized controlled study found no difference in efficacy between valproate and lithium in patients with rapid cycling bipolar disorder who were stabilized on a combination of valproate plus lithium. Consistent with this, the results of a recent Cochrane review indicated that valproate was more effective than placebo in preventing study withdrawal due to any mood episode and that there was no difference in efficacy between lithium and valproate. There is evidence that fewer patients drop out of treatment with valproate compared with placebo or lithium. This may explain why valproate is widely used for maintenance treatment.

Although there is a linear relationship between serum levels of valproate and improvement in acute manic symptoms, there is no data to guide the clinicians with regard to serum valproate levels for the maintenance treatment of bipolar disorder. Therefore, it is a common practice to maintain the same valproate dose that was effective in treating mania for maintenance treatment, provided serum levels are within the range used for epilepsy (45 to 125 µg/mL).

Most patients prefer to take valproate as a single bedtime dose. Valproate can cause nausea and vomiting, particularly in the first few days of commencement of therapy. Some patients experience weight gain and hair loss, women taking valproate should be monitored for polycystic ovary syndrome with questions about menstrual irregularities, fertility issues, hirsutism, and galactorrhea.

**Lamotrigine.** Lamotrigine is approved for prophylaxis of mood episodes in bipolar I disorder by the FDA. Lamotrigine has robust efficacy in preventing depressive relapses/recurrences, but it only has marginal efficacy in preventing manic episodes. There is no data to suggest a relationship between serum levels of lamotrigine and prophylactic efficacy. Lamotrigine add-on to aripiprazole reduces the risk of depressive relapses in bipolar patients who are on maintenance therapy with aripiprazole.

A large randomized open study that compared lamotrigine with lithium found no statistically significant differences in efficacy but as expected, the hazard ratios for lamotrigine relative to lithium were higher (1.91) for mania and lower (0.69) for depression. In rapid cycling bipolar disorder, lamotrigine was no more effective than placebo on the primary measure of time to additional pharmacotherapy, but lamotrigine patients stayed significantly longer in the study compared with those that received placebo.

Lamotrigine is titrated upward slowly due to concerns about skin rash with rapid titration. Other risk factors for skin rash include younger age, a prior history of rash with another drug, and taking lamotrigine in conjunction with valproate. Rash more commonly occurs within the first few weeks of therapy. A recent review concluded that the incidence of skin rash was about 10 percent in prospective studies. The incidence of serious skin rash (i.e., Steven Johnson syndrome or toxic epidermal necrolysis) is rare (about 1 to 10 per 10,000) with slow
dose titration. A recent review reported that about 50 percent of patients with serious skin rash had received lamotrigine in conjunction with valproate.

If a patient on lamotrigine therapy develops skin rash, this needs to be evaluated carefully to determine if it is a benign or serious rash. When in doubt, if immediate dermatological consultation is not available, lamotrigine should be discontinued and the patient should be carefully monitored. If the rash resolves and if it was considered benign, a re-challenge with lamotrigine can be undertaken 4 weeks later if lamotrigine therapy is essential for the management of bipolar disorder. Those with serious skin rash require urgent medical evaluation and treatment.

Apart from cutaneous reactions described above, lamotrigine does not cause weight gain and is in general well tolerated.

Other Anticonvulsants. Gabapentin is not effective for treating acute mania or bipolar depression. In a small controlled trial, surprisingly, gabapentin adjunctive therapy was beneficial in maintaining mood stability. There are no controlled maintenance data for topiramate, levetiracetam, felbamate, or other anticonvulsants.

Antipsychotics

Typical (Conventional) Antipsychotics. Conventional antipsychotics are likely effective in preventing manic episodes. However, there is evidence that conventional antipsychotic therapy is associated with increased risk of depressive symptoms and depressive episodes. Further, patients with bipolar disorder are at higher risk of developing extrapyramidal symptoms including tardive dyskinesia with conventional antipsychotics. Therefore, therapy with conventional antipsychotics including depot preparations should be mainly reserved for those patients who have failed treatment with traditional mood stabilizers and atypical antipsychotics.

Atypical Antipsychotics. Atypical antipsychotics are widely used for treating acute mania and all currently available agents in North America with the exception of lurasidone and clozapine have proven efficacy from double-blind, controlled trials. If a manic patient responds to an atypical antipsychotic agent, whether continuation of that atypical antipsychotic is effective in preventing relapse of mood episodes is an important clinical question. There is evidence that continuation of aripiprazole monotherapy in such patients is effective in preventing mood episodes and manic episodes but not depressive episodes. Similarly, aripiprazole adjunctive therapy to lithium or valproate is also beneficial in preventing manic episodes. Aripiprazole dose range is between 10 and 30 mg/day with a mean dose of about 17 mg/day when it is used as an adjunctive therapy and about 24 mg/day when used as a monotherapy for prophylaxis.

Continuation of olanzapine in manic/mixed episode patients who respond to olanzapine is effective in preventing manic, mixed, and depressive episodes, but the magnitude of benefit appears to be greater for preventing mania and mixed episodes relative to depression. Olanzapine appears to be as effective as lithium and valproate in preventing mood episodes. Olanzapine adjunctive therapy to lithium or divalproex appears to be useful in preventing symptomatic relapse of mood episodes.
While oral risperidone has not been assessed for its efficacy, manic patients who responded to oral risperidone and switched to risperidone long-acting injectable (Risperdal Consta) are less likely to experience relapse of mood episodes. Like aripiprazole, Risperdal Consta is effective in preventing manic episodes but not depressive episodes. Most patients require about 25 mg of Risperdal Consta every 2 weeks for preventing manic episodes. Risperdal Consta adjunctive therapy is also effective in preventing relapse of mood episodes and manic episodes but not depressive episodes in frequently relapsing bipolar patients.

Paliperidone ER monotherapy (mean dose of 6 mg/day) continuation in manic patients who responded to paliperidone is effective in prolonging time to and reducing the risk of relapse of mood episodes and manic episodes but not depressive episodes. In schizoaffective patients, paliperidone palmitate once monthly (between 78 and 234 mg monthly) given as either monotherapy or adjunctive therapy is also beneficial in reducing the risk of relapse of manic, depressive, and psychotic symptoms.

Quetiapine is effective in preventing mood episodes, manic/mixed episodes, and depressive episodes in bipolar patients who responded to quetiapine during acute mania or bipolar depression. Quetiapine appears to be equally effective in preventing both mania and depression. The mean doses of quetiapine in the maintenance studies ranged from 527 to 562 mg/day. Quetiapine adjunctive therapy to lithium or divalproex is also effective in preventing both manic and depressive episodes, and the magnitude of benefit of adjunctive therapy for prevention of mania and depression is similar with hazard ratios around 0.3. This means that there is approximately a 70 percent reduction in risk of manic and depressive episodes with quetiapine adjunctive therapy compared with lithium or valproate monotherapy.

While ziprasidone monotherapy is effective in treating acute mania, there is no data to guide clinicians with regard to whether continuation of ziprasidone in such patients is useful in preventing mood episodes. However, ziprasidone adjunctive therapy to lithium or valproate is effective in preventing mood episodes and manic episodes but not depressive episodes.

A recent and as yet unpublished double blind placebo controlled trial showed that asenapine monotherapy was more effective than placebo in preventing relapse of mood episodes in recently stabilized manic/mixed episode patients. Numerically fewer patients in the asenapine group had relapse of manic, mixed and depressive mood episodes. The studies assessing the efficacy of lurasidone in preventing mood episodes are ongoing. Clozapine is likely effective at least in preventing mania but no controlled studies have been conducted to date. In refractory bipolar/schizoaffective patients, clozapine add-on has been reported to be beneficial in reducing manic and psychotic but not depressive symptom scores on rating scales.

**Antidepressants.** There is evidence that TCAs increase risk of manic switch and are not recommended for treating acute bipolar depression. The maintenance studies that compared imipramine with lithium or lithium plus imipramine confirmed increased risk of manic switch with both imipramine mono and adjunctive therapy, and hence TCAs are clearly not appropriate for maintenance therapy of bipolar disorder.

If modern antidepressants are used as adjuncts to treat acute bipolar depression, is continuation of antidepressant therapy beneficial? This issue was addressed in a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial that randomized patients who responded to adjunctive antidepressant therapy to continuation for 1 to 3 years
versus discontinuation within 2 weeks. The results showed that continuation of antidepressant therapy was associated with a trend toward less depressive symptom burden without increasing manic/hypomanic symptoms. Further, the time to depressive episode was significantly delayed in the antidepressant continuation group. There was no evidence of increase in manic episode risk. Interestingly, a rapid cycling course predicted a threefold increase in depressive episodes in patients who continued antidepressants versus those who discontinued. A recent meta-analysis of modern antidepressant adjunctive therapy showed an increased risk of manic switch with long-term therapy with a NNH of 19. Therefore, clinicians are advised to carefully assess the risks and benefits of the need for long term antidepressant adjunctive therapy for each patient and tailor the treatment accordingly.

**CLINICAL RECOMMENDATIONS FOR MAINTENANCE TREATMENT / PROPHYLAXIS OF BIPOLAR I DISORDER**

**General Principles of Management**

Most experts agree the need for long-term prophylaxis in all patients with bipolar I disorder and that prophylaxis should begin after the first manic episode. This is because bipolar disorder is a highly recurrent illness, frequently characterized by residual symptoms and chronicity. Over 90 percent of patients have recurrence of a mood episode within 5 years. A recent meta-analysis suggests that recurrence rates are lower in first manic episode patients with about 60 percent experiencing a mood episode within 4 years. Bipolar I patients experience syndromal or subsyndromal symptoms 50 percent of the time with depressive symptom periods predominating by a ratio of 3:1 to manic/hypomanic symptoms. There is evidence that subsyndromal symptoms increase the risk of full-blown mood episodes. Multiple mood episodes are more likely to be associated with cognitive impairment, structural brain changes, and functional impairment. Frequent episodes alter response to treatment such that those that have had multiple mood episodes are less likely to respond to treatment during acute mood episodes as well as to prophylactic pharmacotherapy and adjunct psychotherapy.

Therefore, the goals of the long-term treatment include prevention of mood episodes, prevention of improvement in subsyndromal symptoms, prevention of suicidal behavior, and improvement in treatment adherence, quality of life, cognitive, social, and work function.

While pharmacotherapy is the mainstay of the long-term prophylactic treatment of bipolar disorder, there is evidence that adjunct psychological treatments are helpful in reducing risk of relapse in bipolar patients. Group or individual psychoeducation is effective in reducing relapse rates by 25 percent to 30 percent. Patients should be educated about illness, adverse effects of medication, early warning symptoms of mood episodes, triggers for mood episodes such as substance use and psychosocial stressors, as well as coping strategies. IPSRT and FFT are also effective. Bipolar patients who recovered from mood episodes tend to benefit from adjunct individual CBT that reduces relapse rates and prolongs time to mood episode. The STEP-BD study reported that recovery rates at 1 year were significantly greater in acute bipolar depressed patients who received CBT, IPSRT, or FFT compared with those that received collaborative care. Thus, adjunct psychological treatments are essential components of the long-term treatment of bipolar disorder to improve treatment adherence and mood symptoms and reduce relapse rates.
Treatment Selection for Maintenance Treatment

Several factors are important in aiding the treatment selection for the maintenance treatment. These include information about course of the illness in the patient, response (lack of response), and tolerability to various treatments during acute episodes and maintenance treatment, predictors of response to various medications, predominant polarity of the illness, comorbidity, and whether the most recent episode was manic or depressive and what treatment/s were effective in remitting this episode. Family history of bipolar disorder if present and treatment response in family members are also helpful in some cases.

First-Line Treatments

Lithium, valproate, lamotrigine, and some atypical antipsychotics are effective and are recommended as first-line agents for the maintenance treatment of bipolar disorder (see Table 13.7–7). However, it is important to note that the benefits of these agents in reducing relapse rates have been demonstrated in bipolar patients who were responders to acute therapy with the same agents. The only exception to this is lithium that has been shown to be effective in the maintenance treatment regardless of whether patients were treated for an acute episode with lithium or not.

Table 13.7–7. Recommendations for Maintenance Pharmacotherapy of Bipolar Disorder

| First line | Monotherapy: Lithium, lamotrigine (limited efficacy in preventing mania), divalproex; olanzapine, quetiapine, risperidone LAI (mainly for prevention of mania), aripiprazole (mainly for preventing mania), asenapine  
Adjunctive therapy with lithium or divalproex. Quetiapine, risperidone LAI (mainly for prevention of mania), aripiprazole (mainly for preventing mania), ziprasidone (mainly for preventing mania)  

| Second line | Monotherapy: Carbamazepine, paliperidone ER, paliperidone palmitate  
Combination therapy: Lithium + divalproex, lithium + carbamazepine, lithium or divalproex + olanzapine, lithium + risperidone, lithium + lamotrigine |

| Third line | Monotherapy: Ziprasidone, risperidone  
Adjunctive therapy: Clozapine, ECT, omega-3 fatty acids, oxcarbazepine, gabapentin  

Not recommended | Monotherapy: Gabapentin, topiramate, or antidepressants  
Adjunctive therapy: Flupenthixol |

*Given the metabolic side effects, use should be carefully monitored.

†Manic patients who responded to these, continuation is appropriate as a first line.

LAI, long-acting injection; ECT, electroconvulsive therapy; ER, extended release.

Which First-Line Treatment? If a patient was recently treated for an acute manic episode with monotherapy with one of the first-line agents listed in Table 13.7–7, it is advisable to continue the same medication for the maintenance treatment. Risperidone and ziprasidone are first-line agents for mania but not for the maintenance therapy because of lack of data. However, given that the other atypical agents that are effective in mania are also effective in maintenance treatment, clinicians may choose to continue these agents for the maintenance treatment after discussing the potential benefits and risks with such strategy. Although paliperidone ER is effective in maintenance treatment, it was less effective than olanzapine, and hence, it is listed as a second-line treatment for maintenance, but in manic patients who...
were responders to paliperidone ER, clinicians may also choose to continue this medication for prophylaxis.

It is important to note that most atypical antipsychotic medications with the exception of quetiapine and possibly olanzapine are effective mainly in preventing mania. Hence, if a patient’s illness course is characterized by predominant depressive polarity, clinicians are advised to consider adding lamotrigine or lithium to an atypical antipsychotic agent or replacing the atypical antipsychotic agent with either lithium or quetiapine for prophylaxis.

Manic patients who were treated with a combination of lithium or valproate with an atypical antipsychotic, there is evidence that continuation of combination therapy is more effective than lithium or valproate monotherapy for preventing relapse of mood episodes. A recent study that compared different durations of atypical antipsychotic adjunctive therapy with risperidone or olanzapine for the maintenance treatment reported that adjunctive therapy is beneficial for the first 6 months after remission of mania, but continuation beyond this period was associated with significant weight gain liability with no apparent additional benefit in efficacy. Hence, clinicians are advised to carefully assess the need for the continuation of atypical antipsychotic adjunctive therapy beyond 6 months after mania remission. For instance, a longer duration of adjunctive therapy may be appropriate in bipolar patients with a previous history of insufficient prophylaxis with lithium or valproate monotherapy.

All first-line monotherapy agents for acute bipolar depression with the exception of lurasidone are also effective in maintenance treatment of bipolar disorder, and hence should be continued for prophylaxis. In a bipolar depressed patient treated with lurasidone monotherapy, clinicians may choose to continue this medication for prophylaxis despite lack of maintenance data given its D2 blockade (likely confers acute and prophylactic antimanic efficacy) properties. Lamotrigine monotherapy is effective mainly in preventing mania, and hence in bipolar patients with previous severe manic episodes, clinicians are well advised to add a prophylactic antimanic agent such as lithium or an atypical antipsychotic for optimal prophylaxis.

If a bipolar depressed patient responded to adjunctive modern antidepressant therapy, is continuation of adjunctive therapy with antidepressant beneficial? There is preliminary evidence that continuation in non-rapid cycling bipolar patients is beneficial in reducing the risk of depressive relapses without destabilizing mood. The CANMAT/ISBD guidelines recommend tapering and discontinuing antidepressants about 8 weeks after remission of depression, based on the assumption that antidepressants are primarily needed to cover the natural duration of the depressive episode, and beyond this, there is a risk of potential destabilization.

In making a decision with regard to the maintenance medication for bipolar patients who are currently not on any treatment, clinicians need to consider several factors outlined in treatment selection section above. If lithium and quetiapine have not been tried previously, given the robust evidence for efficacy in preventing both mania and depression, they are the most appropriate first-line agents for such patients. Patients with a history of alcohol or substance abuse or mixed features may be more appropriate for valproate therapy. For those with predominant manic polarity, any first-line agent with the exception of lamotrigine would be appropriate.
What If a First-Line Agent Is Ineffective? If a patient experiences breakthrough subsyndromal symptoms or relapse while on monotherapy with one of the first-line agents, a switch to an alternative first-line agent or a combination therapy is appropriate. For instance, if a patient on lithium experiences depressive symptoms, consider adding lamotrigine or quetiapine. If manic symptoms emerge on lithium, consider adding an atypical antipsychotic or valproate or if there are tolerability issues, consider switch to an alternate first-line agent. It is recommended that monotherapy or combination therapy with several first-line agents be tried before embarking on second-line strategies for the maintenance therapy.

Second-Line Treatments

Given that the evidence for prophylactic efficacy of carbamazepine and paliperidone is less robust, these options are mainly considered for bipolar patients who failed or had tolerability issues to monotherapy with first-line agents. Carbamazepine does not cause weight gain and is effective in preventing relapses, particularly in patients with atypical forms of bipolar disorder.

However, many patients who failed several first-line agents are unlikely to respond to monotherapy. Hence, combination therapy strategies outlined in Table 13.7–7 are most appropriate for such patients.

Third-Line Treatments

Clinical experience and some controlled data suggest that clozapine adjunctive therapy is very effective in refractory bipolar disorder. However, in addition to the risk of agranulocytosis, clozapine is associated with significant weight gain and metabolic side effects, and hence patients need to be monitored closely for these adverse events and treated appropriately. For some refractory patients, maintenance ECT is an option. Adjunctive therapy with omega-3-fatty acids and other agents can be considered for patients who have tolerability issues or suboptimally controlled with other combination strategies.

TREATMENT OF BIPOLAR II DISORDER

Although bipolar II disorder is common, associated with significant morbidity and mortality, few clinical trials investigated the efficacy of treatments for various phases of bipolar II disorder. The limited data that is currently available is derived from studies of bipolar I disorder or major depressive disorder that had included a few patients with bipolar II disorder. Therefore, in the absence of controlled clinical trial data, by necessity, extrapolation is made from the treatment studies in bipolar I disorder, to aid clinical decisions in managing bipolar II disorder.

Treatment of Hypomania

It is generally believed that medications that are effective in treating acute mania are also effective in treating hypomania. Indeed, small placebo-controlled trials or open-label studies demonstrated that valproate, quetiapine, and risperidone are effective in treating hypomanic symptoms. These findings are consistent with clinical experience of experts in the field.

Thus, bipolar II patients with persistent hypomanic symptoms could be treated with an antimanic agent to rapidly alleviate hypomanic symptoms. Prior history of treatment
response, adverse effects of medications, and patient preferences are important considerations in treatment selection. If a patient had been taking a prophylactic antimanic agent, an increase in the dose of that medication may be sufficient in some cases. Medications that could potentially be contributing to hypomanic symptoms such as antidepressants should be discontinued.

**Treatment of Bipolar II Depression**

The data for efficacy of various treatments is even more limited for treating acute bipolar II depression relative to bipolar I depression. Quetiapine is the only medication with some evidence for efficacy from placebo-controlled trials with adequate sample sizes in treating acute bipolar II depression. In three out of five studies, quetiapine/(XR) was more effective than placebo in improving depression with improvement apparent as early as week 1. Hence, quetiapine is an appropriate first-line option for bipolar II depressed patients who are drug naïve or have never tried quetiapine.

Most experts recommend lithium, lamotrigine, valproate, and lurasidone as appropriate monotherapy agents for some patients with bipolar II depression despite limited and conflicting data.

Modern antidepressants are widely used to treat bipolar II depression, although the evidence is limited and conflicting. Given the limited effective options for treating bipolar II depression, modern antidepressant adjunctive therapy is appropriate for treating some patients with bipolar II depression. A meta-analysis suggests that the risk of antidepressant mood elevation is lower in bipolar II disorder compared with bipolar I disorder (7 percent in acute and 14 percent in maintenance trials versus 14 percent and 23 percent, respectively for bipolar I). Therefore, there is less disagreement among experts about the use of modern antidepressant adjunctive therapy for bipolar II depression. This advice is consistent with the recommendations of a recent ISBD Task Force that endorses its use in bipolar II depression except in patients with rapid cycling bipolar disorder and in those with mixed features. Although a series of small studies suggest that antidepressant monotherapy is effective and is not associated with increased risk of switch, such strategy is not recommended for most bipolar II depressed patients.

ECT is an effective treatment of bipolar II depression. Although the evidence is very limited, adjunctive therapy with pramipexole, modafinil, omega-3 fatty acids or n-acetyl cysteine could be considered for treating bipolar II depressed patients who are refractory to above strategies.

**Maintenance Treatment of Bipolar II Disorder**

Syndromal or subsyndromal depressive symptoms comprise the vast majority of symptomatic periods in patients with bipolar II disorder. Therefore, the major challenge in the management of bipolar II disorder is not only to treat depressive episodes to full remission but also to prevent relapse/recurrence of depressive episodes without increasing the risk of hypomanic switch.

Clinicians typically continue the medication that worked for the acute episode for the maintenance treatment. While such strategy has not been widely studied in bipolar II disorder, there is some evidence that bipolar II depressed patients who respond to quetiapine...
or lamotrigine benefit from continuation of the same medication for the maintenance treatment. Lithium is beneficial for maintenance regardless of whether it was used to treat acute episodes or not. If a patient has responded to adjunctive modern antidepressant therapy, continuation of the combination may be beneficial for some patients. Some studies suggest that patients who responded to fluoxetine monotherapy may benefit from continuation of this medication for prophylaxis. Although these studies did not report increased hypomanic switch rates, clinicians are well advised to warn patients about the potential risk of hypomanic/mania switch if such strategy was chosen. If the above options are ineffective, open-label data and clinical experience support the use of combinations of mood stabilizers or a mood stabilizer and an atypical antipsychotic with or without a modern antidepressant or pramipexole or other agents such as NAC or omega-3 fatty acids.

TREATMENT OF BIPOLAR DISORDER WITH COMORBIDITY

Both psychiatric and medical comorbidity is highly prevalent in patients with bipolar disorder and impacts clinical outcome. In general, bipolar patients with comorbidities tend to have poorer outcomes as they are less likely to respond or take longer time to respond to treatments and are more likely to relapse. Therefore, the optimal management of such patients includes treating not only symptoms associated with bipolar disorder but also addressing comorbidities without destabilizing bipolar disorder. However, clinical trials conducted for regulatory approval of treatments for bipolar disorder have systematically excluded patients with comorbidities. Therefore, in the absence of evidence-based strategies for the management of patients with bipolar disorder with psychiatric comorbidity, the treatment decisions for the management of comorbidity would have to be made by necessity, based on the secondary analysis of data on comorbid symptoms in trials of bipolar disorder and the treatment efficacy data from clinical trials of primary condition. In choosing treatments for managing comorbidity, clinicians must carefully weigh the risks of adjunctive treatments such as their propensity to destabilize bipolar disorder and adverse events versus benefits in treating comorbidity and the consequential positive impact on the outcome of bipolar disorder.

Anxiety Disorders

Since several psychological treatments such as CBT have been shown to be effective in treating primary anxiety disorders, their use is preferable in treating the comorbid anxiety disorders in bipolar patients as they pose little risk of illness destabilization.

Generalized Anxiety Disorder. Generalized anxiety disorder/anxiety symptoms are common in bipolar disorder, impact clinical outcomes, and hence must be treated. In addition to psychological treatments, if a patient has been taking an anticonvulsant such as lamotrigine or valproate or an atypical antipsychotic such as quetiapine or olanzapine plus fluoxetine combination for bipolar disorder, these should be optimized as there is some evidence from secondary analysis of clinical trials or open-label data to support their efficacy. If optimization of ongoing pharmacotherapy is ineffective in resolving symptoms, medications that have been shown to be effective in treating primary anxiety disorder should be considered. Among these, pregabalin and quetiapine are preferable as they are not associated with the risk of destabilization of bipolar disorder. Gabapentin is also useful as anecdotal evidence supports its efficacy in treating comorbid anxiety symptoms in bipolar patients. Some SSRI antidepressants (escitalopram, paroxetine, sertraline) are effective and widely used in clinical practice. Similarly, some newer antidepressants such as agomelatine and
vortioxetine are also effective in treating GAD; the risk of illness destabilization appears to be lower with agomelatine while no data are available as yet for vortioxetine. However, it must be remembered that since anxiety disorders/symptoms pose chronic symptom burden in bipolar disorder, the long-term use of SSRIs or other antidepressants in bipolar patients may pose the considerable risk of illness destabilization. Hence, other strategies outlined above should be tried first before considering the use of SSRIs. If SSRIs are used on a longer term basis, patients need to be on adequate cover with antimanic mood stabilizing medications (i.e., a combination of two mood stabilizers or a mood stabilizer and an atypical antipsychotic). Although SNRIs such as duloxetine and venlafaxine are effective in primary anxiety disorder, their use in bipolar patients is not recommended due to their potential higher risk of mood destabilization.

**Social Anxiety Disorder.** While the estimates of social anxiety disorder (SAD) in bipolar disorder vary, the National Comorbidity Survey reported that 39 percent of patients with any type of bipolar disorder have SAD. There is virtually no controlled efficacy data in this comorbid population. CBT is very effective in treating primary SAD and likely useful in comorbid patients as well. Among the agents shown to be effective in treating primary SAD, pregabalin and gabapentin are preferred options as they have no propensity to destabilize bipolar disorder. In nonresponders, SSRIs could be considered provided patients with bipolar disorder are on adequate mood stabilization. Beta-blockers such as propranolol and atenolol are not recommended as they do not appear to be beneficial in primary SAD.

**Panic Disorder.** Between 14 to 27 percent of patients with bipolar disorder have panic disorder and up to 35 percent of patients with bipolar disorder report experiencing panic attacks. There is limited open-label data to support the use of valproate in bipolar disorder with comorbid panic disorder. There is post hoc evidence that gabapentin is useful in severe PD. If optimization of anticonvulsant therapy is ineffective, addition of an atypical antipsychotic such as quetiapine or risperidone may be appropriate. As with other anxiety disorders, SSRIs are effective but these should be given preferably in conjunction with an atypical antipsychotic and possibly a mood stabilizer in order to minimize the risk of manic/hypomanic switch. Clonazepam, alprazolam, and lorazepam are also effective and they may be appropriate for the short-term use to control panic attacks.

**Post-Traumatic Stress Disorder.** Lifetime post-traumatic stress disorder (PTSD) rates range from 16 to 39 percent in patients with bipolar disorder. Childhood sexual abuse, adult sexual assault, and adult survival of the suicide, homicide, or accidental death of a close friend or relative are commonly associated with comorbid PTSD in bipolar disorder. Anticonvulsants are likely beneficial and should be preferred particularly in light of their efficacy in reducing cravings for alcohol, as comorbid alcohol abuse is common in patients with PTSD. Atypical antipsychotic mono or adjunctive therapy has been reported to be beneficial for primary PTSD particularly in treating symptoms of intrusion, and hence are appropriate options in anticonvulsant nonresponders. As with other anxiety disorders, SSRIs are effective but should be used preferably in conjunction with an atypical antipsychotic. Benzodiazepines are not effective and there is anecdotal evidence that they may worsen symptoms.

**Obsessive–Compulsive Disorder and Related Disorders.** About 10 to 25 percent of patients with bipolar disorder have a lifetime history of OCD. The symptoms of OCD are
particularly exaggerated during depressive episodes. Sexual and religious obsessions tend to be more common in bipolar disorder and their severity tends to wax and wane over lifetime. Psychological treatments such as CBT should be offered first. There is no controlled data for pharmacotherapy in comorbid patient population, but there is some evidence that adjunctive treatment with lamotrigine, topiramate, or atypical antipsychotics such as risperidone, aripiprazole, olanzapine or quetiapine is effective in treating primary refractory OCD. Since these medications with the exception of topiramate are effective in treating bipolar disorder, they should be optimized first. In those that continue to manifest OCD symptoms, therapy with topiramate or a combination of an atypical antipsychotic with an SSRI (i.e., escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) may be considered. The need for ongoing SSRI treatment should be evaluated periodically, and the risk versus benefit analysis should determine the duration of SSRI treatment. While clomipramine is effective in primary OCD, it is not recommended in bipolar patients due to higher risk of manic switch.

**Alcohol and Substance Use Disorders**

About 50 percent of patients with bipolar disorder have alcohol or substance use comorbidity. There is evidence that valproate is effective in reducing various indices of alcohol use in bipolar patients with comorbid alcohol use, and hence is a preferred option in this population. Lamotrigine is also beneficial for some patients with alcohol comorbidity. Other anticonvulsants such as gabapentin and topiramate have shown efficacy in primary alcoholism and could be used as adjuncts to primary treatments for bipolar disorder in some patients to address alcohol comorbidity. While naltrexone and disulfiram are effective in primary alcohol use disorder, disulfiram is not recommend in bipolar patients given its inhibitory effects on dopamine β-hydroxylase and the potential for worsening of mania. There is some evidence for naltrexone add-on therapy in bipolar patients with alcohol comorbidity. While quetiapine is effective in primary bipolar disorder, it does not appear to have any utility in reducing alcohol-related behaviors.

Valproate, lamotrigine, quetiapine, and risperidone mono or add-on therapy appears to provide some benefit in patients with cocaine abuse. Add-on NAC or modafinil may be useful in some patients.

**Attention-Deficit Hyperactivity Disorder**

The estimates for the prevalence of ADHD in patients with bipolar disorder range from 9 to 30 percent, and therefore, all patients with bipolar disorder should be routinely screened for comorbid ADHD. Bipolar patients with ADHD tend to have an earlier age at onset of mood symptoms, more frequent mood episodes, more suicide attempts, and other psychiatric comorbidities. ADHD symptoms persist during euthymia and contribute to impairment in function. The diagnosis of comorbid ADHD in bipolar patients can be challenging, given the overlapping symptoms. Therefore, clinicians need to be aware of the possibility of both under-diagnosis and over-diagnosis of ADHD in bipolar disorder. Persistent impulsivity and impaired ability for sustained attention despite treatment with mood stabilizing medications and the absence of other symptoms of mood episodes should raise the index of suspicion for ADHD.

If ADHD symptoms and functional impairment persist despite psychoeducation and behavioral interventions in bipolar patients optimized on mood stabilizing medications, institution of specific pharmacotherapy targeting ADHD symptoms is appropriate. However,
clinicians must be aware that ADHD treatments can destabilize the course of bipolar disorder. Adjunctive bupropion is often the first choice, particularly in bipolar patients with comorbid ADHD and frequent depressive episodes/depressive symptoms, as it is less likely to induce manic switch compared with stimulants. In nonresponders, adjunctive modafinil or mixed amphetamine salts or methylphenidate could be considered. If a patient responds, clinicians are advised to periodically evaluate the need for ongoing treatment with stimulants and offer psychoeducation to patients on monitoring for the emergence of manic symptoms.

FUTURE DIRECTIONS IN THE TREATMENT OF MOOD DISORDERS

The ultimate goal is a stratified approach to the personalized treatment of major depressive disorder, bipolar disorders, and other mood disorders. However, this is limited by the failure of clinical phenotypes to inform selection of psychotropic medication. While the search for validated molecular, neuroimaging, and other biomarkers to subgroups within the major depressive disorder and bipolar disorders is underway, this has not yet influenced treatment selection or patient outcomes. A dimensional approach to diagnosis proposed by the National Institute of Mental Health, known as Research Domain Criteria, should facilitate a dimensional approach to evaluating behavioral characteristics associated with different psychiatric disorders at cellular, molecular, neuroanatomical, and behavioral levels.

REFERENCES


Psychotherapy, in various forms, has been one of the cornerstones of therapeutics for mood disorders for decades. Even before controlled studies were available to document the utility of these approaches, there was substantial clinical support or face validity for treating depression psychotherapeutically; depression frequently occurs during times of significant psychosocial stress and often is associated with relevant intra- and interpersonal vulnerabilities. As the field has become more evidence-based and awareness of issues such as cost-effectiveness and disseminability has grown, greater emphasis has been placed on models of therapy that are procedurally specified and empirically tested. These trends were first evident in the introduction of shorter-term or time-limited therapies, particularly those that emphasize more pragmatic behavioral, cognitive behavioral or interpersonal formulations, and interventions. More recently, time-limited and manual-based models of psychodynamic psychotherapy have been introduced for the treatment of mood disorders. All of these therapies aim to improve upon the considerable beneficial effects of supportive clinical management, with the potential for theoretically driven, mode-specific benefits in addition to relief of depressive symptoms. This chapter will review the current status of these therapies.

HISTORY OF PSYCHOTHERAPY FOR DEPRESSION

Psychotherapy for depression arose from psychoanalytic and subsequent psychodynamic models of intervention. Early theories conceptualized depression as an intrapsychic phenomenon stemming from internalized anger that arose from unconscious conflicts. Therefore, treatment was long-term, focused on developing awareness of these internal conflicts through identification and interpretation of historical experiences that reflected such conflicts. Intervention emphasized developing insight into these conflicts through the use of free association and the therapist’s interpretations. This treatment also used the patient’s projections onto the therapist (the transference neurosis) as a means of studying early object relationships and conflicts.

In contrast to more traditional approaches, behavioral theories of depression treatment emphasized observable factors, such as decreased participation in potentially rewarding or pleasurable activities, and suggested that the negative emotional symptoms of depression could be understood as a consequence of withdrawal of reinforcement. Treatment interventions initially were guided by learning theories, but by the 1970s had broadened to include cognitive components (e.g., to increase self-efficacy or decrease negative thoughts or
beliefs about self, world, and future). Some models emphasized social skills or problem-solving strategies, whereas others focused more on increasing positive activities or remediating cognitive symptoms and vulnerabilities. Whatever the differences in specific models of CBT, all emphasized the role of the therapist as a teacher of specific skills that are intended to help the depressed person reduce depressive symptoms and/or improve coping. Moreover, virtually all models of CBT emphasize the importance of homework assignments to enhance mastery and generalization of these skills in “real world” environments.

Arguably the most impactful of the models of CBT to emerge from the 1970s was the approach developed by Beck and colleagues. More commonly known as cognitive therapy (CT), this form of therapy focused more on identifying the negatively valenced automatic thoughts associated with depressed moods and using strategies to both test the accuracy of the negative thoughts and consider more rational (and less depressogenic) alternatives. As many people in the midst of a depressive state evince various kinds of cognitive distortions (e.g., thinking in a more overly general and absolute way or selective recall of negative mood relevant memories or associations), a skilled CT therapist can help most non-psychotically depressed people see examples of “cause and effect” relationships between cognition, mood, and behavior within the first hour of treatment.

Whereas early models of behavior therapy either minimized the value of the therapeutic relationship or were silent about its importance, Beck and colleagues emphasized a collaborative approach between the therapist and the patient, referred to as collaborative empiricism, and specifically structured therapy sessions in discrete 10 to 20 minute segments to ensure that the patient had the opportunity to give feedback (e.g., whether the particular topic was personally relevant or made sense) and express reservations. A collaborative process using Socratic questioning was similarly incorporated to guide and facilitate mastery of techniques for testing and remediating negative thoughts and beliefs, and the patient practices these techniques.

Beyond CT’s initial focus on automatic negative thoughts (“surface” cognitions), Beck’s model of therapy also emphasized the vulnerability to depression was linked to “deeper” forms of cognition, including dysfunctional attitudes and schema. Schemas are underlying cognitive structures that help the brain organize information in memory, guide awareness, and predispose action. The complex thoughts and actions involved in tying a bow are an example of a simple, non-affectively relevant schema. Schemas that are associated with depression are often reflected by automatic negative thoughts or abiding beliefs about competence (“I’m just not good enough”) or intimacy (“No one will ever really love me”), which may be activated by thematically relevant life events. Thus, another distinguishing feature of CT is a specific stress-diathesis model of vulnerability. As such schemas are “silent” (i.e., they must be inferred from the predominant themes or beliefs revealed in automatic negative thoughts), and Beck’s model of CT did deviate significantly from the zeitgeist of the behavior therapy movement. Nevertheless, the fully developed model of therapy developed by Beck and colleagues incorporated more conventional behavioral strategies such as activity scheduling and graded task assignments.

Interpersonal psychotherapy (IPT), developed by Klerman, Weissman and colleagues, emerged in the 1980s as the leading alternative to CBT. Drawing upon psychodynamically influenced interpersonal models (Meyer and Sullivan) and attachment theory (Bowlby), IPT incorporated many of the more pragmatic methods used by social workers in case management to develop a time-limited therapy that addresses the common problematic
patterns in relationships that plague the lives of people with depression, including unresolved grief, role disputes, role transitions, and interpersonal deficits. Beyond eliciting an interpersonal inventory and identifying the area or areas of interpersonal difficulty of greatest relevance to a particular patient, the interventions used in IPT are relatively eclectic and can include psychoeducation, nondirective questioning and empathic support, and role playing and social problem solving. IPT thus may be particularly well-suited for more traditionally trained psychotherapists or counselors who find it difficult to implement the structure, activity level, and the more directive posture that characterize most models of CBT. Significantly, IPT was the first psychotherapy outside of CBT to be evaluated in comparison to antidepressant medications using RCT method.

Several adaptations of IPT have particular utility of patients with more complex depressive disorders. Frank and colleagues incorporated the importance of social rhythm disruption and the adaptive value of social rhythm stability (i.e., the consistency of regular activities such as bedtime and meal times) in their adaptation of IPT, which was primarily targeted for recurrent forms of affective illness, including bipolar disorder. Known as interpersonal and social rhythm therapy (IPSRT), this approach adds an assessment of social rhythm stability and activity scheduling tailored to strengthen the role of social zeitgebers (time givers) in helping patients prevent recurrent affective episodes and promote recovery. Shear and colleagues adapted IPT to focus on complicated bereavement, including clinical presentations in which the thoughts, feelings, and behaviors pertaining to bereavement overlap with the signs/symptoms of PTSD.

More recent innovations in psychotherapy have incorporated techniques from a long-standing meditation tradition, and done so using an evidence-based approach. Mindfulness meditation, developed from Buddhist techniques, emphasizes two skills: observing one’s perceived sensations and accepting and experiencing those sensations nonjudgmentally. In the application of this technique to depression, sensations include cognition and emotional states, as well as input through the five senses. Segal, Teasdale, and colleagues propose that these techniques are relevant for three reasons. First, the training in observation facilitates gathering evidence, which is a central component in CBT. Second, learning to view thoughts—even the most negative or damning ones—as discrete, limited experiences helps patients dampen affective arousal in response to them, which in turn improves their ability considering alternate perspectives. Third, the emphasis in meditation on nonjudgmental observing moves the therapy toward a focus on acceptance rather than change per se. For more chronic depressive disorders, a focus on acceptance—rather than change—can offer a novel therapeutic component, particularly when ability to tolerate distress has interfered with coping behaviors.

Several models of treatment now incorporate mindfulness techniques and are often referred to as “third wave” techniques, reflecting the path from behavioral to cognitive to now mindfulness and acceptance-based interventions within the CBT tradition. Mindfulness-based cognitive therapy (MBCT) is a treatment intervention specifically developed to reduce risk of relapse in individuals who have a history of recurrent depression. Acceptance and commitment therapy (ACT), developed by Steven Hayes and colleagues, emphasizes identifying core values and committing to acting on those values rather than focusing on avoiding suffering. This model was particularly designed for addressing chronic depression. Another closely related therapy, dialectical behavior therapy (DBT), has recently been adapted for work with patients with more treatment-resistant depressions. Initially developed by Linehan and colleagues, DBT is a behaviorally oriented system of therapy that also places
a strong emphasis on mindfulness and acceptance and has well-replicated effects on reduction in suicidal ideations and behaviors.

Family support is an important asset in life and is generally a favorable prognostic indicator across mood disorders. Conversely, there is an increased risk of relapse/recurrence for patients whose families show high levels of criticism and emotional expression. Drawing upon these observations, Miklowitz and colleagues developed FFT, which has primarily been adapted for the treatment of adolescents and young adults with bipolar disorder. This treatment focuses on educating both patients and family members on the disorder and helping them gain a shared perspective of the disorder. From this shared perspective, the therapist guides the family in developing a relapse prevention plan, including ways that the family can identify symptom exacerbations, an agreement about how they will share this observation with the patient, and an understanding of how the patient will respond to this information. Options for managing symptoms are generated (e.g., visiting the doctor for medication adjustment or increasing structure in the home). Family members are also trained in communicating effectively in ways with the patient and reducing the level of hostility and criticism in the environment.

REVIEW OF RESEARCH FINDINGS

Unipolar Disorders

A number of forms of psychotherapy (see Table 13.8–1) have been shown to be either efficacious or probably efficacious for outpatients with major depressive disorder. These treatments have been shown to be effective in outpatients treated in a variety of settings (e.g., psychiatric clinics, psychology clinics, college counseling centers, community mental health centers, and primary care clinics) and meta-analyses suggest that, across modes of therapy, differences tend to be modest to nonexistent. By contrast, no form of psychotherapy is indicated as the primary treatment of bipolar disorder, although a growing literature supports the value of several different forms of psychotherapy as adjuncts to ongoing therapy with mood stabilizers.

CBT has been evaluated in numerous RCTs, including placebo-controlled studies that included first- and second-generation antidepressants as active comparators. Although the findings of one very influential multicenter trial, the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program (TDCRP), suggested that CT may be less effective than pharmacotherapy in patients with more severe depressive symptoms, the findings of a number of other RCTs do not support such a relationship and, overall, outpatients with higher symptom severity scores tend to respond slower or less favorably to many different interventions. In general, depressed patients treated with CBT are as likely to respond/remit across 8 to 16 weeks of treatment as are patients treated with antidepressant medications.

A number of studies have likewise demonstrated that IPT also is an effective treatment of depressed outpatients. Although results of the NIMH TDCRP study revealed trends favoring IPT over CT among the more severely symptomatic subset of patients, the findings of several other subsequent comparisons have not revealed any meaningful differences. Although there are numerically more studies of CBT than IPT for most depressive disorders, there is a particularly strong literature supporting the use of IPT for the treatment of depressions during and after pregnancy.
The results of several studies suggest that simpler behavioral interventions may be as effective for depressed outpatients as more elaborate models of CBT that include cognitive restructuring. The performance of a “pure” behavioral activation (BA) intervention was particularly strong for patients with more severe levels of depression in one study. Whether BA and CT might be sequenced for patients at increased risk of relapse or recurrence is an interesting topic for future research, particularly because it is now possible to provide a lead a portion of the curriculum covered in CBT over the internet, with additional benefit resulting from telephone support.

Although RCTs of time-limited variations in psychodynamic psychotherapy were sparse in recent years, there is now a sufficient body of research to conclude that these are efficacious for the treatment of depressed outpatients (as compared to waiting list control conditions) and have outcomes across 8 to 16 weeks that are comparable to CBT or IPT. To date, no reliable indicators of preferential responsiveness to psychodynamic psychotherapy versus other forms of psychotherapy have emerged.

Across studies and types of psychotherapies, there is evidence that a response to psychotherapy may be more durable or persistent for weeks or months after therapy is stopped than is the case following withdrawal of antidepressant medications. As a result, differences in the cost of delivering care that might favor pharmacotherapy in the short-run may dissipate or actually shift in favor of psychotherapy when the need for prophylactic therapy is taken into account. Ongoing psychotherapy may, however, be useful when a typically adequate course of individual therapy (8 to 16 weeks) only leads to an incomplete remission. In one study of incompletely remitted patients judged to be at high risk for relapse, the provision of 8 months of continuation phase CBT had a relapse prevention effect that was comparable to pharmacotherapy. Whereas psychotherapies may not warrant ongoing care for
relapse prevention, it is less certain that an effective course of time limited psychotherapy actually reduces the longer term risks of recurrent depression. In the classic study of maintenance phase therapies conducted by Frank and colleagues, patients with highly recurrent forms of major depressive disorder who recovered with the combination of IPT and imipramine were significantly more like to remain well when their maintenance treatment included the active imipramine than when they received monthly sessions of “maintenance” IPT. Nevertheless, other studies have indicated that the addition of CBT or MBCT during an ongoing course of continuation or maintenance phase therapy may improve residual symptoms and reduce the risk of recurrent illness after discontinuation of antidepressant medication.

**Group and Couples Therapy.** A number of studies indicate that cognitive and behavioral therapies are well-suited for delivery in groups. Group delivery of CBT may not only be a cost-effective alternative to individual therapy, but may have particular value for groups with subsyndromal symptoms, for whom individual treatment might be judged not to be necessary. Depressed individuals with marital discord similarly have been shown to benefit from behavioral marital therapy (BMT). In controlled studies, BMT appears to have an impact on depressive symptoms that is comparable to individual CBT, with the added value of greater improvements in marital functioning than CBT

**Combined Psychotherapy and Pharmacotherapy.** Many psychiatrists favor combining psychotherapy and pharmacotherapy, particularly for the treatment of outpatients with more chronic, severe, or treatment-resistant forms of depression. Although the effect sizes typically favoring combined treatment over competently administered monotherapies have tended to be modest, in a pooled analysis of participants from a series of studies conducted at the University of Pittsburgh the advantage of combined treatment was particularly large for patients with more severe, recurrent depressive disorders. Results of several larger scale, multicenter studies likewise showed advantages for patients with more severe or chronic depressions. Similarly, several studies that have adapted IPT and CBT to inpatient settings have shown that the addition of focused therapy improves outcomes in comparison to treatment as usual conditions that include antidepressant medication and milieu therapies. As noted earlier, sequential studies of pharmacotherapy followed by focused psychotherapy have likewise shown advantages for promoting recovery or facilitating discontinuation of pharmacotherapy.

**Bipolar Disorders**

In addition to the models of psychotherapy described earlier, group psychoeducation has emerged as a cost-effective form of adjunctive intervention for people with bipolar disorder. As developed by Colom and colleagues in Barcelona, this practical treatment can be conducted in groups as large as 30 to 50 participants and their families and focuses on risk factors, warning signs, and coping strategies. Although the acute efficacy of psychoeducation has never been studied for bipolar depression, it has been shown in several studies to have a significantly positive effect on treatment adherence and relapse prevention.

With respect to the treatment of bipolar disorder, no form of psychotherapy has been shown to be effective as a monotherapy for the treatment of mania or mixed states. Like group psychoeducation, most formal therapies have been studied as adjuncts to mood stabilizers with the goal of prevention of relapses or recurrences. Looking across interventions, the evidence is fairly convincing that adjunctive therapies, including psychoeducation, IPSRT,
FFT, and CBT, significantly increase well time and reduce the risk of relapses and recurrence. Although one should be cautious comparing across studies, it appears that the magnitude of benefit for adjunctive psychotherapy, as compared to no adjunctive treatment or treatment as usual alone, may be comparable to the prophylactic effects of mood stabilizers such as lamotrigine, compared to placebo in contemporary studies (see Table 13.8–2).

It is less certain if focused psychotherapies are effective treatments of acute bipolar depression, although the same caveat could be stated about pharmacotherapy with antidepressants or mood stabilizers. In one component study of the large-scale US study known by the acronym STEP-BD, adjunctive psychotherapy with FFT, IPST, or CBT had significant effects on both depressive symptoms and social functioning. The nature of this study did not permit valid comparison among the psychotherapies. Given the hazards of treatment-emergent affective switches and the potential for inducing rapid cycling associated with antidepressants in bipolar disorder, the potential for focused psychotherapies for adjunctive treatment of bipolar I depressive episodes warrants further exploration. Likewise, the use of focused psychotherapy alone for selected patients with bipolar II depressive episodes deserves further study.

Table 13.8–2. Efficacious Treatments for Bipolar Disorder

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Conceptualization of Disorder Etiology</th>
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| Cognitive-behavioral therapy | Biological vulnerability interacting with stress  
Skills deficits limit ability to manage symptoms                                               |
| Interpersonal and social rhythm therapy | Interpersonal vulnerabilities arising from early attachment and learned relationship patterns, 
plus disruption of social rhythms                                        |
| Family focused therapy      | Biological vulnerability exacerbated by negative expressed emotion in family environment.               |

<table>
<thead>
<tr>
<th>Sample Interventions</th>
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<tbody>
<tr>
<td>Identify and challenge automatic thoughts that interfere with treatment adherence</td>
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<tr>
<td>Engage in rewarding activities that provide increased routine and stability</td>
</tr>
<tr>
<td>Practice communication skills with providers</td>
</tr>
<tr>
<td>Develop awareness of patterns in primary relationships and the therapeutic relationship</td>
</tr>
<tr>
<td>Track and stabilize social rhythms</td>
</tr>
<tr>
<td>Interpersonal skills training</td>
</tr>
<tr>
<td>Communication analysis</td>
</tr>
<tr>
<td>Education regarding the disorder, including precipitants, risk factors, and effective treatment</td>
</tr>
<tr>
<td>Establish relapse prevention plan, agreed upon by all involved family members</td>
</tr>
<tr>
<td>Communication skills training</td>
</tr>
<tr>
<td>Problem-solving skills training</td>
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**APPLYING THE RESEARCH TO CLINICAL PRACTICE**

There have been important advances in the understanding the roles of psychotherapy in the treatment of mood disorders, and several good psychotherapy options for both unipolar and bipolar disorders now exist. Nonetheless, clinicians are often faced with providing treatment to patients who may not match the typical participant in research trials and need to extrapolate from the available data to develop a treatment plan for their patient. Of course, several important critical questions remain, including which treatment is best for which
patient, what are optimal doses (e.g., number and length of sessions), and how best to address comorbid disorders. It is also not clear how critical specific techniques associated with these interventions are for the successful treatment of mood disorders. A study of the therapeutic process of IPT (i.e., the actual in-session behaviors of the therapist and patient) found that the process was more consistent with ideal CBT than ideal IPT. A meta-analysis examining comparisons between specific psychotherapies and placebo conditions found that the difference between treatments was related to the adequacy of the placebo design. Studies with placebo comparisons deemed adequate (e.g., using nonspecific therapy techniques for the placebo condition and matching for level of contact with therapists) showed smaller differences between active interventions and placebo than those studies with placebo conditions that were inadequate (e.g., less therapist contact or constraint of topics to issues not related to the patient’s disorder). These findings suggest that differences between psychotherapy techniques may be less critical than some of the shared components (e.g., positive therapeutic relationship, shared goals, and facilitated behavior change). There are also no definitive answers regarding the underlying models of depression. Although BA, CBT, and IPT are based on empirical models of psychopathology that all have supportive evidence, the development of these treatments and the conceptualization of depression are extrapolations beyond the available data.

Clinicians then are faced with how to use this knowledge in treating patients. One key approach, regardless of model, is the development of a case formulation to guide treatment.

TREATMENT OF MAJOR DEPRESSIVE DISORDER WITH CBT

CBT is based on the assumption that dysfunctional beliefs, learned in response to life experiences, lead to dysfunctional behavioral and emotional responses. Treatment therefore modifies these beliefs to reduce problematic responses and to increase functional responses. Patients learn to modify beliefs by first learning to observe their thinking, affect, and behavior and then evaluating how thoughts influence mood and actions. As the patient becomes aware of these processes, the therapist teaches skills in questioning and testing the validity of beliefs and developing alternative, more accurate, functional beliefs. The long-term goal of treatment is for patients to learn the skills to such an extent that they are able to be their own therapist.

Assessment and measurement, by the therapist and the patient, are central to effective CBT. The therapist teaches the patient to quantify the issues of concern. Patients learn to observe and define their own assumptions that lead to depression and then to engage in a series of experiments to improve their mood. Patients learn to measure the effects of these experiments, so that they test the previous assumptions and can develop new, more constructive beliefs and actions that reduce depression and other problematic moods and behaviors.

A 23-year-old, unmarried, African-American woman presented to a community mental health clinic. The patient was in the midst of her first semester at law school. Her primary physician had referred her to the clinic after the patient reported frequent crying and feeling hopeless. Symptoms included depressed mood nearly every day; crying spells “out of the blue”; anhedonia; early, middle, and late insomnia; decreased appetite; weight loss; difficulty concentrating; feeling worthless; thoughts of death; and suicidal ideation.

CBT, like most other psychotherapies, uses a case conceptualization approach to determining treatment of each patient. In CBT, the conceptualization is developed based on an
understanding of how different aspects of cognition are related. Aaron Beck and, later, Judith Beck proposed that cognition could be divided into three levels: automatic thoughts, intermediate beliefs, and cognitive schemata. The most accessible, labeled, automatic thoughts represented the conscious response to stimuli. For example, the previously mentioned patient, when studying, often thought, “I’ll never understand this.”

The second level, intermediate beliefs, is assumptions about the self, the world, and the future that led to the automatic thought occurring in response to a particular stimulus. Using the previous example, the patient believed that she was not competent and that she was not good enough; she perceived the world (in this case, professors and classmates) as attacking and critical. She anticipated that the future would be filled with failure. At times when things went well, she was not unduly distressed. However, in the face of failure or criticism, she quickly experienced self-critical thoughts that were consistent with these beliefs.

The content (e.g., the beliefs) and the organization of that content define the third level, cognitive schema. An individual’s schema determines which stimuli are most likely noticed and encoded in memory, which stimuli are ignored or discounted, how encoded information is linked or associated in memory, and which memories are most easily recalled. For the previously mentioned patient, she may suffer from a schema that could be conceptualized as, “I’m not good enough.” She tends to notice information consistent with this belief and tends to ignore or to discount other information.

As the therapist completes an initial assessment and establishes a treatment plan, a central goal is to elaborate a case conceptualization that will facilitate treatment. By understanding the unique meaning of experiences to the patient, the therapist can be more effective in identifying interventions that truly test the beliefs and produce meaningful improvement.

Several authors have described models for developing case formulations in CBT, and they generally are based on gathering evidence to propose an underlying schema. Once the automatic thoughts, beliefs, and schema are identified, interventions are chosen based on these hypothesized structures. The therapist continues to gather evidence throughout treatment, refining the formulation over time.

**Initial Assessment**

Specificity and accurate data gathering are a key focus of CBT. In particular, assessment of diagnosis and symptoms is necessary. Primary assessment preferably includes standardized measures, such as the Structured Clinical Interview for DSM-5 (SCID), the Hamilton Rating Scale for Depression, and the Beck Depression Index (BDI). The assessment also needs to include the dimensions of functioning: interpersonal relationships, work and achievement, health, and recreation. As treatment progresses, a formulation is developed regarding the patient’s case conceptualization, as well as particular cognitive and behavioral coping strategies that the patient uses.

The previously presented patient experienced impairments in several areas of functioning. The patient had not contacted family or friends for several weeks, which was unusual for her. She had no current close friends at her school and had not had a dating relationship for several years. She reported that she was skipping classes and that she believed she was failing her program. The patient made statements such as, “I’m just a total loser” and “I don’t belong.” Despite excellent grades in college, she believed she was only accepted to law school due to her minority status. She primarily coped with stress by ruminating and had stopped many rewarding activities (e.g., exercise).
She had several relevant experiences from her early childhood. The patient had been adopted shortly after her birth by a white couple and was their only child. She grew up in an almost exclusively white neighborhood. She reported that, although she had some friends, she had no African-American friends and that she often felt discriminated against by whites and the few African-Americans with whom she had contact, who criticized her for “trying to be white.” The patient described that, despite having devoted parents, she had a sense of not being good enough and being out of place since approximately 6 years of age, when she first started school.

**Course of Therapy**

In the initial session, the therapist has several goals, including (1) orienting the patient to the treatment approach, (2) establishing rapport, (3) identifying problems and treatment targets, (4) assessing current symptom and problem severity, (5) providing some initial symptom relief, and (6) introducing an initial homework assignment. In reality, these components tend to overlap. For example, it is often helpful to illustrate the CBT model using a life experience of the patient and, in doing so, to provide a chance at some symptom relief. An example could be processing a situation such as being late to a first therapy appointment:

Therapist: You mentioned that you were upset because you were late. Can you tell me what you were thinking when you realized you were late?

Patient: I figured you’d be angry.

Therapist: Okay, and when you thought I’d be angry, how did you feel?

Patient: Pretty nervous.

Therapist: So that is what we will focus on in here, how your thinking in different situations influences how you feel. In this case, you were late, thought “he’ll be angry,” and felt nervous. Our goal is to test out the beliefs, like “he’ll be angry,” and change them when they aren’t healthy or accurate. The great thing is that you sort of implicitly tested out the belief that I’ll be angry by showing up. Was I angry?

Patient: You didn’t seem angry.

Therapist: How anxious did you feel once we started talking?

Patient: Well, I’m feeling more comfortable.

Therapist: What thoughts do you have now about me being angry?

Patient: I don’t think you’re angry.

Therapist: So, this is an example of what we’re going to be doing in therapy—I’ll be helping you to identify thoughts that make you feel bad. We’re then going to work together to come up with ways to check them out and change them if they’re not true or accurate. You checked out whether I was angry by observing me, and you changed your thought, and, now, I get the impression that you feel better.

In this example, the model of CBT is described for the patient and illustrated using her own thoughts, behaviors, and feelings. In particular, the effect of behavioral testing of beliefs (i.e., coming into session late and finding out if the therapist actually was angry) is pointed out. To increase her sense of efficacy, the therapist points out that her current actions can lead to
mood change (feeling more relaxed after coming in late) and that she is already demonstrating some of the necessary skills to benefit from CBT.

To facilitate skills, an agenda is explicitly set forth and agreed on by the therapist and the patient every session. In the early sessions, the patient is oriented and trained in thought tracking and activity tracking. The decision of which thoughts or behaviors are targets for intervention is based on the specific needs of the patient, which the therapist assesses using the case formulation. In the case described, the patient reported feeling “miserable” when she arrived at class. The therapist used the situation to train the patient in using a thought record, as shown in 13.8–2. The specific situation is identified, and the emotional response and the thought or thoughts are recorded as well as the patient’s belief in the thought.

Patients learn techniques for modifying unhelpful thinking, including identifying factual inaccuracies (e.g., “I don’t understand anything” is all-or-nothing thinking) and biased information processing (ignoring evidence that she does know some things) and generating more accurate thoughts by the use of logic and testing beliefs.

Therapist: Okay, in this situation, you are feeling miserable. Now let’s check this thought. What problems do you see with the thought, “I don’t understand anything?”

Patient: Well, it’s pretty all-or-nothing, but it feels like it’s true.

Therapist: Can you think of any times when you felt something was true and it wasn’t?

Patient: Sure, I felt sure I wouldn’t get into law school or college for that matter.

Therapist: What does that tell you about this thought?

Patient: Well, it might not be true either.

Therapist: Okay, what would be other evidence that this thought isn’t completely true?

Patient: Well, I do know some things.

Therapist: What is your evidence? Have you taken any tests or completed any assignments?

Patient: Yeah—and I got a B on the first test.

Therapist: So, what can we write in the rational responses column?

Patient: It isn’t all-or-nothing; I do know some stuff.

Therapist: How miserable do you feel if you tell yourself that?

Patient: Well, a little less.
FIGURE 13.8–1. Thought record example.

<table>
<thead>
<tr>
<th>Situation</th>
<th>Emotions (strength, 0–100)</th>
<th>Automatic Thoughts (strength of belief, 0–100)</th>
<th>Rational Responses</th>
<th>New Emotion (0–100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entering class</td>
<td>Miserable (70–80)</td>
<td>I don’t understand anything going on in this class! (100)</td>
<td>That’s all-or-nothing and emotional reasoning</td>
<td>Miserable (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In the past, some things I felt were true didn’t turn out to be true</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>I do know something, or I would not have gotten a B.</td>
<td></td>
</tr>
</tbody>
</table>

In this case, the patient experiences several types of distortion, including all-or-nothing thinking and emotional reasoning (i.e., “I feel it is true; therefore, it must be true”). The patient is asked to generate evidence that challenges the negative belief. The evidence reduces but does not eliminate the negative feeling. This is often the case, particularly when working with retrospective examples and patients experiencing significant depression. One approach to increase the efficacy of thought challenging and evidence gathering in CBT is by developing behavioral experiments to test the belief. In this case, the patient later conducted an experiment to test the “I don’t know anything” belief. She wrote down her own answers to questions asked in the class as well as the answers that other students made. She found that her knowledge was on par with her classmates, and she was able to answer most of the questions. This experiment also addressed her “belonging,” because she got evidence of her equivalence to her peers.

As treatment progresses, the therapist points out recurring themes and helps the patient to identify and challenge core beliefs. In this example, the patient repeatedly experienced thoughts about not being good enough. She said that she felt this way all her life and attributed this to her sense of being different from her parents and her European-American friends and her experience of persistent racism.

One approach to changing schema is to generate alternative core beliefs and to help the patient to identify behaviors and cognitions that are consistent with the new beliefs. In this case, a belief of “I belong just like everyone belongs; others may not believe it or act that way, but I do” was consistent with the patients’ values and overriding experience. The therapist would therefore challenge thoughts by asking “is that the ‘old self’ or ‘new self’ talking?” This provided a shorthand for identifying dysfunctional thoughts and generating new ones consistent with the alternative schema.

In the final sessions, the tasks shift to reviewing progress, identifying potential future challenges, and learning to administer interventions independently. Returning to the example, the patient showed significant improvement in her mood. Interventions that had been
beneficial were attending the university gym on a regular schedule (activity scheduling), joining a study group (activity scheduling, assertiveness training, and social interaction), and gathering evidence regarding beliefs about being good enough and belonging (thought challenging and experiments). In addition, another student had invited the patient on several dates. At the end of therapy, the patient had a depression score on the BDI in the nondepressed range, her school attendance and grades had improved, and she had daily contact with friends and family.

In preparation for termination, it is important to identify the improvements that the patient has made, the skills that have been learned, and potential challenges that may arise in the future. This client identified her risk factors for increased depression as a rejection if she started dating or failure at school. She also noted that, although she now did not fear attending class and she was doing well, she still was not talking in class unless she was called on.

Therapist: Is not answering questions in class a problem?

Patient: Yeah.

Therapist: Okay, you’ve been doing this a while, what do you think would be a good homework for you?

Patient: Well, I guess I could just plan to answer one or two questions in class, and see what happens.

Therapist: When you say “see what happens,” what could you track?

Patient: Maybe how many I get right and my thoughts and feelings after each question.

Therapist: Sounds good. What are some things you can do to make that easy in the class setting?

Because CBT is a skills-based model, it is critical that the patient demonstrates an ability to use skills independently of the therapist. In this case, she is able to take on the role of therapist and to assign herself a task that can help her to modify her beliefs and behavior.

ADJUNCTIVE PSYCHOTHERAPY FOR BIPOLAR DISORDER

Psychotherapy for bipolar disorder is an adjunct to pharmacotherapy for the management of symptoms. As such, interventions including CBT, FFT, and IPSRT emphasize education about the disorder, learning to track symptoms and warning signs of relapse, and improving adherence to pharmacotherapy. In CBT, additional interventions include identifying thoughts and beliefs that can either (a) exacerbate symptoms or (b) increase the risk of relapse. In CBT and IPSRT, there is an emphasis on establishing stable routines to reduce triggers for mania. Finally, FFT emphasizes the role of educating the entire family system about the disorder and enlisting family members to aid patients with the management of their disorder. The current vignette describes a case from a cognitive-behavioral conceptualization that incorporates techniques from other approaches.

A 47-year-old, divorced Caucasian man was referred for psychotherapy by his treating psychiatrist. The patient was currently unemployed, although he volunteered 5 hours per week at his church. Although he had a long history of symptoms, this was the first time that he had been referred for psychotherapy. At the time of referral, the patient reported mixed symptoms of depression and
mania. Depressive symptoms included depressed and sad mood, feelings of guilt, and suicidal ideation. Currently, the patient reported manic symptoms of irritability, racing thoughts, decreased need for sleep, and impulsive spending. In addition, the patient was preoccupied with religious ideation.

In considering integrative interventions, it is key to have an organizing structure with which to work. In this current case, the psychotherapist starts from a cognitive-behavioral framework but then incorporates techniques associated with other approaches based on the formulation.

**Initial Assessment**

As with a unipolar disorder, accurate assessment of diagnosis and symptoms is necessary for effective treatment. In addition, it is particularly important in the treatment of bipolar disorder to assess level of activity, stability of routine, and supportive social networks. This is also an important point to identify patient beliefs regarding bipolar disorder. These could include beliefs about benefits of mania, fears that treatment would eliminate these benefits, concerns about medication side effects, or questioning the diagnosis. These issues will be key targets of treatment in any intervention.

The current patient presented for the treatment secondary to several significant life events. He reported that he had several arguments with other volunteers at his church. This had led to a warning from his pastor that he would not be able to continue volunteering if these conflicts continued. The patient was also under severe financial stress. Although he received disability income, he had spent the entirety of his most recent check on religious memorabilia and charitable donations and was at risk of eviction from his subsidized housing.

The patient had a long history of disorder. He reported that he was raised in an intact family by his mother and father and had two younger sisters. He reported that his childhood was uneventful and his parents loving and supportive. He had done well in high school and had joined the army. He served 4 years in the military as a communications specialist. While in the military he married a German woman that he met while stationed in Germany.

His first symptoms occurred while in the military. He reported a manic episode, leading to hospitalization, characterized by religious delusions, elated mood, goal-directed behavior (attempting to convert other soldiers to his beliefs), excessive spending, alcohol and drug use, and sexual acting out. This first episode led to his medical discharge from the military and divorce from his wife. After discharge from the hospital, the patient reported ongoing depressive symptoms extending several years, punctuated by periods of mixed depression and mania. He reported three additional hospitalizations, one following an additional manic episode and two following suicide attempts secondary to severe depression.

**Course of Therapy**

Psychotherapy for bipolar disorder is an adjunctive treatment to pharmacotherapy, and initial sessions reflect this. As with unipolar disorders, treatment included education about the treatment model, establishing rapport, and identifying problems and goals and assessing symptoms. In addition, the therapist both assesses knowledge about bipolar disorder and provides education to both expand on that understanding and correct any misconceptions. An example of such education is below.

Therapist: What do you know about your diagnosis of bipolar one?
Patient: Well, it means I have ups and downs, and they get pretty bad.

Therapist: What else do you know about it?

Patient: Well, my doctor says I have to take my meds or else it will get worse.

Therapist: How do you feel about taking your medication?

Patient: I really don’t like to.

Therapist: How come?

Patient: I’m just not me when I’m taking them. I feel like I am slowed down and I just can’t think. I just don’t know if they help. I’m taking them now, and I don’t feel much better. And they don’t fix the real problems I’ve got.

Therapist: Which are?

Patient: I have no friends, I have no girlfriend, I have no job, I have no money, no one helps me, my family’s disowned me. And when I’m taking my medication, I just become a lump, and none of that gets better.

Therapist: That sounds pretty depressing. I am going to write down those things you listed as items for your problem list, including job, money, dating, family, friends, and medications.

Patient: OK.

Therapist: And one thing that stands out to me is that you aren’t happy with taking medications. That is an important thing for us to deal with as well.

In this example, the question about the patient’s understanding of his disorder was to actually get information for the problem list. In addition, it elicits information about concerns regarding medication. The therapist here now has the opportunity to both demonstrate the development of the problem list and over time educate the patient about medication use.

One issue that complicates treatment when patients are receiving combined pharmacotherapy and psychotherapy is whether the psychotherapist is also the prescribing provider. In the case where there is one provider, coordination of pharmacotherapy and psychotherapy is obviously easier, but frequently the prescriber does not have time and/or expertise to provide psychotherapy. Therefore, frequently separate providers do psychotherapy and pharmacotherapy, and therefore it is critical for these providers to be in frequent contact and coordination.

From a CBT perspective, the key aspects of psychotherapy for bipolar disorder will include tracking symptoms and functioning, identifying and modifying cognitions that may exacerbate symptoms or impair functioning, and behavioral interventions designed to increase rewarding activities without producing manic activation. To do this, interventions can include those from other models, including the education and involvement of family or other support resources, and stabilization of social rhythms through the establishment of consistent routine as in IPSRT. The example below reviews identifying strategies to reduce risk of relapse following recent symptom exacerbation.
Therapist: What do you think led to you feeling worse?

Patient: I think that I felt like I had to do all the work for the church to prepare for the holidays. I started doing more and more, and I got really stressed.

Therapist: All right, so taking on too much is a problem. One thing we’re going to do today is work on a list of warning signs that your symptoms are getting worse. Then we have to figure out how to help you notice when they come up and do something about them. Do you have anyone around who you trust who could help you notice when this is happening?

Patient: No. You know that.

Therapist: I was thinking about co-workers, like one of the other volunteers or your pastor. You’ve mentioned that he has been really supportive, and he knows about your symptoms.

Patient: Yeah, I know he gets worried about me.

Therapist: One thing we can do is practice asking him to give you feedback about your actions and to let you know when he notices warning signs that your symptoms are getting worse.

Patient: I just worry that I’m asking too much.

Therapist: Well, let’s practice in here how you would ask. Also, let’s generate some other ways to notice warning signs….

In this situation, identifying warning signs can help the patient apply skills to prevent full symptom exacerbation. However, patients often don’t notice as symptoms are worsening, and therefore it is useful to enlist family members or other support to provide feedback. For this to be effective, it is helpful to (a) meet with the support person and educate them about the disorder and the goal of tracking warning signs and (b) to work with both the patient and the support person to agree on how the support person will inform the patient about concerns and how the patient will respond. In the current case, the patient’s pastor eventually attended a session, and the patient and he developed a plan for tracking symptoms and responding when symptoms were exacerbated. This both provided pragmatic support and also challenged the patient’s perception that no one cared. In this case, the fact that the provider was the pastor was also beneficial given that the patient had symptoms of hyper-religiosity when becoming manic. By educating the pastor and patient regarding these symptoms, they could quickly notice when there was a change and intervene through thought challenging, working with structure, attending to medication adherence, and working with the prescribing provider to adjust medications.

During the course of treatment of bipolar disorder, the role of the therapist is to facilitate the patient identifying warning signs, implementing skills practice, and providing support and encouragement (Table 13.8–3).

As with unipolar treatment, later sessions emphasize not only continued practice of learned skills but challenging of core beliefs that may contribute to the risk of symptom relapse. For the current patient, the belief “I’m damaged and will never be accepted by anyone” was a key theme that came up. He perceived his bipolar disorder as a flaw that meant that he could never have a “normal” life and that others would always reject him. Assumptions that arose from this belief were that he could never have a romantic relationship, that he could never
reconnect with his family, and that he could never have paid employment. He also was
ambivalent about his treatment (particularly medication), doubting that he could make any
improvement. Therefore, the later sessions focused on both challenging unhelpful beliefs and
developing alternatives to unhelpful core beliefs.

At the end of treatment, the goals are for the patient to be able to identify symptom changes,
have a range of skills with which to respond to those changes, and have improved
communication with their pharmacotherapist so that medication adherence is consistent and
appropriate changes in pharmacotherapy can be made as needed. In addition, if family
members are available, the goal is that the patient and family have developed improved
understanding of the disorder and communication skills so as to facilitate stable mood.

### Table 13.8–3. Examples of Warning Signs

<table>
<thead>
<tr>
<th>Warning Signs</th>
<th>Depressed</th>
<th>Warning Sign Normal</th>
<th>Warning Sign Manic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep</td>
<td>Sleeping &gt;10 hours</td>
<td>8 hours &gt;7 hours</td>
<td>No sleep and energized</td>
</tr>
<tr>
<td>Energy</td>
<td>Cannot get out of bed</td>
<td>Tired in the evening</td>
<td>Up at alarm clock, able to work through day</td>
</tr>
<tr>
<td>Spending</td>
<td>Isolating—not buying necessities</td>
<td>It is an effort to get food</td>
<td>Normal</td>
</tr>
<tr>
<td>Mood</td>
<td>Crying easily</td>
<td>Pessimistic “OK”</td>
<td>Optimistic</td>
</tr>
<tr>
<td>Guilt</td>
<td>Thoughts of failure</td>
<td>Sensitive to criticism</td>
<td>Flippant not concerned about others</td>
</tr>
<tr>
<td>Religion</td>
<td>Abandoned by God</td>
<td>Feeling cynical and doubting</td>
<td>Comfortable with faith</td>
</tr>
<tr>
<td>Suicide</td>
<td>Start planning to kill self</td>
<td>Thoughts of being dead</td>
<td>None</td>
</tr>
</tbody>
</table>

**FUTURE DIRECTIONS**

Some basic guidelines can be derived in treatment. In general, it is incumbent on the clinician
to apply interventions for which there is empirical support. In the case of mood disorders,
there are several psychotherapeutic options that are now available. There are some patient
characteristics that could recommend treatment, including the presence of significant marital
distress, amenability to a particular validated treatment modality, and chronic depression.

An important component of good psychotherapy, regardless of model, is that the therapist has
a treatment rationale that guides decisions regarding interventions. This is a shared theme of
all of the current validated treatments for mood disorders. However, such a model is not
likely sufficient for effective treatment. Psychotherapies generally are built around
mediational models of change, with modification of the target symptom (e.g., depressed
mood) being achieved through intervention on a more accessible construct (e.g., an irrational
belief, a rewarding activity, increase in medication adherence, or a transference reaction in therapy). What distinguishes excellent clinicians, regardless of orientation, is their ability to hold a conceptual framework in mind and to apply that framework to the unique challenges of the patient.

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It has been thought for centuries that at least some forms of depression are either caused by or maintained by disturbances of brain function, and since the 1960s, it has been possible to study selected neurobiological processes that are linked to the etiology and pathogenesis of mood disorders. Several key sets of observations have informed research in this area. First, the heritability of mood disorders has suggested that the neurobiological underpinnings of depression may be related to specific genes. Second, more detailed understanding of the neurobiology of stress response has informed interactive stress-diathesis models of vulnerability. Third, the discovery of the first generation of “somatic” treatments (i.e., ECT and the TCA and MAOI antidepressants) in the 1940s and 1950s pointed to potentially reversible neurobiologic targets for intervention. As the methodology for studying the neurobiology of mood disorders has grown more sophisticated, investigations utilizing indirect indicators of brain function, such as the levels of monoamine metabolites, cortisol, or CSF, have largely been supplanted by translationally guided studies of gene transcripts and proteomics. Likewise, coarse measures of regional brain function, such as recordings of evoked potentials or electroencephalographic (EEG) activity patterns during waking and sleeping, largely have given way to neuroimaging strategies that permit the activity of regions or specific neural circuits to be examined at rest and during provocative challenges. This chapter will survey the neurobiology of mood disorders, emphasizing clinically relevant associations with phenomenology, course of illness, and treatment outcomes.

**CLINICAL PHENOMENOLOGY**

The signs, symptoms, and subjective experiences associated with depression have long suggested dysfunction of basic central nervous system (CNS) processes. With respect to cortical function, depression involves multiple disturbances of information processing. Most depressed people automatically interpret experiences from a negative perspective, and their access to memory is negatively biased. In more severe depressive states, cognition and problem-solving skills are further compromised by poor concentration and decreased ability to use abstract thought. A virtual monologue of negative thoughts and images seems to run on autopilot, and, unlike normal states of sadness, ventilation to a confidante has little beneficial effect. In more extreme cases, delusions or hallucinations, or both, grossly distort reality testing. These neurocognitive changes point to dysfunction involving the hippocampus, prefrontal cortex (PFC), and the amygdala and other limbic structures.

Another biologically based characteristic of depression involves decreased interest and a loss of mood reactivity: Spontaneous, goal-directed activities decrease, and events that should improve mood have little or no effect. One correlate of loss of interest is decreased reinforcer
salience. Even basic appetitive functions, such as appetite and libido, are diminished in severe depression. Anhedonia and decreased appetitive behavior point to dysfunction of the neural circuits involved in the anticipation and consummation of rewards, which involve the thalamus, hypothalamus, nucleus accumbens, anterior cingulate, and PFC.

Alterations in the initiation, expression, and spontaneity of movement are common in severe depression. A background state of decreased animation referred to as psychomotor retardation is sometimes accompanied by a superimposed state of agitation. In addition to the pacing and frequent postural shifts, stereotypical signs or behaviors, such as a furrowed brow, hair pulling, biting at the lips or nail beds, and compulsive scratching, are observed in severe depressive states. Anhedonia and psychomotor disturbances are more pronounced among older depressed patients and in recurrent depressive episodes, with agitation typically limited to the most severe depressive syndromes. These observable signs point to dysfunction of subcortical circuits connecting the thalamus, basal ganglia, and striatum.

Almost all depressed people report low energy or fatigue and some difficulty involving sleep. Although insomnia is much more common (prevalence rates of 2/3rds to 4/5ths in most clinical samples), hypersonmolenence is not uncommon, particularly earlier in life. Clinicians have long noted an association of hypersonomnia with other “reversed” neurovegetative signs and symptoms, such as increased appetite and weight gain. The classical sleep disturbances of depression, such as difficulty maintaining sleep and early morning awakening, also tend to be more pronounced and severe in older individuals with a history of recurrent illness. Such terminal insomnia is, in turn, linked to diurnal mood variation, in which morning is the worst time of the day. Disturbances of these normally well-entrained circadian rhythms are indicative of dysregulation of nuclei in the thalamus, hypothalamus, and brain stem.

For most of the past century, clinical researchers have viewed the tendency for these signs and symptoms to co-aggregate or cluster together to reflect the neurobiological basis for the classical subtypes of depression. For example, anhedonia, loss of mood reactivity, and psychomotor disturbance are more commonly associated with weight loss, terminal insomnia, or diurnal mood disturbance, or a combination of these. This constellation forms the basis of the syndrome of melancholia (also known over the past five decades as autonomous, biological, or endogenous forms of depression). As these depressions are often recurrent and discrete episodes can begin without the provocation of a significant stressor, they were proposed to have an internal (i.e., neurobiological) etiology. The fact that such depressions were slow to remit spontaneously yet were quite responsive to ECT further reinforced perceptions of underlying biological dysfunction. The stable nature of this syndrome over the centuries has been recognized by the contemporary use of the ancient Greek term melancholia, even though black bile is no longer implicated in the pathophysiology of severe depressive states.

In contrast to melancholia, the depressions more commonly seen in young adult life often seemed inextricably tied to personality problems, interpersonal problems, and maladaptive responses to psychosocial difficulties. The terms non-endogenous and reactive were used to represent the observation that depression in young adults is almost invariably associated with stressful life events. As suggested by the names, these depressions were presumed to be mediated by non-biological factors related to personality and resilience to stress. The association of an early age of onset with co-occurring anxiety (both symptoms and discrete disorders)—coupled with a low incidence of psychotic symptoms (i.e., delusions or hallucinations)—further solidified impressions that younger depressed patients had a neurotic
disorder. Another hallmark of a putatively neurotic disorder, persistence or chronicity, also characterized many early-onset depressions. The presumed primacy of psychosocial factors in neurotic or non-endogenous depression was further suggested by the too frequently poor responses to ECT and TCAs. That the onset of depression in early life may, of course, distort personality development, limit one’s repertoire of coping skills and diminish resilience, change brain structure and function, and alter drug responsivity (i.e., pathoplasty) was not yet appreciated. It was also not yet known that early-onset depressions are associated with a relatively high familial loading in genetic studies (i.e., a hallmark of a biologically mediated disorder). Likewise, neither the heritability of neuroticism nor the neural basis of the characteristically increased reactivity to emotional stimuli had yet been established.

One historically important subgroup of patients with non-endogenous or neurotic depression was defined in part by reverse neurovegetative symptoms (i.e., increased appetite, weight gain, and hypersomnolence). As the patients treated by the hospital-based psychopathologists of the 1940s and 1950s seldom had such symptoms, this presentation was described as atypical depression. The notion of atypicality was reinforced by a relative poor response to ECT and TCAs and, by contrast, relatively preferential response to MAOIs. Importantly, as clinical research shifted to ambulatory settings and greater numbers of younger and less severely symptomatic people began to seek treatment of mood disorders, it was recognized that about 15 to 25 percent of depressed people have reversed vegetative features, which means that—despite the name—this presentation was not so atypical.

**RISK FACTORS**

**Genetic Influences**

Mood disorders and suicide clearly run in families, yet the contributions of nature and nurture have provoked intense debates for decades. It is now well established that bipolar affective disorder is more heritable than other mood disorders, heritability increases in proportion to the amount of shared genetic material, and that an early age of onset is associated with greater heritability. Thus, identical twins have greater heritable risk than fraternal twins, who are at approximately the same risk of other first-degree relatives (i.e., siblings and parents). First-degree relatives, in turn, have greater shared risk than half-siblings, grandparents, or cousins. Research comparing same-sex fraternal and identical twins and studies using the adopted-away paradigm further demonstrated that heritable risk transcends environmental influences. Research using modern molecular genetic methods will eventually lead to identification of the gene products that transmit this risk. Already it is clear that a number of alleles are associated with a small but replicable increase in the risk of depression; yet others may be associated with relative resilience. Among the numerous genes associated with an increased risk of depression are the alleles that code for the promoter region of the serotonin transporter (5-HTT), which has been found by a number of researchers to moderate the association between stressful life events and the risk of depression (Fig. 13.9–1). Other genes, while showing no relation to risk of depression, are relevant to response to specific antidepressants. Whether batteries of these genes can improve the process of matching individual patients remains to be seen.
Although the significance of genetics cannot be disputed, considerable variability exists within and across groups with comparable heritable risks. For example, identical twins do not have 100 percent concordance of bipolar affective disorder. Early-onset depressions are more heritable, and, conversely, late-onset mood disorders (i.e., after 60 years of age) have the lowest rates of heritability, presumably because of the greater impact of acquired risk factors such as cerebrovascular disease. In some pedigrees, men are at greater risk of alcoholism and sociopathy, and women are at greater risk of depression. There is some evidence that different environmental experiences may influence whether a woman develops depression or a generalized anxiety disorder. Conversely, for men, alcohol or drug use disorders may constitute an alternate illness trajectory to early onset depressive disorders. Genetics thus constitute just one pathway of vulnerability.

Predispositions to various emotional states (i.e., mood set points or temperament) also appear to be partly heritable. Of particular importance is a temperament characterized by excessive emotional reactivity and behavioral inhibition. Modern theories of temperament and personality converge around several related dimensions, including high levels of harm avoidance (neuroticism) and low levels of novelty seeking (introversion).

These temperaments, which can be recognized in infancy, are associated with increased vulnerability to depression and anxiety, presumably via increased limbic reactivity and heightened sensitivity to the impact of stressful life events. Childhood onset of dysthymia similarly presages extremely high rates of depression and bipolar disorder in adulthood.

One reason for inconsistency in genetic research is the process known as epigenetics. This term refers to functionally relevant modification of genes—typically induced by DNA methylation or histone modification—in response to environmental stimulation that do not
actually change the DNA sequence of the gene. Epigenetic changes in gene expression, both activating and inhibiting, are typically irreversible (i.e., will last for the life of the cell) and may persist across multiple generations. Intensive ongoing research indicates that some of the changes in brain function attributable to the impact of chronic stress may be mediated by epigenetic changes in key regions of the brain.

**ETIOLOGY OF EMOTIONS**

Some consider depression to be an extreme expression of sadness, a normal mood, with elation to be the healthier counterpart of the euphoria of mania. Such continuity between normal and pathological mood states is illustrated by bereavement. On the one hand, grief is a universal experience, yet, on the other hand, it can segue into a severe and disabling depressive state. Although there are less obvious parallels to mania, the intensity of new romantic love or other peak emotional experiences is associated with changes in perception, cognition, behavior, and judgment that border on manic excitement. The euphorogenic effects of cocaine and other psychostimulants amply document that the hard wiring for manic states exists in many if exposed to the right neurochemical milieu.

There is now considerable agreement that several basic emotions are observed across human cultures. Sadness and crying, for example, may be a universally recognized interpersonal distress signal. Moreover, the capacity to recognize the emotional states of others develops at such an early age that innate processes are undoubtedly implicated.

At the risk of anthropomorphizing excessively, basic emotional states are also observable across mammalian species. Behavioral predispositions toward aggressivity (or passivity) and social dominance (or subordination) appear to extend across vertebrate species. However, by virtue of a large neocortex, humans are distinguished by a greater capacity to modify expression of basic emotional states via abstraction, integration, and synthesis of complex symbolic representations, communication of experiences to others in direct or elaborated forms, and development of self-concepts that guide behavior, both in relation to others and an anticipated future. The domains of competence are similarly broader and diverse. Whereas a highly competent primate may quickly gain a position of dominance if placed in a new troupe, only the human can intentionally misrepresent his or her competence, conceal motivations, or be thwarted by archival documentation of past behaviors.

When compared to other mammals, the relatively greater importance and intensity of attachment bonds facilitate the protracted task of human child rearing and enhance the advantages of kinship. Indeed, for hundreds of thousands of years, the ancestors of man lived in a world in which the survival into adulthood was uncommon. Indeed, it is only in the past few centuries that average life expectancy has exceeded 40 years. Young humans are arguably the most vulnerable of mammals and certainly remain dependent on their caregivers for the longest period of time. Certain necessary divisions of labor no doubt increased the chances of viable offspring and may have slowly shaped gender differences in affectivity and affiliative behavior that underpin gender differences in the risk of depressive disorders. Ethological considerations also may help to explain why rates of depression appear to be increasing. The profound changes in social systems and lifestyles that have taken place in the past several centuries have forced adaptations that are too rapid for natural selection. In relative terms, the breathtaking sociocultural and technological changes of the past century have taken place in less than 0.00001th of hominid experience! The stressors faced in modern
life thus present complexities that, despite such a large neocortex and complex social systems, sometimes overwhelm basic adaptive capacities.

Modern affective neuroscience focuses on the importance of four brain regions in the regulation of normal emotions: the PFC, the anterior cingulate, the hippocampus, and the amygdala (Fig 13.9–2). The PFC is viewed as the structure that holds representations of goals and appropriate responses to obtain these goals. Such activities are particularly important when multiple, conflicting behavioral responses are possible or when it is necessary to override affective arousal. The dorsolateral region of the PFC is particularly active in suppression of negative affects and is a key constituent in the cognitive control network (CNN). The medial PFC, along with the posterior cingulate and hippocampus (see below), are important hubs in the default mode network (DMN), an interconnected circuit of regions that are active during resting wakefulness, self-referential thinking (i.e., autobiographical memory), or daydreaming. The DMN appears to show hyperconnectivity in depressive disorders, which predisposes to negative recall and rumination. There also is evidence of some hemispherical specialization in PFC function. For example, left-sided activation of regions of the PFC is more involved in goal-directed or appetitive behaviors, whereas regions of the right PFC are implicated in avoidance behaviors and inhibition of appetitive pursuits.

The anterior cingulate cortex (ACC) is thought to serve as the point of integration of attentional and emotional inputs. Two subdivisions have been identified: an affective subdivision in the rostral and ventral regions of the ACC and a cognitive subdivision involving the dorsal ACC. The former subdivision shares extensive connections with other limbic regions, and the latter interacts more with the PFC and other cortical regions. It is proposed that activation of the ACC as part of a CNN facilitates effortful control of emotional arousal, particularly when goal attainment has been thwarted or when novel problems have been encountered. There is evidence that connectivity among the components of the CCN is diminished in depressive states and, if persistent, such decreased connectivity may contribute to relapse/recurrence risk.

The hippocampus is most clearly involved in various forms of learning and memory, including fear conditioning, as well as inhibitory regulation of the HPA-axis activity. Importantly, the hippocampus is also one of the few sites of the brain capable of neurogenesis (i.e., the process of differentiation of stem cells into potentially functional neurons). Emotional or contextual learning appears to involve a direct connection between the hippocampus and the amygdala.

The amygdala appears to be a crucial way station for processing novel stimuli of emotional significance and coordinating or organizing cortical responses. Located just above the hippocampi bilaterally, the amygdala has long been viewed as the functional center of the limbic system. Although most research has focused on the role of the amygdala in responding to fearful or painful stimuli, novelty and ambiguity can also bring the amygdala “on line.”
FIGURE 13.9–2. Composite coronal and sagittal sections of positron emission tomography scans show areas in which cerebral glucose metabolism is decreased in depressed patients relative to matched healthy controls. PFC, prefrontal cortex; VLPFC, ventrolateral prefrontal cortex. (From Wayne Drevets, M.D., and Annu Rev Med. 2002:49 by Annual Reviews, http://annualreviews.org/.)

STRESS AND ANIMAL MODELS OF DEPRESSION

Studies of rodents, dogs, cats, and nonhuman primates have demonstrated that acute stress responses involve activation of central and peripheral components of two interactive psychoneuroendocrine systems: the cortical HPA axis and the sympathomedullary (SM) axis. Acute responses to stress are phenomenologically and neurobiologically more akin to fear and anxiety than depression. However, whereas stress initially signals threat, it is the anticipation of loss and the meaning of the loss—as well as the loss of hope—that can provoke the transition from anxiety to sadness and despair.

Acute stress activates cell bodies of norepinephrine (NE) neurons in the locus ceruleus, whose ascending axons signal noradrenergically mediated increases in cortical arousal and whose descending axons signal increased adrenergic (predominantly epinephrine) output by the sympathetic nervous system and adrenal medulla. Behaviorally, the perception of acute stress elicits perceptual vigilance, preparedness for response, and inhibition of appetitive activities, such as foraging and pursuit of sexual activity.

Stress simultaneously triggers and releases corticotropin-releasing hormone (CRH) from neurons in the hypothalamus and cerebral cortex. Hypothalamic CRH activates synthesis and
release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which, in turn, triggers release of cortisol and other glucocorticoids (from the adrenal cortex). CRH also synergistically increases locus ceruleus activity and, directly or indirectly, increases synthesis of other stress-reactive gene products and anti-inflammatory responses and decreases synthesis of key neuropeptides such as BDNF. The excitatory amino acid glutamate may synergistically heighten CNS arousal in response to stress. The acute response to stress is counterbalanced by homeostatic or adaptive mechanisms. These include feedback inhibition by glucocorticoid receptors in the hippocampus and pituitary, downregulation of postsynaptic noradrenergic receptors, and inhibitory auto- and heteroreceptors on presynaptic NE neurons. As is discussed subsequently, parallel input from serotonergic, GABA, and glycinergic neurons exerts dampening or inhibitory effects.

Exposure to prolonged, inescapable stress is associated with numerous adaptations in neurobehavioral responses. Although CRH levels in the brain and corticosteroid levels in the periphery may remain elevated, levels of NE, 5-HT, dopamine (DA), and GABA in the brain stem and forebrain eventually decrease. Animals trapped in such a state eventually cease trying to resist or to escape and show decreased grooming and appetitive behavior. The behavior persists outside of the experimental situation. There are significant individual differences in the development of such learned helplessness, as well as differences across pedigrees, strains, and species. Like other forms of chronic stress, the negative behavioral effects of learned helplessness may be sustained by epigenetic changes in key regions of the brain. Importantly, antidepressant drugs have been shown to prevent, attenuate, or reverse learned helplessness across species.

Studies of the experiences of primates in the wild, of course, are more relevant to the stresses faced by people than a rat’s response to inescapable, painful, electric shock. These naturalistic studies demonstrate not only that central 5-HT activity is partly under genetic control but also that loss of a dominant role within a primate social hierarchy results in decreased 5-HT neurotransmission and increased HPA. In the wild, animals with low levels of the serotoninergic metabolite 5-hydroxyindoleacetic acid (5-HIAA) are likely to be more aggressive, more socially subordinate, and less sexually active. When social status is manipulated by creating a new troupe from a cohort of subordinate primates, a new dominance hierarchy emerges, and the more dominant animals experience a corresponding increase in 5-HT function. Conversely, during times of adversity, such as drought or famine, it is the socially dominant primates that experience the largest increases in HPA activity.

MALTREATMENT AND EARLY ADVERSITY

Physical, verbal, and sexual abuse and parental neglect have an indelible effect on one’s life trajectory. Although it has been known for decades that such maltreatment plays a key role in the pathogenesis of PTSD and borderline personality disorder, it is now clear that such a history results in a two- to threefold increase in the risk of depression and is associated with important phenomenological and biological differences in depressive states.

Studies of animal models confirm that lasting alterations in neuroendocrine and behavioral responses can result from severe early stress. Animal studies further indicate that even transient periods of maternal deprivation can alter subsequent responses to stress. This vulnerability has been shown to be the result of enduring changes in gene expression. For example, protracted stress thus can induce changes in the functional status of neurons via inducing epigenetic changes and may suppress neurogenesis in the hippocampus. Recent
studies in depressed humans indicate that a history of early trauma is associated with long-
lasting changes in responsivity of the HPA axis, including accompanied by structural changes
in the hippocampus and perhaps other focal regions within the cerebral cortex.

**MONOAMINE SYSTEMS: FUNCTION AND DYSFUNCTION**

An area of scientific inquiry is chosen, in part, because of the knowledge base and
experimental paradigms available to investigators. In the early 1960s, Nobel prize-winning
research had just elucidated the importance of monoamines in neurotransmission. Moreover,
it was possible to measure the metabolites of the catecholamine NE in various body fluids
and 5-HIAA, the principal metabolite of 5-HT, in CSF. Visualization of the functional brain,
by contrast, was essentially limited by the low sensitivity of recording neuronal activity from
the surface electrodes used for EEGs. Specifically, whereas the paroxysmal spikes in
electrical activity caused by epileptogenic foci or the diffuse slowing associated with delirium
could be documented by EEGs, the more subtle changes in brain activity or regional cerebral
metabolism associated with affective states could not.

In addition, there were multiple lines of evidence from pharmacological studies implicating
perturbations of monoamine systems in the therapeutic and iatrogenic effects of various
medications. The relevant pharmacotherapies of the time, the TCAs and MAOIs, were known
to increase the amount of neurotransmitter available at monoamine synapses. Conversely, the
monoamine-depleting compound reserpine was known to cause depression as a side effect
during the treatment of hypertension. Intoxication with potent noradrenergic agonists, such as
amphetamine and cocaine, also was known to induce states of sleepless euphoria and
activated psychosis, followed by a crashing, depression-like withdrawal.

The early monoamine hypotheses formulated by Joseph J. Schildkraut, Alexander H.
Glassman, Arthur J. Prange, Jr., John Davis, Herman van Praag, Jonathan Cole, and others
have undergone much revision, and it is now known that these ancient neuromodulatory
systems comprise only a small fraction of the brain’s neurons. Nevertheless, NE and 5-HT
neurotransmission is still thought to play an important role in the pathophysiology of mood
disorders and most antidepressant medications initiate their actions through these neurons. A
third monoamine, the catecholamine DA, was thought to play a greater role in the
pathophysiology and treatment of schizophrenia and thus received less emphasis.
Nevertheless, evidence of DA dysfunction in at least some forms of depression has emerged.
Knowledge about monoamine receptor families, second messengers, neurokinins, excitatory
amino acids, and gene transcription factors has added layers of complexity to the original
monoamine hypotheses. As a result, there has been a progressive shift away from focusing on
disturbances of single neurotransmitter systems in favor of studying neurobehavioral systems,
near circuits, and more intricate neuroregulatory mechanisms. The monoaminergic systems
are thus now viewed primarily as broader, neuromodulatory systems, and disturbances are as
likely to be secondary or epiphenomenal effects as they are directly or causally related to
etiology and pathogenesis.

**NORADRENERGIC SYSTEMS**

The cell bodies of almost all noradrenergic neurons in the brain are located in the locus
ceruleus of the brain stem and project rostrally to the hypothalamus, basal ganglia, limbic
system, and cerebral cortex. This diffuse distribution belies NE’s role in initiating and
maintaining limbic and cortical arousal, as well as modulation of other neuronal systems.
Noradrenergic projections to the amygdala and hippocampus are implicated in emotional memory and behavioral sensitization to stress, and prolonged activation of the locus ceruleus contributes to the state of learned helplessness. The medial forebrain bundle (MFB) is the key ascending NE pathway to anterior cortical structures. Stimulation of the MFB elicits increased levels of goal-directed and reward-seeking behavior. Sustained stress eventually results in decreased MFB neurotransmission, which may account for anergia, anhedonia, and diminished libido in depression. The locus ceruleus also is the origin of neurons that project rostrally to interact with the cell bodies of the sympathetic nervous system and, hence, the adrenal medulla. The locus ceruleus is phasically active. Increased activity is provoked by the perception of novel stimuli; decreased activity accompanies eating and sleeping. As noted previously, there is an additive interaction (i.e., positive feedback loop) between noradrenergic neurons in the locus ceruleus and CRH from the hypothalamus, as well as cortical regions. Other negative feedback loops must exert inhibitory control over this alerting synergism to prevent sustained pathological activation. For example, increased noradrenergic output stimulates $\alpha_2$ heteroreceptors on co-localized inhibitory 5-HT neurons, and a sustained increase in CRH drives results in decreased hypothalamic release of ACTH, which blunts HPA activity. Changes in cognitive processing of sensory input can further dampen corticolimbic and sympathoadrenal responses to sustained threatening or painful stimuli.

**SEROTONINERGIC SYSTEMS**

Serotonergic neurons project from the brain stem dorsal raphe nuclei to the cerebral cortex, hypothalamus, thalamus, basal ganglia, septum, and hippocampus. The 5-HT pathways have inhibitory and facilitatory functions in the brain. For example, much evidence suggests that 5-HT is an important regulator of sleep, appetite, body temperature, metabolism, and libido. Moreover, 5-HT inhibits aggressive behavior across mammalian and reptilian species. Serotonergic neurons projecting to the suprachiasmatic nucleus (SCN) of the hypothalamus help regulate circadian rhythms (e.g., sleep–wake cycles, body temperature, and HPA-axis function). The 5-HT also permits or facilitates goal-directed motor and appetitive behaviors in conjunction with NE and DA.

As noted previously, there is some evidence that 5-HT neurotransmission is partly under genetic control, and a functional polymorphism of the 5-HTT has been shown to moderate risk of depression within the context of life stress. The 5-HT “tone” also shows a seasonal fluctuation and shows a characteristic temporal response to stress. Specifically, acute stress increases 5-HT release transiently, whereas chronic stress eventually causes decreased 5-HT activity and depletion of 5-HT stores. Chronic stress may also increase synthesis of 5-HT type 1A (5-HT$_{1A}$) autoreceptors in the dorsal raphe nucleus, which further decrease 5-HT transmission. Elevated glucocorticoid levels tend to enhance 5-HT functioning and thus may have significant compensatory effects in chronic stress.

**DOPAMINERGIC SYSTEMS**

There are four relatively discrete DA pathways in the brain. The tuberoinfundibular system projects from cell bodies in the hypothalamus to the pituitary stalk, exerting inhibitory control over prolactin secretion. The nigrostriatal system originates from cell bodies in the substantia nigra and projects to the basal ganglia, regulating involuntary motor activity. The cell bodies of the mesolimbic pathway are located in the ventral tegmentum and project diffusely to the nucleus accumbens, amygdala, hippocampus, medial dorsal nucleus of the thalamus, and
cingulate gyrus. This pathway modulates emotional expression, learning and reinforcement, and hedonic capacity. The fourth DA pathway, also originating in the ventral tegmentum, is the mesocortical pathway, which projects to the orbitofrontal and the prefrontal cortical regions. The mesocortical pathway helps regulate motivation, concentration, and initiation of goal-directed and complex executive cognitive tasks. Decreased mesocortical and mesolimbic DA activity has obvious implications in the cognitive, motor, and hedonic disturbances that are associated with depression and is a target for action for some investigational compounds. Across pathways, increased DA activity is potentiated by nicotinic inputs and glucocorticoids, and DA levels are inversely correlated with indices of brain 5-HT activity.

**SUMMARY OF RESEARCH ON MONOAMINES IN DEPRESSION**

After nearly 30 years of research, it can be concluded that subsets of depressed people manifest one or more abnormalities of monoamine neurotransmission. Decreased central NE activity can be inferred, in part, from decreased urinary excretion of the metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG). However, a partly overlapping subgroup of patients manifest elevated circulating levels of NE and its metabolites. This suggests a dissociation of NE activity in the MFB and SM systems. Functionally increased noradrenergic activity is also reflected by blunted α1, β, and β-coupled second messenger (i.e., cyclic adenosine monophosphate [cAMP]) responses.

Chronic treatment with NE reuptake inhibitors (NRIs) (such as the TCA desipramine or the more selective drug reboxetine) causes a time-dependent decrease in firing of NE neurons and downregulation of postsynaptic β receptors. The antidepressant effects of NRIs are reversed by transiently decreasing the availability of NE in the brain by administration of the NE synthesis inhibitor α-methyl-p-tyrosine (AMPT).

5-HT dysfunction has been documented in overlapping subgroups of patients using a variety of methods, ranging from low CSF levels of 5-HIAA to decreased regional cerebral metabolism in response to a 5-HT agonist, such as D-fenfluramine. 5-HT dysfunction also is reflected by blunted responses to specific (e.g., the specific 5-HT1A compound ipsapirone) and nonselective (e.g., L-tryptophan or D-fenfluramine) agonists, decreased neuroendocrine responses, and decreased 5-HT uptake sites on blood platelets. As discussed subsequently, decreased 5-HT neurotransmission also can be inferred from the findings of HPA and EEG sleep studies. Dietary depletion of L-tryptophan induces 5-HT mediated abnormalities in a subset of vulnerable individuals. Likewise, L-tryptophan depletion reverses responses to MAOIs and SSRIs but does not diminish the effect of interventions that target other systems (e.g., the antidepressant bupropion, cognitive therapy, or transcranial magnetic stimulation).

Low levels of the DA metabolite homovanillic acid have been implicated in psychomotor retardation. Some evidence suggests that increased DA activity, perhaps mediated by elevated glucocorticoid levels or lower levels of the enzyme DA β-hydroxylate, may contribute to the development of delusions and hallucinations.

**OTHER NEUROTRANSMITTER DISTURBANCES**

Acetylcholine (ACh) is found in neurons that are distributed diffusely throughout the cerebral cortex. Cholinergic neurons have reciprocal or interactive relationships with all three monoamine systems. Abnormal levels of choline, which is a precursor to ACh, have been found at autopsy in the brains of some depressed patients, perhaps reflecting abnormalities in
cell phospholipid composition. In an animal model of depression, strains of mice that are super- or subsensitive to cholinergic agonists have been found to be prone to or more resistant to developing learned helplessness. Cholinergic agonists can induce changes in HPA activity and sleep that mimic those associated with severe depression. Indeed, some remitted patients with mood disorders, as well as their never-ill first-degree relatives, have a trait-like increase in sensitivity to cholinergic agonists. Cholinergic agonist and antagonist drugs have differential clinical effects on depression and mania. Agonists can produce lethargy, anergia, and psychomotor retardation in normal subjects, can exacerbate symptoms in depression, and can reduce symptoms in mania. These effects generally are not sufficiently robust to have clinical applications, although some recent research has suggested that parenteral scopolamine can have rapid antidepressant effects. More conventional antidepressants that target serotonergic or adrenergic neurons also indirectly decrease cholinergic tone.

GABA has an inhibitory effect on ascending monoamine pathways, particularly the mesocortical and mesolimbic systems. Reductions in GABA have been observed in plasma, CSF, and brain GABA levels in depression. Animal studies have also found that chronic stress can reduce and eventually deplete GABA levels. By contrast, GABA receptors are upregulated by antidepressants, and some GABAergic medications have weak antidepressant effects.

The amino acids, glutamate and glycine, are the major excitatory and inhibitory neurotransmitters in the CNS. Glutamate and glycine bind to sites associated with the N-methyl-D-aspartate (NMDA) receptor, and an excess of glutamatergic stimulation can cause neurotoxic effects. Importantly, there is a high concentration of NMDA receptors in the hippocampus. Glutamate may thus work in conjunction with hypercortisolemia to mediate the deleterious neurocognitive effects of severe recurrent depression and may be proximally implicated in atrophic changes documented in some regions of the cerebral cortex, perhaps by first reducing the connectivity of neurons and volume of supporting glia. The potential significance NMDA receptors in the pathophysiology of depressive states is likewise suggested by growing evidence that a subanesthetic dose of ketamine (Ketalar), which noncompetitively antagonizes NMDA receptors, can exert large and rapid antidepressant effects that persist for 3 to 7 days. However, the effects require that ketamine is administered parenterally (e.g., intravenous [IV] infusion) and, because of well-characterized psychotomimetic and dissociative effects at somewhat higher doses, ketamine is considered a controlled substance (Schedule III) by the Drug Enforcement Administration. Development of drugs that produce antidepressant effects similar to ketamine that are easier to administer and/or have lower abuse potential is an area of intense research activity.

SECOND MESSENGERS AND INTRACELLULAR CASCADES

The binding of a neurotransmitter and a postsynaptic receptor triggers a cascade of membrane-bound and intracellular processes mediated by second messenger systems. Receptors on cell membranes interact with the intracellular environment via guanine nucleotide-binding proteins (G proteins). The G proteins, in turn, connect to various intracellular enzymes (e.g., adenylate cyclase, phospholipase C, and phosphodiesterase) that regulate utilization of energy and formation of second messengers, such as cyclic nucleotide (e.g., cAMP and cyclic guanosine monophosphate [cGMP]), as well as phosphatidylinositols (e.g., inositol triphosphate and diacylglycerol) and calcium–calmodulin.
Second messengers regulate the function of neuronal membrane ion channels, neurotransmitter synthesis and release, and protein kinase activity. Protein kinase, for example, catalyzes phosphorylation, an energy-liberating process involved in the synthesis and degradation of receptors, ion channels, G proteins, and gene transcription and translation factors. Some studies have reported abnormalities in platelet adenylate cyclase activity, phosphoinositide hydrolysis, intracellular calcium metabolism, and G-protein function in depressive disorders. Moreover, the synaptic effects of antidepressants initiate a series of intracellular reactions that ultimately alter gene activity, resulting in downregulation of selected monoamine receptors and increased synthesis of BDNF. There is increasing evidence that mood stabilizing drugs similarly act on G proteins or other second messengers.

ALTERATIONS OF HORMONAL REGULATION

HPA Activity

As noted previously, elevated HPA activity is a hallmark of mammalian stress responses and one of the clearest links between depression and the biology of chronic stress. Hypercortisolemia in depression suggests one or more of the following central disturbances: decreased inhibitory 5-HT tone; increased drive from NE, ACh, or CRH; or decreased feedback inhibition from the hippocampus.

Evidence of increased HPA activity is apparent in 20 to 40 percent of depressed outpatients and 40 to 60 percent of depressed inpatients. Older patients, particularly those with highly recurrent or psychotic depressive disorders, are the most likely to manifest increased HPA activity. Although hypercortisolism is one of the best-replicated biological correlates of melancholia or endogenous depression, it is hardly a specific abnormality. For example, a short period of starvation or several weeks of partial sleep deprivation can induce hypercortisolism in otherwise healthy people.

Elevated HPA activity in depression has been documented via excretion of urinary free cortisol (UFC), 24-hour (or shorter time segments) IV collections of plasma cortisol levels, salivary cortisol levels, and tests of the integrity of feedback inhibition. A disturbance of feedback inhibition is tested by administration of dexamethasone (Decadron) (.5 to 2.0 mg), a potent synthetic glucocorticoid, which normally suppresses HPA-axis activity for 24 hours. Non-suppression of cortisol secretion at 8:00 AM the following morning or subsequent escape from suppression at 4:00 PM or 11:00 PM is indicative of impaired feedback inhibition. Hypersecretion of cortisol and dexamethasone non-suppression are imperfectly correlated (approximately 60 percent concordance), suggesting that they may measure overlapping but different aspects of HPA dysfunction. A more recent development to improve the sensitivity of the test utilizes an infusion of CRH to stimulate cortisol secretion after dexamethasone suppression.

Neither the sensitivity nor the specificity of these tests of feedback inhibition is sufficient for use as a diagnostic test, and adrenocortical hyperactivity (albeit usually less prevalent) is observed in mania, schizophrenia, dementia, and other psychiatric disorders. Non-suppression may implicate a loss of inhibitory hippocampal glucocorticoid receptors more so than increased CRH drive, which also may account for the strong age dependence of cortisol non-suppression. As noted previously, dexamethasone non-suppression in adulthood is also associated with a history of early trauma, which may result from an enduring reduction in
synthesis of glucocorticoid receptors, hippocampal cell death, and/or chronic hypersecretion of CRH.

Elevated HPA activity in depression is typically not associated with the physical stigmata of Cushing syndrome but is sufficient to be implicated in the genesis of neurocognitive and neuro-immunological disturbances. Patients with increased HPA activity are typically less responsive to attention placebo interventions and psychotherapy. Hypercortisolemic depressed patients thus may have a relatively greater need for active pharmacotherapy or ECT. Hypercortisolism does, however, usually resolve with effective treatment. When persistent despite effective treatment, increased HPA activity is associated with a high risk of relapse. This is presumably a consequence of incomplete resolution of the pathophysiology of the depressive episode. One implication of these relationships is that interventions that suppress HPA activity, including dexamethasone and the cortisol synthesis inhibitor ketoconazole (Nizoral), are sometimes used to treat patients with more refractory depressive disorders. Attempts to develop compounds that directly antagonize central CRH receptors as antidepressants are ongoing.

**Thyroid Axis Activity**

Approximately 5 to 10 percent of people evaluated for depression have previously undetected hypothyroidism, as reflected by low levels of circulating thyroid hormone, an elevated basal TSH level, or an increased TSH response to a 500-mg infusion of the hypothalamic neuropeptide thyroid-releasing hormone (TRH). Such abnormalities are often associated with elevated anti-thyroid antibody levels and, unless corrected with hormone replacement therapy, may compromise response to antidepressant medication.

An even larger subgroup of depressed patients (20 to 30 percent) shows a blunted TSH response to TRH challenge. This type of response would usually suggest hyperthyroidism, yet few depressed patients have clinically significant elevations of thyroid hormones. A blunted TSH response in a euthyroid person thus may result from pituitary downregulation consequent to increased TRH “drive.” As neurons containing TRH have been identified in a variety of cortical regions, this abnormality may have a suprathalamic origin. Increased central TRH secretion, in turn, could result from a homeostatic response to decreased noradrenergic neurotransmission. The therapeutic benefits of adjunctive therapy with L-triiodothyronine (T₃) or other thyroid hormones may be mediated by a dampening of this failed homeostatic response. This abnormality may be most common in individuals who have reduced ability to convert thyroxine to T₃. The major therapeutic implication of a blunted TSH response is evidence of an increased risk of relapse despite preventive antidepressant therapy. Of note, unlike the dexamethasone suppression test (DST), blunted TSH response to TRH often does not normalize with effective treatment. (Sadock 1716)

**GROWTH HORMONE**

Growth hormone (GH) is secreted from the anterior pituitary after stimulation by NE and DA. Secretion is inhibited by somatostatin, a hypothalamic neuropeptide, and CRH. Pulsatile GH secretion follows a 24-hour circadian rhythm, with a characteristic secretory surge during the first few hours of sleep. The most consistent finding in depression is a blunted GH response to clonidine, an a₂-receptor agonist. Secretory responses after the onset of sleep or the administration of nonselective adrenergic agonists, such as desipramine, are also blunted in depression.
Although the hypothalamus has the highest concentrations of somatostatin, significant concentrations are also found in the amygdala, hippocampus, nucleus accumbens, PFC, and locus ceruleus. In addition to inhibition of GH release, somatostatin inhibits release or antagonizes the effects of CRH, GABA, and TSH. Decreased CSF somatostatin levels have been reported in depression, and increased levels have been observed in mania.

**Prolactin**

Prolactin is released from the pituitary by 5-HT stimulation and inhibited by DA. Most studies have not found significant abnormalities of basal or circadian prolactin secretion in depression, although a blunted prolactin response to various 5-HT agonists has been described. This response is uncommon among premenopausal women, suggesting that estrogen has a moderating effect.

**ALTERATIONS OF SLEEP NEUROPHYSIOLOGY**

Sleep is regulated by complex, temporally, and environmentally cued interactions between the monoamine neuromodulatory systems, neuroendocrine secretion, and neuropeptides. At the broadest levels, there is a seasonal tendency for longer and deeper sleep in winter and a circadian propensity for the onset of sleep (i.e., after dark and after midday). Onset of sleep is promoted by a surge in secretion of the pineal hormone melatonin (after the onset of darkness). Sleep onset is followed by the nocturnal surge in GH secretion, which occurs within the first 90 minutes of sleep onset. A reduction in core body temperature and diurnally low levels of cortisol secretion further promote the maintenance of sleep. Orchestrated across each 24-hour period is an oscillating, 90-minute, infradian cycle defined by rapid eye movement (REM) sleep. Within each cycle, there is a characteristic progression from light to deeper levels of sleep (defined by different types of EEG activity), culminating in the paradoxical central activation of REM sleep, during which most of the night’s dreaming occurs. An 8-hour night of sleep thus typically includes four or five cycles consisting of non-rapid eye movement (NREM) sleep and REM sleep. The propensity for deep sleep is greatest within the first 3 hours after sleep onset. REM sleep periods, by contrast, tend to become longer and more intense as the night of sleep progresses.

Prefrontal cortical metabolism is normally decreased during NREM sleep, a time of physical and metabolic rest. The frontal cortex is essentially off line during deep sleep, and the characteristic rhythm of brain activity consists of slow (delta) desynchronized waves of thalamocortical origin. REM sleep, by contrast, is characterized by fast, low-amplitude electrical activity and increased glucose metabolism in the limbic system. REMs are under the direct control of cholinergic neurons in the pons, which are tonically inhibited by the reticular activating system (predominately by histaminergic and noradrenergic neurotransmission) during wakefulness. During sleep, inhibitory 5-HT projections from the dorsal raphe nuclei phasically suppress REM. Pharmacological manipulations that increase central cholinergic activity lighten sleep and increase phasic REM activity. Dietary depletion of 5-HT and exogenous administration of glucocorticoids similarly can increase phasic REM indices. Injections of CRH and ingestion of potent noradrenergic agonists decrease total sleep time, reduce slow wave sleep, and suppress REM sleep.

Depression is associated with a premature loss of deep (slow wave) sleep and an increase in nocturnal arousal. The latter is reflected by four types of disturbance: (1) an increase in nocturnal awakenings, (2) a reduction in total sleep time, (3) increased phasic REM sleep,
and (4) increased core body temperature. The combination of increased REM “drive” and decreased slow wave sleep results in a significant reduction in the first period of NREM sleep, a phenomenon referred to as reduced REM latency. Results of family and twin studies suggest that these related abnormalities are partly heritable. Consistent with the expected behavior of a heritable trait, reduced REM latency and deficits of slow wave sleep typically persist after recovery of a depressive episode. Blunted secretion of GH after sleep onset is associated with decreased slow wave sleep and shows similar state-independent or trait-like behavior. Difficulties maintaining sleep and increased phasic REM sleep are associated with hypercortisolism and increased limbic blood flow and glucose metabolism; although some forms of pharmacotherapy can distort sleep profiles, recovery from depression usually is accompanied by at least a partial reversal of these abnormalities. The combination of reduced REM latency, increased REM density, and decreased sleep maintenance identifies approximately 40 percent of depressed outpatients and 80 percent of depressed inpatients. False-negative studies are commonly seen in younger, hypersonolent patients, who may actually experience an increase in slow wave sleep during episodes of depression. Approximately 10 percent of otherwise healthy individuals have abnormal sleep profiles, and, like dexamethasone non-suppression, profiles associated with depression are not uncommonly seen in other psychiatric disorders.

Despite clear limitations as a diagnostic test, EEG sleep recordings continue to be an important research tool. For example, patients manifesting a characteristically abnormal sleep profile have been found to be less responsive to psychotherapy and to have a greater risk of relapse or recurrence and may benefit preferentially from pharmacotherapy. Most antidepressants suppress REM sleep, probably by directly or indirectly activating postsynaptic 5-HT1A receptors. The efficacy of antidepressants that do not suppress REM sleep, such as bupropion, nefazodone (Serzone), and agomelatine (Valdoxan), in patients with pathologically increased REM sleep warrants further study. The effects of antidepressants on sleep maintenance and slow wave sleep are more variable and are largely mediated by antihistaminic effects and antagonism of 5-HT2 and, possibly, melatonin receptors.

**STRUCTURAL AND FUNCTIONAL BRAIN IMAGING**

Modern magnetic resonance imaging (MRI) scans permit visualization of the living brain, with high resolution of cortical structures such as the hippocampus and anterior cingulate, as well as white matter lesions. One abnormality commonly observed in the depressive disorders is increased frequency of hyperintensities in subcortical regions such as periventricular regions, the basal ganglia, and the thalamus. More common in bipolar I disorder and among the elderly, these hyperintensities appear to reflect atherosclerotic change and, as such, illustrate the deleterious effects of the interaction of aging and recurrent affective episodes. Ventricular enlargement, cortical atrophy, and sulcal widening have been observed in some studies of patients with more severe recurrent affective illness. More recent studies utilizing higher resolution MRI scans have documented reduced volume in a number of relevant regions, including the hippocampus, medial orbital cortex, and anterior cingulate. Diffuse and focal areas of atrophy have been associated with increased illness severity and increased cortisol levels. In several studies, the hippocampal volume reduction has been associated with measures of illness chronicity, such as lifetime days of untreated depression. Volume reduction is thought to partly result from reduction in the glial matter that supports neurons; suppression of BDNF-mediated connectivity and, ultimately, neurogenesis also may be implicated. Nevertheless, reduced hippocampal volume has been documented in a study of
individuals suffering from a first depressive episode and has been shown to be partly under heritable control in primates.

Positron emission tomography (PET) and functional MRI (fMRI) scanning are now widely used for research aimed at visualizing brain activity during rest and various states of activation. Normal sadness is associated with an increase in blood flow and neuronal activity in the thalamus and medial PFC, which may be thought of as a nonspecific change associated with diverse emotional responses. More specific activation is seen in the left amygdala, hippocampal formation, and parahippocampal gyrus. Sadness generated by one’s own thoughts (as opposed to a video scenario) and anticipatory anxiety are associated with a relative increase in blood flow to the anterior insular cortex. The most widely replicated fMRI findings associated with depression pertain to resting state connectivity, which is abnormally increased in the DMN and decreased connectivity within the CNN.

The most widely replicated PET finding in depression is decreased anterior brain metabolism, which is generally more pronounced on the left side. Thus, depression may be characterized by a relative increase in non-dominant hemispheric activity. Decreased cerebral blood and reduced glucose metabolism in regions such as the dorsolateral PFC appears to be a severity-dependent process and is correlated with difficulties inhibiting affective expression with higher cognitive processes such as abstraction and executive problem-solving skills. Abnormalities of regional cerebral metabolism have been observed in unipolar and bipolar depressions and appear to be somewhat state dependent. Furthermore, there is a reversal of hypofrontality after shifts from depression into hypomania, such that there are greater left hemisphere reductions in depression compared to greater right hemisphere reductions in mania. Other studies have observed more specific reductions in reduced cerebral blood flow or metabolism, or both, in the dopaminergically innervated tracts of the mesocortical and mesolimbic systems in depression. Again, there is evidence that antidepressants at least partially normalize these changes.

In addition to a global reduction in anterior cerebral metabolism, increased glucose metabolism has been observed in several limbic regions, particularly among patients with relatively severe recurrent depression and a family history of mood disorder (Fig 13.9–3). During episodes of depression, increased glucose metabolism is correlated with intrusive ruminations. Of note, increased metabolic activity in the amygdalae and decreased activity in the dorsolateral PFC appear to be independent dysfunctions. Increased paralimbic metabolism appears to be reversible with effective pharmacotherapy, but, in one study, the abnormality re-emerged when recently remitted patients were restudied off medication. State-dependent or trait-like paralimbic hypermetabolism has been proposed to be an “emotional amplifier” that helps to distort the signal of various stressors in those at high risk of depression. Consistent with this, studies using fMRI have established that increased amygdalar activity in response to emotionally relevant stimuli is associated with the less functional short or s allele of the gene coding for the promoter region of the 5-HT transporter.

**IMMUNOLOGICAL DISTURBANCE**

Depressive disorders are associated with several immunological abnormalities, including decreased lymphocyte proliferation in response to mitogens and other forms of impaired cellular immunity. These lymphocytes produce neuromodulators, such as CRF, and cytokines, peptides known as interleukins. There appears to be an association with clinical severity, hypercortisolism, and immune dysfunction, and the cytokine interleukin-1 may
induce gene activity for glucocorticoid synthesis. There is increasing evidence that depression is a proinflammatory illness, which may partly explain the high incidence of comorbid disorders such as obesity, diabetes, and atherosclerosis. Research is now underway to determine if strategies that dampen neuroinflammation can have antidepressant effects.

**FIGURE 13.9–3.** Key brain regions involved in affect and mood disorders. **A:** Orbital prefrontal cortex and the ventromedial prefrontal cortex. **B:** Dorsolateral prefrontal cortex. **C:** Hippocampus and amygdala. **D:** Anterior cingulated cortex.

**SUMMARY**

More severe and persistent depressive states, including those classified as major depressive disorder, are associated with a wide-range neurobiological disturbances, which in turn are linked to at least some of the differences observed in clinical presentations and response to specific treatments. Some of the disturbances are better understood as traits, which may be either inherited or acquired, whereas others are clearly state dependent and are reversible by treatment or spontaneous remission. Some of the state-dependent abnormalities associated with major depressive disorder, which occur more commonly in older patients with more severe symptomatology, include increased phasic REM sleep, poor sleep maintenance, hypercortisolism, impaired cellular immunity, reductions in anterior cerebral blood flow and glucose metabolism, and increased glucose metabolism in the amygdala. Together, these changes appear to reflect the progressive effects of otherwise adaptive short-term responses to sustained stress. Once manifest in this form, such severe or melancholic depressive episodes tend to be longer, more disabling, more prone to relapse, and more likely to benefit from pharmacotherapy or ECT (vis-à-vis nonspecific or psychotherapeutic interventions).
More trait-like abnormalities, which may include decreased slow wave sleep, reduced REM latency, blunted nocturnal GH secretion, and increased connectivity within the DMN. These abnormalities are associated with an early age of onset and increased vulnerability to recurrent illness. The heritability of these abnormalities, which at least partly reflects decreased 5-HT inhibition of responses to stress or threat, is both inferred from family studies and other at-risk paradigms and has been linked to inheritance of the s allele of the 5-HT transporter.

Examples of more persistent, but acquired abnormalities may include global and focal changes, such as volume reduction in the hippocampus and anterior cingulate, hypertrophy of the adrenal cortex, periventricular hyperintensities, and alterations in CRH synthesis. Blunted TSH response (to a TRH infusion) and dexamethasone non-suppression may represent hybrids, in that these abnormalities can be slow to normalize and, when persistent after remission, convey a high risk of relapse. Aging and the accumulating consequences of recurrent depressive episodes are inextricably connected. However, the diseases of aging that ravage brain function definitely increase the risk of depression and decrease responsivity to conventional forms of treatment. The late-onset form of depression associated with cerebral atherosclerosis illustrates the subtle interplay between brain function and mood disorder.

There is no doubt that vulnerability to mood disorders is partly heritable. This type of heritability is most likely polygenetic and, in all likelihood, will be best understood through models that include gene–environment interactions. Nevertheless, increased heritability is associated with an earlier age of onset, greater comorbidity, increased risk of recurrent illness, and an increased likelihood of hypomanic or manic episodes. Is it ironic that two of the more heritable forms of mood disorder, early onset chronic depressions and bipolar depression, are relatively less likely to be associated with state-dependent neurobiological disturbances? Different genetic vulnerabilities, different clinical presentations, and age-dependent differences in the effects of depression on brain function depression are likely to explain this apparent paradox.

Ultimately, depression remains a fundamentally human experience, partly because people can all relate to sadness, grief, and the heartbeat of lost love and partly because of the contrived nature of experiments that subject animals to prolonged, inescapable stress. Strong and sustaining affective bonds and an enduring sense of self-worth and competence are simply too important, and assaults on these fundamental aspects of well-being are too frequent for some humans to withstand without becoming depressed. That some are more vulnerable to depression than others is without question, as is the association of stress, depression, and numerous reproducible changes in brain function. Understanding the mechanisms of successful and unsuccessful adaptation and elucidating the alterations in brain function that predispose to and maintain depressive disorders represent the best hope to prevent and relieve the misery and suffering of tens of millions of people.

REFERENCES


