13 - 8 Mood Disorders

01 - 8.1 Major Depression and Bipolar Disorder

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Mood Disorders 8.1 Major Depression and Bipolar Disorder Mood can be defined as a pervasive and sustained emotion or feeling tone that influences a person’s behavior and colors his or her perception of being in the world. Disorders of mood—sometimes called affective disorders—make up an important category of psychiatric illness consisting of depressive disorder, bipolar disorder, and other disorders, which are discussed in this section and in the section that follows. A variety of adjectives are used to describe mood: depressed, sad, empty, melancholic, distressed, irritable, disconsolate, elated, euphoric, manic, gleeful, and many others, all descriptive in nature. Some can be observed by the clinician (e.g., an unhappy visage), and others can be felt only by the patient (e.g., hopelessness). Mood can be labile, fluctuating or alternating rapidly between extremes (e.g., laughing loudly and expansively one moment, tearful and despairing the next). Other signs and symptoms of mood disorders include changes in activity level, cognitive abilities, speech, and vegetative functions (e.g., sleep, appetite, sexual activity, and other biological rhythms). These disorders virtually always result in impaired interpersonal, social, and occupational functioning. It is tempting to consider disorders of mood on a continuum with normal variations in mood. Patients with mood disorders, however, often report an ineffable, but distinct, quality to their pathological state. The concept of a continuum, therefore, may represent the clinician’s overidentification with the pathology, thus possibly distorting his or her approach to patients with mood disorder. Patients with only major depressive episodes are said to have major depressive disorder or unipolar depression. Patients with both manic and depressive episodes or patients with manic episodes alone are said to have bipolar disorder. The terms “unipolar mania” and “pure mania” are sometimes used for patients who are bipolar but who do not have depressive episodes. Three additional categories of mood disorders are hypomania, cyclothymia, and dysthymia. Hypomania is an episode of manic symptoms that does not meet the criteria for manic episode. Cyclothymia and dysthymia as disorders that represent less severe forms of bipolar disorder and major depression, respectively. The field of psychiatry has considered major depression and bipolar disorder to be two separate disorders, particularly in the past 20 years. The possibility that bipolar disorder is actually a more severe expression of major depression has been reconsidered recently, however. Many patients given a diagnosis of a major depressive disorder reveal, on careful examination, past episodes of manic or hypomanic behavior that have gone

undetected. Many authorities see considerable continuity between recurrent depressive and bipolar disorders. This has led to widespread discussion and debate about the bipolar spectrum, which incorporates classic bipolar disorder, bipolar II, and recurrent depressions. HISTORY The Old Testament story of King Saul describes a depressive syndrome, as does the story of Ajax's suicide in Homer's Iliad. About 400 BCE, Hippocrates used the terms mania and melancholia to describe mental disturbances. Around 30 AD, the Roman physician Celsus described melancholia (from Greek melan ["black"] and chole ["bile"]) in his work De re medicina as a depression caused by black bile. The first English text (Fig. 8.1-1) entirely related to depression was Robert Burton's Anatomy of Melancholy, published in 1621.

FIGURE 8.1-1 Frontispiece of Robert Burton's Anatomy of Melancholy (1621). (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins, 2009.) In 1854, Jules Falret described a condition called folie circulaire, in which patients experience alternating moods of depression and mania. In 1882, the German psychiatrist Karl Kahlbaum, using the term cyclothymia, described mania and depression as stages of the same illness. In 1899, Emil Kraepelin, building on the knowledge of previous French and German psychiatrists, described manic-depressive psychosis using most of the criteria that psychiatrists now use to establish a diagnosis of bipolar I

disorder. According to Kraepelin, the absence of a dementing and deteriorating course in manic-depressive psychosis differentiated it from dementia precox (as schizophrenia was then called). Kraepelin also described a depression that came to be known as involutional melancholia, which has since come to be viewed as a severe form of mood disorder that begins in late adulthood. Depression A major depressive disorder occurs without a history of a manic, mixed, or hypomanic episode. A major depressive episode must last at least 2 weeks, and typically a person with a diagnosis of a major depressive episode also experiences at least four symptoms from a list that includes changes in appetite and weight, changes in sleep and activity, lack of energy, feelings of guilt, problems thinking and making decisions, and recurring thoughts of death or suicide. Mania A manic episode is a distinct period of an abnormally and persistently elevated, expansive, or irritable mood lasting for at least 1 week or less if a patient must be hospitalized. A hypomanic episode lasts at least 4 days and is similar to a manic episode except that it is not sufficiently severe to cause impairment in social or occupational functioning, and no psychotic features are present. Both mania and hypomania are associated with inflated self-esteem, a decreased need for sleep, distractibility, great physical and mental activity, and overinvolvement in pleasurable behavior. Bipolar I disorder is defined as having a clinical course of one or more manic episodes and, sometimes, major depressive episodes. A mixed episode is a period of at least 1 week in which both a manic episode and a major depressive episode occur almost daily. A variant of bipolar disorder characterized by episodes of major depression and hypomania rather than mania is known as bipolar II disorder. Dysthymia and Cyclothymia Two additional mood disorders, dysthymic disorder and cyclothymic disorder (discussed fully in Section 8.2) have also been appreciated clinically for some time. Dysthymic disorder and cyclothymic disorder are characterized by the presence of symptoms that are less severe than those of major depressive disorder and bipolar I disorder, respectively. Dysthymic disorder is characterized by at least 2 years of depressed mood that is not sufficiently severe to fit the diagnosis of major depressive episode. Cyclothymic disorder is characterized by at least 2 years of frequently occurring hypomanic symptoms that cannot fit the diagnosis of manic episode and of depressive symptoms that cannot fit the diagnosis of major

depressive episode. EPIDEMIOLOGY

Incidence and Prevalence Mood disorders are common. In the most recent surveys, major depressive disorder has the highest lifetime prevalence (almost 17 percent) of any psychiatric disorder. The lifetime prevalence rate of different forms of depressive disorder, according to community surveys, are shown in Table 8.1-1. The lifetime prevalence rate for major depression is 5 to 17 percent. The lifetime prevalence rates of different clinical forms of bipolar disorder are shown in Table 8.1-2. The annual incidence of bipolar illness is considered generally to be less than 1 percent, but it is difficult to estimate because milder forms of bipolar disorder are often missed. Table 8.1-2 Lifetime Prevalence Rates of Bipolar I Disorder, Bipolar II Disorder, Cyclothymic Disorder, and Hypomania Table 8.1-1 Lifetime Prevalence Rates of Depressive Disorders Sex An almost universal observation, independent of country or culture, is the twofold greater prevalence of major depressive disorder in women than in men. The reasons for the difference are hypothesized to involve hormonal differences, the effects of childbirth, differing psychosocial stressors for women and for men, and behavioral models of learned helplessness. In contrast to major depressive disorder, bipolar I disorder has an

equal prevalence among men and women. Manic episodes are more common in men, and depressive episodes are more common in women. When manic episodes occur in women, they are more likely than men to present a mixed picture (e.g., mania and depression). Women also have a higher rate of being rapid cyclers, defined as having four or more manic episodes in a 1-year period. Age The onset of bipolar I disorder is earlier than that of major depressive disorder. The age of onset for bipolar I disorder ranges from childhood (as early as age 5 or 6 years) to 50 years or even older in rare cases, with a mean age of 30 years. The mean age of onset for major depressive disorder is about 40 years, with 50 percent of all patients having an onset between the ages of 20 and 50 years. Major depressive disorder can also begin in childhood or in old age. Recent epidemiological data suggest that the incidence of major depressive disorder may be increasing among people younger than 20 years of age. This may be related to the increased use of alcohol and drugs of abuse in this age group. Marital Status Major depressive disorder occurs most often in persons without close interpersonal relationships and in those who are divorced or separated. Bipolar I disorder is more common in divorced and single persons than among married persons, but this difference may reflect the early onset and the resulting marital discord characteristic of the disorder. Socioeconomic and Cultural Factors No correlation has been found between socioeconomic status and major depressive disorder. A higher than average incidence of bipolar I disorder is found among the upper socioeconomic groups. Bipolar I disorder is more common in persons who did not graduate from college than in college graduates, however, which may also reflect the relatively early age of onset for the disorder. Depression is more common in rural areas than in urban areas. The prevalence of mood disorder does not differ among races. A tendency exists, however, for examiners to underdiagnose mood disorder and overdiagnose schizophrenia in patients whose racial or cultural background differs from theirs. COMORBIDITY Individuals with major mood disorders are at an increased risk of having one or more additional comorbid disorders. The most frequent disorders are alcohol abuse or dependence, panic disorder, obsessive-compulsive 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, whereas men more frequently present with substance use disorders, women more frequently present with comorbid anxiety and eating disorders. In general, patients who are bipolar more frequently show comorbidity of substance use and anxiety disorders than do patients with unipolar major depression. In the Epidemiological Catchment Area (ECA) study, the lifetime history of substance use disorders, panic disorder, and OCD was approximately twice as high among patients with bipolar I disorder (61 percent, 21 percent, and 21 percent, respectively) than in patients with unipolar major depression (27 percent, 10 percent, and 12 percent, respectively). Comorbid substance use disorders and anxiety disorders worsen the prognosis of the illness and markedly increase the risk of suicide among patients who are unipolar major depressive and bipolar. ETIOLOGY Biological Factors Many studies have reported biological abnormalities in patients with mood disorders. Until recently, the monoamine neurotransmitters—norepinephrine, dopamine, serotonin, and histamine—were the main focus of theories and research about the etiology of these disorders. A progressive shift has occurred from focusing on disturbances of single neurotransmitter systems in favor of studying neurobehavioral systems, neural circuits, and more intricate neuroregulatory mechanisms. The monoaminergic systems, thus, are now viewed 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. Biogenic Amines. Of the biogenic amines, norepinephrine and serotonin are the two neurotransmitters most implicated in the pathophysiology of mood disorders. NOREPINEPHRINE. The correlation suggested by basic science studies between the downregulation or decreased sensitivity of β-adrenergic receptors and clinical antidepressant responses is probably the single most compelling piece of data indicating a direct role for the noradrenergic system in depression. Other evidence has also implicated the presynaptic β2-receptors in depression because activation of these receptors results in a decrease of the amount of norepinephrine released. Presynaptic β2-receptors are also located on serotonergic neurons and regulate the amount of serotonin released. The clinical effectiveness of antidepressant drugs with noradrenergic effects—for example, venlafaxine (Effexor)—further supports a role for norepinephrine in the pathophysiology of at least some of the symptoms of depression. SEROTONIN. With the huge effect that the selective serotonin reuptake inhibitors (SSRIs) —for example, fluoxetine (Prozac)—have made on the treatment of depression, serotonin has become the biogenic amine neurotransmitter most commonly associated with depression. The identification of multiple serotonin receptor subtypes has also

increased the excitement within the research community about the development of even more specific treatments for depression. Besides that SSRIs and other serotonergic antidepressants are effective in the treatment of depression, other data indicate that serotonin is involved in the pathophysiology of depression. Depletion of serotonin may precipitate depression, and some patients with suicidal impulses have low cerebrospinal fluid (CSF) concentrations of serotonin metabolites and low concentrations of serotonin uptake sites on platelets. DOPAMINE. Although norepinephrine and serotonin are the biogenic amines most often associated with the pathophysiology of depression, dopamine has also been theorized to play a role. The data suggest that dopamine activity may be reduced in depression and increased in mania. The discovery of new subtypes of the dopamine receptors and an increased understanding of the presynaptic and postsynaptic regulation of dopamine function have further enriched research into the relation between dopamine and mood disorders. Drugs that reduce dopamine concentrations—for example, reserpine (Serpasil)—and diseases that reduce dopamine concentrations (e.g., Parkinson’s disease) are associated with depressive symptoms. In contrast, drugs that increase dopamine

concentrations, such as tyrosine, amphetamine, and bupropion (Wellbutrin), reduce the symptoms of depression. Two recent theories about dopamine and depression are that the mesolimbic dopamine pathway may be dysfunctional in depression and that the dopamine D1 receptor may be hypoactive in depression. 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. Cholinergic agonist and antagonist drugs have differential clinical effects on depression and mania. Agonists can produce lethargy, anergia, and psychomotor retardation in healthy subjects, can exacerbate symptoms in depression, and can reduce symptoms in mania. These effects generally are not sufficiently robust to have clinical applications, and adverse effects are problematic. In an animal model of depression, strains of mice that are super- or subsensitive to cholinergic agonists have been found susceptible or more resistant to developing learned helplessness (discussed later). Cholinergic agonists can induce changes in hypothalamic–pituitary adrenal (HPA) activity and sleep that mimic those associated with severe depression. Some patients with mood disorders in remission, as well as their never-ill first-degree relatives, have a trait-like increase in sensitivity to cholinergic agonists. γ-Aminobutyric acid (GABA) has an inhibitory effect on ascending monoamine pathways, particularly the mesocortical and mesolimbic systems. Reductions of 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 can 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 Nmethyl-D-aspartate (NMDA) receptor, and an excess of glutamatergic stimulation can cause neurotoxic effects. Importantly, a high concentration of NMDA receptors exists in the hippocampus. Glutamate, thus, may work in conjunction with hypercortisolemia to mediate the deleterious neurocognitive effects of severe recurrent depression. Emerging evidence suggests that drugs that antagonize NMDA receptors have antidepressant effects. 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., cyclic adenosine monophosphate [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. Increasing evidence also indicates that mood-stabilizing drugs act on G proteins or other second messengers. Alterations of Hormonal Regulation. Lasting alterations in neuroendocrine and behavioral responses can result from severe early stress. Animal studies indicate that even transient periods of maternal deprivation can alter subsequent responses to stress. Activity of the gene coding for the neurokinin brain-derived neurotrophic growth factor (BDNF) is decreased after chronic stress, as is the process of neurogenesis. Protracted stress thus can induce changes in the functional status of neurons and, eventually, cell death. Recent studies in depressed humans indicate that a history of early trauma

is associated with increased HPA activity accompanied by structural changes (i.e., atrophy or decreased volume) in the cerebral cortex. Elevated HPA activity is a hallmark of mammalian stress responses and one of the clearest links between depression and the biology of chronic stress. Hypercortisolema in depression suggests one or more of the following central disturbances: decreased inhibitory serotonin tone; increased drive from norepinephrine, ACh, or corticotropinreleasing hormone (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. Elevated HPA activity in depression has been documented via excretion of urinaryfree cortisol (UFC), 24-hour (or shorter time segments) intravenous (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) (0.5 to 2.0 mg), a potent synthetic glucocorticoid, which normally suppresses HPA axis activity for 24 hours. Nonsuppression 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 nonsuppression are imperfectly correlated (approximately 60 percent concordance). A more recent development to improve the sensitivity of the test involves infusion of a test dose of CRH after dexamethasone suppression. These tests of feedback inhibition are not used as a diagnostic test because adrenocortical hyperactivity (albeit usually less prevalent) is observed in mania, schizophrenia, dementia, and other psychiatric disorders. THYROID AXIS ACTIVITY. Approximately 5 to 10 percent of people evaluated for depression have previously undetected thyroid dysfunction, as reflected by an elevated basal thyroid-stimulating hormone (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 antithyroid antibody levels and, unless corrected with hormone replacement therapy, can compromise response to treatment. An even larger subgroup of depressed patients (e.g., 20 to 30 percent) shows a blunted TSH response to TRH challenge. To date, 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 does not usually normalize with effective treatment. GROWTH HORMONE. Growth hormone (GH) is secreted from the anterior pituitary after stimulation by NE and dopamine. Secretion is inhibited by somatostatin, a hypothalamic neuropeptide, and CRH. 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 serotonin stimulation and inhibited by dopamine. Most studies have not found significant abnormalities of basal or circadian prolactin secretion in depression, although a blunted prolactin response to various serotonin agonists has been described. This response is uncommon among premenopausal women, suggesting that estrogen has a moderating effect. Alterations of Sleep Neurophysiology. 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 rapid eye movement (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 non-REM (NREM) sleep, a phenomenon referred to as reduced REM latency. 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.

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 findings are commonly seen in younger, hypersomnolent 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, as with dexamethasone nonsuppression, false-positive cases are not uncommonly seen in other psychiatric disorders. 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. 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 corticotropin-releasing factor (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. Structural and Functional Brain Imaging. Computed axial tomography (CAT) and magnetic resonance imaging (MRI) scans have permitted sensitive, noninvasive methods to assess the living brain, including cortical and subcortical tracts, as well as white matter lesions. The most consistent abnormality observed in the depressive disorders is increased frequency of abnormal hyperintensities in subcortical regions, such as periventricular regions, the basal ganglia, and the thalamus. More common in bipolar I disorder and among elderly adults, these hyperintensities appear to reflect the deleterious neurodegenerative effects of recurrent affective episodes. Ventricular enlargement, cortical atrophy, and sulcal widening also have been reported in some studies. Some depressed patients also may have reduced hippocampal or caudate nucleus volumes, or both, suggesting more focal defects in relevant neurobehavioral systems. Diffuse and focal areas of atrophy have been associated with increased illness severity, bipolarity, and increased cortisol levels. The most widely replicated positron emission tomography (PET) finding in depression is decreased anterior brain metabolism, which is generally more pronounced on the left side. From a different vantage point, depression may be associated with a relative increase in nondominant hemispheric activity. Furthermore, a reversal of hypofrontality occurs after shifts from depression into hypomania, such that greater left hemisphere reductions are seen in depression compared with greater right hemisphere reductions in mania. Other studies have observed more specific reductions of reduced cerebral blood flow or metabolism, or both, in the dopaminergically innervated tracts of the mesocortical and mesolimbic systems in depression. Again, evidence suggests that antidepressants at least partially normalize these changes. In addition to a global reduction of 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. During episodes of depression, increased glucose metabolism is correlated with intrusive ruminations. Neuroanatomical Considerations. Both the symptoms of mood disorders and biological research findings support the hypothesis that mood disorders involve pathology of the brain. Modern affective neuroscience focuses on the importance of four brain regions in the regulation of normal emotions: the prefrontal cortex (PFC), the anterior cingulate, the hippocampus, and the amygdala. 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. Evidence indicates some hemispherical specialization in PFC function. For example, whereas leftsided activation of regions of the PFC is more involved in goal-directed or appetitive behaviors, regions of the right PFC are implicated in avoidance behaviors and inhibition of appetitive pursuits. Subregions in the PFC appear to localize representations of behaviors related to reward and punishment. 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 facilitates control of emotional arousal, particularly when goal attainment has been thwarted or when novel problems have been encountered. 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. 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 heart of the limbic system. Although most research has focused on the role of the amygdala in responding to fearful or painful stimuli, it may be ambiguity or novelty, rather than the aversive nature of the stimulus per se, that brings the amygdala on line (Fig. 8.1-2).

FIGURE 8.1-2 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 cingulate cortex. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins, 2009.) Genetic Factors Numerous family, adoption, and twin studies have long documented the heritability of mood disorders. Recently, however, the primary focus of genetic studies has been to identify specific susceptibility genes using molecular genetic methods. Family Studies. Family studies address the question of whether a disorder is familial. More specifically, is the rate of illness in the family members of someone with the disorder greater than that of the general population? Family data indicate that if one parent has a mood disorder, a child will have a risk of between 10 and 25 percent for mood disorder. If both parents are affected, this risk roughly doubles. The more members of the family who are affected, the greater the risk is to a child. The risk is 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. Unipolar disorder is typically the most common form of mood disorder in families of bipolar probands. This familial overlap suggests some degree of common genetic underpinnings between these two forms of mood disorder. The presence of more severe illness in the family also conveys a greater risk (Fig. 8.1-3). FIGURE 8.1-3 Many different models of genetic transmission have been considered and tested to see if they would explain the transmission of mood disorders. This is a selection of some of the more prominent models. In Mendelian or single major locus transmission, one gene transmits the illness. In polygenic quantitative trait (QTL) model, 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 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 the bottom panel, some possible models or genetic heterogeneity are illustrated. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia:

Lippincott Williams & Wilkins, 2009.) Adoption Studies. Adoption studies provide an alternative approach to separating genetic and environmental factors in familial transmission. Only a limited number of such studies have been reported, and their results have been mixed. One large study found a threefold increase in the rate of bipolar disorder and a twofold increase in unipolar disorder in the biological relatives of bipolar probands. Similarly, in a Danish sample, a threefold increase in the rate of unipolar disorder and a sixfold increase in the rate of completed suicide in the biological relatives of affectively ill probands were reported. Other studies, however, have been less convincing and have found no difference in the rates of mood disorders. Twin Studies. Twin studies provide the most powerful approach to separating genetic from environmental factors, or "nature" from "nurture." The twin data provide compelling evidence that genes explain only 50 to 70 percent of the etiology of mood disorders. Environment or other nonheritable factors must explain the remainder. Therefore, it is a predisposition or susceptibility to disease that is inherited. Considering unipolar and bipolar disorders together, these studies find a concordance rate for mood disorder in the monozygotic (MZ) twins of 70 to 90 percent compared with the same-sex dizygotic (DZ) twins of 16 to 35 percent. This is the most compelling data for the role of genetic factors in mood disorders. Linkage Studies. DNA markers are segments of DNA of known chromosomal location, which are highly variable among individuals. They are used to track the segregation of specific chromosomal regions within families affected with a disorder. When a marker is identified with disease in families, the disease is said to be genetically linked (Table 8.1-3). Chromosomes 18q and 22q are the two regions with strongest evidence for linkage to bipolar disorder. Several linkage studies have found evidence for the involvement of specific genes in clinical subtypes. For example, the linkage evidence on 18q has been shown to be derived largely from bipolar II–bipolar II sibling pairs and from families in which the probands had panic symptoms. Table 8.1-3 Selected Chromosomal Regions with Evidence of Linkage to Bipolar Disorder

Gene-mapping studies of unipolar depression have found very strong evidence of linkage to the locus for cAMP response element-binding protein (CREB1) on chromosome 2. Eighteen other genomic regions were found to be linked; some of these displayed interactions with the CREB1 locus. Another study has reported evidence for a gene–environment interaction in the development of major depression. Subjects who underwent adverse life events were shown, in general, to be at an increased risk for depression. Of such subjects, however, those with a variant in the serotonin transporter gene showed the greatest increase in risk. This is one of the first reports of a specific gene–environment interaction in a psychiatric disorder. Psychosocial Factors Life Events and Environmental Stress. A long-standing clinical observation is that stressful life events more often precede first, rather than subsequent, episodes of mood disorders. This association has been reported for both patients with major depressive disorder and patients with bipolar I disorder. One theory proposed to explain this observation is that the stress accompanying the first episode results in long-lasting changes in the brain's biology. These long-lasting changes may alter the functional states of various neurotransmitter and intraneuronal signaling systems, changes that

may even include the loss of neurons and an excessive reduction in synaptic contacts. As a result, a person has a high risk of undergoing subsequent episodes of a mood disorder, even without an external stressor. Some clinicians believe that life events play the primary or principal role in depression; others suggest that life events have only a limited role in the onset and timing of depression. The most compelling data indicate that the life event most often associated with development of depression is losing a parent before age 11 years. The environmental stressor most often associated with the onset of an episode of depression is the loss of a spouse. Another risk factor is unemployment; persons out of work are three times more likely to report symptoms of an episode of major depression than those who are employed. Guilt may also play a role.

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. (Courtesy of JC Markowitz, M.D., and BL Milrod, M.D.) Personality Factors. No single personality trait or type uniquely predisposes a person to depression; all humans, of whatever personality pattern, can and do become depressed under appropriate circumstances. Persons with certain personality disorders— OCD, histrionic, and borderline—may be at greater risk for depression than persons with antisocial or paranoid personality disorder. The latter can use projection and other externalizing defense mechanisms to protect themselves from their inner rage. No evidence indicates that any particular personality disorder is associated with later development of bipolar I disorder; however, patients with dysthymic disorder and cyclothymic disorder are at risk of later developing major depression or bipolar I disorder. Recent stressful events are the most powerful predictors of the onset of a depressive episode. From a psychodynamic perspective, the clinician is always interested in the meaning of the stressor. Research has demonstrated that stressors that the patient experiences as reflecting negatively on his or her self-esteem are more likely to produce depression. Moreover, what may seem to be a relatively mild stressor to outsiders may be devastating to the patient because of particular idiosyncratic meanings attached to the event. Psychodynamic Factors in Depression. The psychodynamic understanding of

depression defined by Sigmund Freud and expanded by Karl Abraham is known as the classic view of depression. That theory involves four key points: (1) disturbances in the infant–mother

relationship during the oral phase (the first 10 to 18 months of life) predispose to subsequent vulnerability to depression; (2) depression can be linked to real or imagined object loss; (3) introjection of the departed objects is a defense mechanism invoked to deal with the distress connected with the object's loss; and (4) because the lost object is regarded with a mixture of love and hate, feelings of anger are directed inward at the self. 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, Ms. 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. (Courtesy of JC Markowitz, M.D., and BL Milrod, M.D.) Melanie Klein understood depression as involving the expression of aggression toward loved ones, much as Freud did. Edward Bibring regarded depression as a phenomenon that sets in when a person becomes aware of the discrepancy between extraordinarily high ideals and the inability to meet those goals. Edith Jacobson saw the state of depression as similar to a powerless, helpless child victimized by a tormenting parent. Silvano Arieti observed that many depressed people have lived their lives for someone else rather than for themselves. He referred to the person for whom depressed patients live as the dominant other, which may be a principle, an ideal, or an institution, as well as an individual. Depression sets in when patients realize that the person or ideal for which they have been living is never going to respond in a manner that will meet their expectations. Heinz Kohut's conceptualization of depression, derived from his selfpsychological theory, rests on the assumption that the developing self has specific needs that must be met by parents to give the child a positive sense of self-esteem and self-

cohesion. When others do not meet these needs, there is a massive loss of self-esteem that presents as depression. John Bowlby believed that damaged early attachments and traumatic separation in childhood predispose to depression. Adult losses are said to revive the traumatic childhood loss and so precipitate adult depressive episodes. Psychodynamic Factors in Mania. Most theories of mania view manic episodes as a defense against underlying depression. Abraham, for example, believed that the manic episodes may reflect an inability to tolerate a developmental tragedy, such as the loss of a parent. The manic state may also result from a tyrannical superego, which produces intolerable self-criticism that is then replaced by euphoric self-satisfaction. Bertram Lewin regarded the manic patient's ego as overwhelmed by pleasurable impulses, such as sex, or by feared impulses, such as aggression. Klein also viewed mania as a defensive reaction to depression, using manic defenses such as omnipotence, in which the person develops delusions of grandeur. 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. Before 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. (Courtesy of JC Markowitz, M.D., and BL Milrod, M.D.) Other Formulations of Depression

Cognitive Theory. According to cognitive theory, depression results from specific cognitive distortions present in persons susceptible to depression. These distortions, referred to as depressogenic schemata, are cognitive templates that perceive both internal and external data in ways that are altered by early experiences. Aaron Beck postulated a cognitive triad of depression that consists of (1) views about the self—a negative selfprecept, (2) about the environment—a tendency to experience the world as hostile and demanding, and (3) about the future—the expectation of suffering and failure. Therapy consists of modifying these distortions. The elements of cognitive theory are summarized in Table 8.1-4. Table 8.1-4 Elements of Cognitive Theory Learned Helplessness. The learned helplessness theory of depression connects depressive phenomena to the experience of uncontrollable events. For example, when dogs in a laboratory were exposed to electrical shocks from which they could not escape, they showed behaviors that differentiated them from dogs that had not been exposed to such uncontrollable events. The dogs exposed to the shocks would not cross a barrier to stop the flow of electric shock when put in a new learning situation. They remained passive and did not move. According to the learned helplessness theory, the shocked dogs learned that outcomes were independent of responses, so they had both cognitive motivational deficit (i.e., they would not attempt to escape the shock) and emotional deficit (indicating decreased reactivity to the shock). In the reformulated view of

learned helplessness as applied to human depression, internal causal explanations are thought to produce a loss of self-esteem after adverse external events. Behaviorists who subscribe to the theory stress that improvement of depression is contingent on the patient's learning a sense of control and mastery of the environment. DIAGNOSIS Major Depressive Disorder The DSM-5 diagnostic criteria for major depression are listed in Table 8.1-5; severity descriptors and other specifiers for a major depressive episode are also listed in that table. Table 8.1-5 DSM-5 Criteria for Major Depressive Disorder

Major Depressive Disorder, Single Episode Depression may occur as a single episode or may be recurrent. Differentiation between these patients and those who have two or more episodes of major depressive disorder is justified because of the uncertain course of the former patients' disorder. Several studies have reported data consistent with the notion that major depression covers a heterogeneous population of disorders. One type of study assessed the stability of a diagnosis of major depression in a patient over time. The study found that 25 to 50 percent of the patients were later reclassified as having a different psychiatric condition or a nonpsychiatric medical condition with psychiatric symptoms. A second type of study evaluated first-degree relatives of affectively ill patients to determine the presence and types of psychiatric diagnoses for these relatives over time. Both types of studies found that depressed patients with more depressive symptoms are more likely to have stable diagnoses over time and are more likely to have affectively ill relatives than are depressed patients with fewer depressive symptoms. Also, patients with bipolar I disorder and those with bipolar II disorder (recurrent major depressive episodes with hypomania) are likely to have stable diagnoses over time. Major Depressive Disorder, Recurrent Patients who are experiencing at least a second episode of depression are classified as having major depressive disorder, recurrent. The essential problem with diagnosing recurrent episodes of major depressive disorder is choosing the criteria to designate the resolution of each period. Two variables are the degree of resolution of the symptoms and the length of the resolution. DSM-5 requires that distinct episodes of depression be separated by at least 2 months during which a patient has no significant symptoms of depression. Bipolar I Disorder The DSM-5 criteria for a bipolar I disorder (Table 8.1-6) requires the presence of a distinct period of abnormal mood lasting at least 1 week and includes separate bipolar I disorder diagnoses for a single manic episode and a recurrent episode based on the symptoms of the most recent episode as described below. Table 8.1-6 DSM-5 Diagnostic Criteria for Bipolar I Disorder

The designation bipolar I disorder is synonymous with what was formerly known as bipolar disorder—a syndrome in which a complete set of mania symptoms occurs during the course of the disorder. The diagnostic criteria for bipolar II disorder is characterized by depressive episodes and hypomanic episodes during the course of the disorder, but the episodes of manic-like symptoms do not quite meet the diagnostic criteria for a full manic syndrome. Manic episodes clearly precipitated by antidepressant treatment (e.g., pharmacotherapy, electroconvulsive therapy [ECT]) do not indicate bipolar I disorder. Bipolar I Disorder, Single Manic Episode. According to DSM-5, patients must be experiencing their first manic episode to meet the diagnostic criteria for bipolar I disorder, single manic episode. This requirement rests on the fact that patients who are having their first episode of bipolar I disorder depression cannot be distinguished from patients with major depressive disorder. Bipolar I Disorder, Recurrent. The issues about defining the end of an episode of depression also apply to defining the end of an episode of mania. Manic episodes are considered distinct when they are separated by at least 2 months without significant symptoms of mania or hypomania. Bipolar II Disorder The diagnostic criteria for bipolar II disorder specify the particular severity, frequency, and duration of the hypomanic symptoms. The diagnostic criteria for a hypomanic episode are listed together with the criteria for bipolar II disorder (also in Table 8.1-6). The criteria have been established to decrease overdiagnosis of hypomanic episodes and the incorrect classification of patients with major depressive disorder as patients with bipolar II disorder. Clinically, psychiatrists may find it difficult to distinguish euthymia from hypomania in a patient who has been chronically depressed for many months or years. As with bipolar I disorder, antidepressant-induced hypomanic episodes are not diagnostic of bipolar II disorder. Specifiers

(Symptom Features) In addition to the severity, psychotic, and remission descriptions, additional symptom features (specifiers) can be used to describe patients with various mood disorders. With Psychotic Features. The presence of psychotic features in major depressive disorder reflects severe disease and is a poor prognostic indicator. A review of the literature comparing psychotic with nonpsychotic major depressive disorder indicates that the two conditions may be distinct in their pathogenesis. One difference is that bipolar I disorder is more common in the families of probands with psychotic depression than in the families of probands with nonpsychotic depression. The psychotic symptoms themselves are often categorized as either mood congruent,

that is, in harmony with the mood disorder (“I deserve to be punished because I am so bad”), or mood incongruent, not in harmony with the mood disorder. Patients with mood disorder with mood-congruent psychoses have a psychotic type of mood disorder; however, patients with mood disorder with mood-incongruent psychotic symptoms may have schizoaffective disorder or schizophrenia. The following factors have been associated with a poor prognosis for patients with mood disorders: long duration of episodes, temporal dissociation between the mood disorder and the psychotic symptoms, and a poor premorbid history of social adjustment. The presence of psychotic features also has significant treatment implications. These patients typically require antipsychotic drugs in addition to antidepressants or mood stabilizers and may need ECT to obtain clinical improvement. With Melancholic Features. Melancholia is one of the oldest terms used in psychiatry, dating back to Hippocrates in the 4th century to describe the dark mood of depression. It is still used to refer to a depression characterized by severe anhedonia, early morning awakening, weight loss, and profound feelings of guilt (often over trivial events). It is not uncommon for patients who are melancholic to have suicidal ideation. Melancholia is associated with changes in the autonomic nervous system and in endocrine functions. For that reason, melancholia is sometimes referred to as “endogenous depression” or depression that arises in the absence of external life stressors or precipitants. The DSM-5 melancholic features can be applied to major depressive episodes in major depressive disorder, bipolar I disorder, or bipolar II disorder. With Atypical Features. The introduction of a formally defined depression with atypical features is a response to research and clinical data indicating that patients with atypical features have specific, predictable characteristics: overeating and oversleeping. These symptoms have sometimes been referred to as reversed vegetative symptoms, and the symptom pattern has sometimes been called hysteroid dysphoria. When patients with major depressive disorder with atypical features are compared with patients with typical depression features, the patients with atypical features are found to have a younger age of onset; more severe psychomotor slowing; and more frequent coexisting diagnoses of panic disorder, substance abuse or dependence, and somatization disorder. The high incidence and severity of anxiety symptoms in patients with atypical features have sometimes been correlated with the likelihood of their being misclassified as having an anxiety disorder rather than a mood disorder. Patients with atypical features may also have a long-term course, a diagnosis of bipolar I disorder, or a seasonal pattern to their disorder. The DSM-5 atypical features can be applied to the most recent major depressive episode in major depressive disorder, bipolar I disorder, bipolar II disorder, or dysthymic disorder. Atypical depression may mask manic symptoms as in the following case.

Kevin, a 15-year-old adolescent, 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 findings 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 because it was contrary to his religious beliefs. These findings led to the prescription of desipramine (Norpramin) in a dosage 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. (Courtesy of HS Akiskal, M.D.) With Catatonic Features. As a symptom, catatonia can be present in several mental disorders, most commonly, schizophrenia and the mood disorders. The presence of catatonic features in patients with mood disorders may have prognostic and treatment significance. The hallmark 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 the symptoms of stuporous catatonia and the classic symptoms of mania. Because catatonic symptoms are a behavioral syndrome appearing in several medical and psychiatric conditions, catatonic symptoms do not imply a single diagnosis. Catatonia is discussed in detail in Section 7.5. Postpartum Onset. DSM-5 allows the specification of a postpartum mood disturbance if the onset of symptoms is within 4 weeks postpartum. Postpartum mental disorders commonly include psychotic symptoms. Postpartum disorders are discussed in Section 26.1, Psychiatry and Reproductive Medicine. Rapid Cycling. Patients with rapid cycling bipolar I disorder are likely to be female and to have had depressive and hypomanic episodes. No data indicate that rapid cycling has a familial pattern of inheritance; thus, an external factor such as stress or

drug treatment may be involved in the pathogenesis of rapid cycling. The DSM-5 criteria specify that the patient must have at least four episodes within a 12-month period. Seasonal Pattern. Patients with a seasonal pattern to their mood disorders tend to experience depressive episodes during a particular season, most commonly winter. The pattern has become known as seasonal affective disorder (SAD), although this term is not used in DSM-5. Two types of evidence indicate that the seasonal pattern may represent a separate diagnostic entity. First, the patients are likely to respond to treatment with light therapy, although no studies with controls to evaluate light therapy in nonseasonally depressed patients have been conducted. Second, research has shown that patients evince decreased metabolic activity in the orbital frontal cortex and in the left inferior parietal lobe. Further studies are necessary to differentiate depressed persons with seasonal pattern from other depressed persons. This disorder is discussed further in Section 16.2 on Sleep-Wake Disorders. Non–DSM-5 Types. DSM-5 specifiers for depressive disorders are included in Table 8.1-7. Other systems that identify types of patients with mood disorders usually separate patients with good and poor prognoses or patients who may respond to one treatment or another. They also differentiate endogenous-reactive and primary-secondary schemes. Table 8.1-7 DSM-5 Specifiers for Depressive Disorders

The endogenous-reactive continuum is a controversial division. It implies that endogenous depressions are biological and that reactive depressions are psychological, primarily on the basis of the presence or absence of an identifiable precipitating stress. Other symptoms of endogenous depression have been described as diurnal variation, delusions, psychomotor retardation, early morning awakening, and feelings of guilt; thus, endogenous depression is similar to the DSM-5 diagnosis of major depressive disorder with psychotic features, melancholic features, or both. Symptoms of reactive depression have included initial insomnia, anxiety, emotional lability, and multiple somatic complaints. Primary depressions are what DSM-5 refers to as mood disorders, except for the diagnoses of mood disorder caused by a general medical condition and substanceinduced mood disorder, which are considered secondary depressions. Double depression is the condition in which major depressive disorder is superimposed on dysthymic disorder. A depressive equivalent is a symptom or syndrome that may be a forme fruste of a depressive episode. For example, a triad of truancy, alcohol abuse, and sexual promiscuity in a formerly well-behaved adolescent may constitute a depressive equivalent. CLINICAL FEATURES The two basic symptom patterns in mood disorders are depression and mania.

Depressive episodes can occur in both major depressive disorder and bipolar I disorder. Researchers have attempted to find reliable differences between bipolar I disorder depressive episodes and episodes of major depressive disorder, but the differences are elusive. In a clinical situation, only the patient’s history, family history, and future course can help differentiate the two conditions. Some patients with bipolar I disorder have mixed states with both manic and depressive features, and some seem to experience brief—minutes to a few hours—episodes of depression during manic episodes. Depressive Episodes A depressed mood and a loss of interest or pleasure are the key symptoms of depression. Patients may say that they feel blue, hopeless, in the dumps, or worthless. For a patient, the depressed mood often has a distinct quality that differentiates it from the normal emotion of sadness or grief. Patients often describe the symptom of depression as one of agonizing emotional pain and sometimes complain about being unable to cry, a symptom that resolves as they improve. About two-thirds of all depressed patients contemplate suicide, and 10 to 15 percent commit suicide. Those recently hospitalized with a suicide attempt or suicidal ideation have a higher lifetime risk of successful suicide than those never hospitalized for suicidal ideation. Some depressed patients sometimes seem unaware of their depression and do not complain of a mood disturbance even though they exhibit withdrawal from family, friends, and activities that previously interested them. Almost all depressed patients (97 percent) complain about reduced energy; they have difficulty finishing tasks, are impaired at school and work, and have less motivation to undertake new projects. About 80 percent of patients complain of trouble sleeping, especially early morning awakening (i.e., terminal insomnia) and multiple awakenings at night, during which they ruminate about their problems. Many patients have decreased appetite and weight loss, but others experience increased appetite and weight gain and sleep longer than usual. These patients are classified as having atypical features. Anxiety, a common symptom of depression, affects as many as 90 percent of all depressed patients. The various changes in food intake and rest can aggravate coexisting medical illnesses such as diabetes, hypertension, chronic obstructive lung disease, and heart disease. Other vegetative symptoms include abnormal menses and decreased interest and performance in sexual activities. Sexual problems can sometimes lead to inappropriate referrals, such as to marital counseling and sex therapy, when clinicians fail to recognize the underlying depressive disorder. Anxiety (including panic attacks), alcohol abuse, and somatic complaints (e.g., constipation and headaches) often complicate the treatment of

depression. About 50 percent of all patients describe a diurnal variation in their symptoms, with increased severity in the morning and lessening of symptoms by evening. Cognitive symptoms include subjective reports of an inability to concentrate (84 percent of patients in one study) and impairments in thinking (67 percent of patients in another study).

Depression in Children and Adolescents. School phobia and excessive clinging to parents may be symptoms of depression in children. Poor academic performance, substance abuse, antisocial behavior, sexual promiscuity, truancy, and running away may be symptoms of depression in adolescents. Depression in Older People. Depression is more common in older persons than it is in the general population. Various studies have reported prevalence rates ranging from 25 to almost 50 percent, although the percentage of these cases that are caused by major depressive disorder is uncertain. Several studies indicate that depression in older persons may be correlated with low socioeconomic status, the loss of a spouse, a concurrent physical illness, and social isolation. Other studies have indicated that depression in older persons is underdiagnosed and undertreated, perhaps particularly by general practitioners. The underrecognition of depression in older persons may occur because the disorder appears more often with somatic complaints in older, than in younger, age groups. Further, ageism may influence and cause clinicians to accept depressive symptoms as normal in older patients. Manic Episodes An elevated, expansive, or irritable mood is the hallmark of a manic episode. The elevated mood is euphoric and often infectious and can even cause a countertransferential denial of illness by an inexperienced clinician. Although uninvolved persons may not recognize the unusual nature of a patient’s mood, those who know the patient recognize it as abnormal. Alternatively, the mood may be irritable, especially when a patient’s overtly ambitious plans are thwarted. Patients often exhibit a change of predominant mood from euphoria early in the course of the illness to later irritability. The treatment of manic patients in an inpatient ward can be complicated by their testing of the limits of ward rules, tendency to shift responsibility for their acts onto others, exploitation of the weaknesses of others, and propensity to create conflicts among staff members. Outside the hospital, manic patients often drink alcohol excessively, perhaps in an attempt to self-medicate. Their disinhibited nature is reflected in excessive use of the telephone, especially in making long-distance calls during the early morning hours. Pathological gambling, a tendency to disrobe in public places, wearing clothing and jewelry of bright colors in unusual or outlandish combinations, and inattention to small details (e.g., forgetting to hang up the telephone) are also symptomatic of the disorder. Patients act impulsively and at the same time with a sense of conviction and purpose. They are often preoccupied by religious, political, financial, sexual, or persecutory ideas that can evolve into complex delusional systems. Occasionally, manic patients become regressed and play with their urine and feces. Mania in Adolescents. Mania in adolescents is often misdiagnosed as antisocial

personality disorder or schizophrenia. Symptoms of mania in adolescents may include psychosis, alcohol or other substance abuse, suicide attempts, academic problems, philosophical brooding, OCD symptoms, multiple somatic complaints, marked irritability resulting in fights, and other antisocial behaviors. Although many of these symptoms are seen in normal adolescents, severe or persistent symptoms should cause clinicians to consider bipolar I disorder in the differential diagnosis. Bipolar II Disorder The clinical features of bipolar II disorder are those of major depressive disorder combined with those of a hypomanic episode. Although the data are limited, a few studies indicate that bipolar II disorder is associated with more marital disruption and with onset at an earlier age than bipolar I disorder. Evidence also indicates that patients with bipolar II

disorder are at greater risk of both attempting and completing suicide than patients with bipolar I disorder and major depressive disorder. Coexisting Disorders Anxiety. In the anxiety disorders, DSM-5 notes the existence of mixed anxiety– depressive disorder. Significant symptoms of anxiety can and often do coexist with significant symptoms of depression. Whether patients who exhibit significant symptoms of both anxiety and depression are affected by two distinct disease processes or by a single disease process that produces both sets of symptoms is not yet resolved. Patients of both types may constitute the group of patients with mixed anxiety–depressive disorder. Alcohol Dependence. Alcohol dependence frequently coexists with mood disorders. Both patients with major depressive disorder and those with bipolar I disorder are likely to meet the diagnostic criteria for an alcohol use disorder. The available data indicate that alcohol dependence is more strongly associated with a coexisting diagnosis of depression in women than in men. In contrast, the genetic and family data about men who have both a mood disorder and alcohol dependence indicate that they are likely to have two genetically distinct disease processes. Other Substance-Related Disorders. Substance-related disorders other than alcohol dependence are also commonly associated with mood disorders. The abuse of substances may be involved in precipitating an episode of illness or, conversely, may represent patients' attempts to treat their own illnesses. Although manic patients seldom use sedatives to dampen their euphoria, depressed patients often use stimulants, such as cocaine and amphetamines, to relieve their depression. Medical Conditions. Depression commonly coexists with medical conditions, especially in older persons. When depression and medical conditions coexist, clinicians

must try to determine whether the underlying medical condition is pathophysiologically related to the depression or whether any drugs that the patient is taking for the medical condition are causing the depression. Many studies indicate that treatment of a coexisting major depressive disorder can improve the course of the underlying medical disorder, including cancer. MENTAL STATUS EXAMINATION General Description Generalized psychomotor retardation is the most common symptom of depression, although psychomotor agitation is also seen, especially in older patients. Hand wringing and hair pulling are the most common symptoms of agitation. Classically, a depressed patient has a stooped posture; no spontaneous movements; and a downcast, averted gaze (Figs. 8.1-4 and 8.1-5). On clinical examination, depressed patients exhibiting gross symptoms of psychomotor retardation may appear identical to patients with catatonic schizophrenia. FIGURE 8.1-4

A 38-year-old woman during a state of deep retarded depression (A) and 2 months later after recovery (B). The turned-down corners of her mouth, her stooped posture, her drab clothing, and her hairdo during the depressed episode are noteworthy. (Courtesy of Heinz E. Lehmann, M.D.) FIGURE 8.1-5 The Swiss neuropsychiatrist Otto Veraguth described a peculiar triangle-shaped fold in the nasal corner of the upper eyelid. The fold is often associated with depression and 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 on electromyograms. (Courtesy of Heinz E. Lehmann, M.D.) 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." Mood, Affect,

and Feelings Depression is the key symptom, although about 50 percent of patients deny depressive

feelings and do not appear to be particularly depressed. Family members or employers often bring or send these patients for treatment because of social withdrawal and generally decreased activity. Speech Many depressed patients have decreased rate and volume of speech; they respond to questions with single words and exhibit delayed responses to questions. The examiner may literally have to wait 2 or 3 minutes for a response to a question. Perceptual Disturbances Depressed patients with delusions or hallucinations are said to have a major depressive episode with psychotic features. Even in the absence of delusions or hallucinations, some clinicians use the term psychotic depression for grossly regressed depressed patients— mute, not bathing, soiling. Such patients are probably better described as having catatonic features. Delusions and hallucinations that are consistent with a depressed mood are said to be mood congruent. Mood-congruent delusions in a depressed person include those of guilt, sinfulness, worthlessness, poverty, failure, persecution, and terminal somatic illnesses (such as cancer and a “rotting” brain). The content of mood-incongruent delusions or hallucinations is not consistent with a depressed mood. For example, a moodincongruent delusion in a depressed person might involve grandiose themes of exaggerated power, knowledge, and worth. When that occurs, a schizophrenic disorder should be considered. 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 passability and running commentary indicated a schizophrenic process. Thought Depressed patients customarily have negative views of the world and of themselves. Their thought content often includes nondelusional ruminations about loss, guilt, suicide, and death. About 10 percent of all depressed patients have marked symptoms of a thought disorder, usually thought blocking and profound poverty of content. Sensorium and Cognition

Orientation. Most depressed patients are oriented to person, place, and time, although some may not have sufficient energy or interest to answer questions about these subjects during an interview. Memory. About 50 to 75 percent of all depressed patients have a cognitive impairment, sometimes referred to as depressive pseudodementia. Such patients commonly complain of impaired concentration and forgetfulness. Impulse Control About 10 to 15 percent of all depressed patients commit suicide, and about two-thirds have suicidal ideation. Depressed patients with psychotic features occasionally consider killing a person as a result of their delusional systems, but the most severely depressed patients often lack the motivation or the energy to act in an impulsive or violent way. Patients with depressive disorders are at increased risk of suicide as they begin to improve and regain the energy needed to plan and carry out a suicide (paradoxical suicide). It is usually clinically unwise to give a depressed patient a large prescription for a large number of antidepressants, especially tricyclic drugs, at the time of their discharge from the hospital. Similarly, drugs that may be activating, such as fluoxetine, may be prescribed in such a way that the energizing qualities are minimized (e.g., be given a benzodiazepine at the same time). Judgment and Insight Judgment is best assessed by reviewing patients’ actions in the recent past and their behavior during the interview. Depressed patients’ descriptions of their disorder are often hyperbolic; they overemphasize their symptoms, their disorder, and their life problems. It is difficult to convince such patients that improvement is possible. Reliability In interviews and conversations,

depressed patients overemphasize the bad and minimize the good. A common clinical mistake is to unquestioningly believe a depressed patient who states that a previous trial of antidepressant medications did not work. Such statements may be false, and they require confirmation from another source. Psychiatrists should not view patients' misinformation as an intentional fabrication; the admission of any hopeful information may be impossible for a person in a depressed state of mind. Objective Rating Scales for Depression Objective rating scales for depression can be useful in clinical practice for documenting the depressed patient's clinical state.

Zung. The Zung Self-Rating Depression Scale is a 20-item report scale. A normal score is 34 or less; a depressed score is 50 or more. The scale provides a global index of the intensity of a patient's depressive symptoms, including the affective expression of depression. Raskin. The Raskin Depression Scale is a clinician-rated scale that measures the severity of a patient's depression, as reported by the patient and as observed by the physician, on a 5-point scale of three dimensions: verbal report, displayed behavior, and secondary symptoms. The scale has a range of 3 to 13; a normal score is 3, and a depressed score is 7 or more. Hamilton. The Hamilton Rating Scale for Depression (HAM-D) is a widely used depression scale with up to 24 items, each of which is rated 0 to 4 or 0 to 2, with a total score of 0 to 76. The clinician evaluates the patient's answers to questions about feelings of guilt, thoughts of suicide, sleep habits, and other symptoms of depression, and the ratings are derived from the clinical interview. Manic Episodes General Description. Manic patients are excited, talkative, sometimes amusing, and frequently hyperactive. At times, they are grossly psychotic and disorganized and require physical restraints and the intramuscular injection of sedating drugs. Mood, Affect, and Feelings Manic patients classically are euphoric, but they can also be irritable, especially when mania has been present for some time. They also have a low frustration tolerance, which can lead to feelings of anger and hostility. Manic patients may be emotionally labile, switching from laughter to irritability to depression in minutes or hours. Speech Manic patients cannot be interrupted while they are speaking, and they are often intrusive nuisances to those around them. Their speech is often disturbed. As the mania gets more intense, speech becomes louder, more rapid, and difficult to interpret. As the activated state increases, their speech is filled with puns, jokes, rhymes, plays on words, and irrelevancies. At a still greater activity level, associations become loosened, the ability to concentrate fades, and flight of ideas, clanging, and neologisms appear. In acute manic excitement, speech can be totally incoherent and indistinguishable from that of a person with schizophrenia. Perceptual Disturbances. Delusions occur in 75 percent of all manic patients. Mood-congruent manic delusions are often concerned with great wealth, extraordinary abilities, or power. Bizarre and mood-incongruent delusions and hallucinations also

appear in mania. 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 the author 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, because 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 dosage of a lithium–antipsychotic combination. The consultation was requested because the primary mood symptoms were under control, yet, she had not given up her grandiose delusion. She flippantly remarked, “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 the author could gently challenge her beliefs. 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. (Courtesy of HS Akiskal, M.D.) Thought. The manic patient’s thought content includes themes of self-confidence and self-aggrandizement. Manic patients are often easily distracted, and their cognitive functioning in the manic state is characterized by an unrestrained and accelerated flow of ideas.

Sensorium and Cognition. Although the cognitive deficits of patients with schizophrenia have been much discussed, less has been written about similar deficits in patients with bipolar I disorder. These deficits can be interpreted as reflecting diffuse cortical dysfunction; subsequent work may localize the abnormal areas. Grossly, orientation and memory are intact, although some manic patients may be so euphoric that they answer questions testing orientation incorrectly. Emil Kraepelin called the symptom “delirious mania.” Impulse Control. About 75 percent of all manic patients are assaultive or threatening. Manic patients do attempt suicide and homicide, but the incidence of these behaviors is unknown. Judgment and Insight. Impaired judgment is a hallmark of manic patients. They may break laws about credit cards, sexual activities, and finances and sometimes involve their families in financial ruin. Manic patients also have little insight into their disorder. Reliability. Manic patients are notoriously unreliable in their information. Because lying and deceit are common in mania, inexperienced clinicians may treat manic patients with inappropriate disdain. DIFFERENTIAL DIAGNOSIS Major Depressive Disorder Medical Disorders. The diagnosis of mood disorder due to a general medical condition must be considered. Failure to obtain a good clinical history or to consider the context of a patient’s current life situation can lead to diagnostic errors. Clinicians should have depressed adolescents tested for mononucleosis, and patients who are markedly overweight or underweight should be tested for adrenal and thyroid dysfunctions. Homosexuals, bisexual men, prostitutes, and persons who abuse a substance intravenously should be tested for acquired immune deficiency syndrome (AIDS). Older patients should be evaluated for viral pneumonia and other medical conditions. Many neurological and medical disorders and pharmacological agents can produce symptoms of depression. Patients with depressive disorders often first visit their general practitioners with somatic complaints. Most medical causes of depressive disorders can be detected with a comprehensive medical history, a

complete physical and neurological examination, and routine blood and urine tests. The workup should include tests for thyroid and adrenal functions because disorders of both of these endocrine systems can appear as depressive disorders. In substance-induced mood disorder, a reasonable rule of thumb is that any drug a depressed patient is taking should be considered a potential factor in the mood disorder. Cardiac drugs, antihypertensives, sedatives, hypnotics,

antipsychotics, antiepileptics, antiparkinsonian drugs, analgesics, antibacterials, and antineoplastics are all commonly associated with depressive symptoms. NEUROLOGICAL CONDITIONS. The most common neurological problems that manifest depressive symptoms are Parkinson's disease, dementing illnesses (including dementia of the Alzheimer's type), epilepsy, cerebrovascular diseases, and tumors. About 50 to 75 percent of all patients with Parkinson's disease have marked symptoms of depressive disorder that do not correlate with the patient's physical disability, age, or duration of illness but do correlate with the presence of abnormalities found on neuropsychological tests. The symptoms of depressive disorder can be masked by the almost identical motor symptoms of Parkinson's disease. Depressive symptoms often respond to antidepressant drugs or ECT. The interictal changes associated with temporal lobe epilepsy can mimic a depressive disorder, especially if the epileptic focus is on the right side. Depression is a common complicating feature of cerebrovascular diseases, particularly in the 2 years after the episode. Depression is more common in anterior brain lesions than in posterior brain lesions and, in both cases, often responds to antidepressant medications. Tumors of the diencephalic and temporal regions are particularly likely to be associated with depressive disorder symptoms. PSEUDODEMENTIA. Clinicians can usually differentiate the pseudodementia of major depressive disorder from the dementia of a disease, such as dementia of the Alzheimer's type, on clinical grounds. The cognitive symptoms in major depressive disorder have a sudden onset, and other symptoms of the disorder, such as self-reproach, are also present. A diurnal variation in the cognitive problems, which is not seen in primary dementias, may occur. Whereas depressed patients with cognitive difficulties often do not try to answer questions ("I don't know"), patients with dementia may confabulate. During an interview, depressed patients can sometimes be coached and encouraged into remembering, an ability that demented patients lack. Mental Disorders. Depression can be a feature of virtually any mental disorder, but the mental disorders listed in Table 8.1-8 deserve particular consideration in the differential diagnosis. Table 8.1-8 Mental Disorders That Commonly Have Depressive Features

OTHER MOOD DISORDERS. Clinicians must consider a range of diagnostic categories before arriving at a final diagnosis. Mood disorder caused by a general medical condition and substance-induced mood disorder must be ruled out. Clinicians must also determine whether a patient has had episodes of mania-like symptoms, indicating bipolar I disorder (complete manic and depressive syndromes), bipolar II disorder (recurrent major depressive episodes with hypomania), or cyclothymic disorder (incomplete depressive and manic syndromes). If a patient's symptoms are limited to those of depression, clinicians must assess the severity and duration of the symptoms to differentiate among major depressive disorder (complete depressive syndrome for 2 weeks), minor depressive disorder (incomplete but episodic depressive syndrome), recurrent brief depressive disorder (complete depressive syndrome but for less than 2 weeks per episode), and dysthymic disorder (incomplete depressive syndrome without clear episodes). OTHER MENTAL DISORDERS. Substance-related disorders, psychotic disorders, eating disorders, adjustment disorders, somatoform disorders, and anxiety disorders are all commonly associated with depressive

symptoms and should be considered in the differential diagnosis of a patient with depressive symptoms. Perhaps the most difficult differential is that between anxiety disorders with depression and depressive disorders with marked anxiety. An abnormal result on the dexamethasone-suppression test, the

presence of shortened REM latency on a sleep electroencephalogram (EEG), and a negative lactate infusion test result support a diagnosis of major depressive disorder in particularly ambiguous cases. UNCOMPLICATED BEREAVEMENT. Uncomplicated bereavement is not considered a mental disorder even though about one-third of all bereaved spouses for a time meet the diagnostic criteria for major depressive disorder. Some patients with uncomplicated bereavement do develop major depressive disorder, but the diagnosis is not made unless no resolution of the grief occurs. The differentiation is based on the symptoms' severity and length. In major depressive disorder, common symptoms that evolve from unresolved bereavement are a morbid preoccupation with worthlessness; suicidal ideation; feelings that the person has committed an act (not just an omission) that caused the spouse's death; mummification (keeping the deceased's belongings exactly as they were); and a particularly severe anniversary reaction, which sometimes includes a suicide attempt. In severe forms of bereavement depression, the patient simply pines away, unable to live without the departed person, usually a spouse. 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 suggest that it would be clinically unwise to withhold antidepressants from many persons experiencing such an intense mourning. A 75-year-old widow was brought to 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. Her 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 [dexamethasone suppression test] 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." (Courtesy of HS Akiskal, M.D.) Schizophrenia. Much has been published about the clinical difficulty of distinguishing a manic episode from schizophrenia. Although difficult, a differential diagnosis is possible. Merriment, elation, and infectiousness of mood are much more

common in manic episodes than in schizophrenia. The combination of a manic mood, rapid or pressured speech, and hyperactivity weighs heavily toward a diagnosis of a manic episode. The onset in a manic episode is often rapid and is perceived as a marked change from a patient's previous behavior. Half of all patients with bipolar I disorder have a family history of mood disorder. Catatonic features may be part of a depressive phase of bipolar I disorder. When evaluating patients with catatonia, clinicians should look carefully for a past history of manic or depressive episodes and for a family history of mood disorders. Manic symptoms in persons from minority

groups (particularly blacks and Hispanics) are often misdiagnosed as schizophrenic symptoms. Medical Conditions. In contrast to depressive symptoms, which are present in almost all psychiatric disorders, manic symptoms are more distinctive, although they can be caused by a wide range of medical and neurological conditions and substances. Antidepressant treatment can also be associated with the precipitation of mania in some patients. Bipolar I Disorder When a patient with bipolar I disorder has a depressive episode, the differential diagnosis is the same as that for a patient being considered for a diagnosis of major depressive disorder. When a patient is manic, however, the differential diagnosis includes bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder caused by a general medical condition, and substance-induced mood disorder. For manic symptoms, borderline, narcissistic, histrionic, and antisocial personality disorders need special consideration. Bipolar II Disorder The differential diagnosis of patients being evaluated for a mood disorder should include the other mood disorders, psychotic disorders, and borderline disorder. The differentiation between major depressive disorder and bipolar I disorder, on one hand, and bipolar II disorder, on the other hand, rests on the clinical evaluation of the manialike episodes. Clinicians should not mistake euthymia in a chronically depressed patient for a hypomanic or manic episode. Patients with borderline personality disorder often have a severely disrupted life, similar to that of patients with bipolar II disorder, because of the multiple episodes of significant mood disorder symptoms. Major Depressive Disorder versus Bipolar Disorder The question of whether a patient has major depressive disorder or bipolar disorder has emerged as a major challenge in clinical practice. Numerous studies have shown that bipolar disorder is not only confused with personality, substance use, and schizophrenic disorders but also with depressive and anxiety disorders. Certain features—especially in combination—are predictive of bipolar disorder (Table 8.1-9).

Table 8.1-9 Clinical Features Predictive of Bipolar Disorder More broad indicators of bipolarity include the following conditions, none of which, by itself, confirms 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. COURSE AND PROGNOSIS Studies of the course and prognosis of mood disorders have generally concluded that mood disorders tend to have long courses and that patients tend to have relapses. Although mood disorders are often considered benign in contrast to schizophrenia, they exact a profound toll on affected patients. Major Depressive Disorder Course ONSET. About 50 percent of patients having their first episode of major depressive disorder exhibited significant depressive symptoms before the first identified episode. Therefore, early identification and treatment of early symptoms may prevent the development of a full depressive episode. Although symptoms may have been present,

patients with major depressive disorder usually have not had a premorbid personality disorder. The first depressive episode occurs before age 40 years in about 50 percent of patients. A later onset is associated with the absence of a family history of mood disorders, antisocial personality disorder, and alcohol abuse. DURATION. An untreated depressive episode lasts 6 to 13 months; most treated episodes last about 3 months. The withdrawal of antidepressants before 3 months has elapsed almost always results in the return of the symptoms. As the course of the disorder progresses, patients tend to have more frequent episodes that last longer. Over a 20year period, the mean

number of episodes is five or six. DEVELOPMENT OF MANIC EPISODES. About 5 to 10 percent of patients with an initial diagnosis of major depressive disorder have a manic episode 6 to 10 years after the first depressive episode. The mean age for this switch is 32 years, and it often occurs after two to four depressive episodes. Although the data are inconsistent and controversial, some clinicians report that the depression of patients who are later classified as having bipolar I disorder is often characterized by hypersomnia, psychomotor retardation, psychotic symptoms, a history of postpartum episodes, a family history of bipolar I disorder, and a history of antidepressant-induced hypomania. Prognosis. Major depressive disorder is not a benign disorder. It tends to be chronic, and patients tend to relapse. Patients who have been hospitalized for a first episode of major depressive disorder have about a 50 percent chance of recovering in the first year. The percentage of patients recovering after repeated hospitalization decreases with passing time. Many unrecovered patients remain affected with dysthymic disorder. About 25 percent of patients experience a recurrence of major depressive disorder in the first 6 months after release from a hospital, about 30 to 50 percent in the following 2 years, and about 50 to 75 percent in 5 years. The incidence of relapse is lower than these figures in patients who continue prophylactic psychopharmacological treatment and in patients who have had only one or two depressive episodes. Generally, as a patient experiences more and more depressive episodes, the time between the episodes decreases, and the severity of each episode increases. PROGNOSTIC INDICATORS. Many studies have focused on identifying both good and bad prognostic indicators in the course of major depressive disorder. Mild episodes, the absence of psychotic symptoms, and a short hospital stay are good prognostic indicators. Psychosocial indicators of a good course include a history of solid friendships during adolescence, stable family functioning, and generally sound social functioning for the 5 years preceding the illness. Additional good prognostic signs are the absence of a comorbid psychiatric disorder and of a personality disorder, no more than one previous hospitalization for major depressive disorder, and an advanced age of onset. The possibility of a poor prognosis is increased by coexisting dysthymic disorder, abuse of alcohol and other substances, anxiety disorder symptoms, and a history of more than one previous depressive episode. Men are more likely than women to experience a

chronically impaired course. Bipolar I Disorder Course. The natural history of bipolar I disorder is such that it is often useful to make a graph of a patient’s disorder and to keep it up to date as treatment progresses (Fig. 8.1-6). Although cyclothymic disorder is sometimes diagnosed retrospectively in patients with bipolar I disorder, no identified personality traits are specifically associated with bipolar I disorder. FIGURE 8.1-6 Graphing the course of a mood disorder. Prototype of a life chart. (Courtesy of Robert M. Post, M.D.) Bipolar I disorder most often starts with depression (75 percent of the time in women, 67 percent in men) and is a recurring disorder. Most patients experience both depressive and manic episodes, although 10 to 20 percent experience only manic episodes. The manic episodes typically have a rapid onset (hours or days) but may evolve over a few weeks. An untreated manic episode lasts about 3 months; therefore, clinicians should not discontinue giving drugs before that time. Of persons who have a single manic episode, 90 percent are likely to have another. As the disorder progresses, the time between

episodes often decreases. After about five episodes, however, the interepisode interval often stabilizes at 6 to 9 months. Of persons with bipolar disorder, 5 to 15 percent have four or more episodes per year and can be classified as rapid cyclers. BIPOLAR I DISORDER IN CHILDREN AND OLDER PERSONS. Bipolar I disorder can affect both the very young and older persons. The

incidence of bipolar I disorder in children and adolescents is about 1 percent, and the onset can be as early as age 8 years. Common misdiagnoses are schizophrenia and oppositional defiant disorder. Bipolar I disorder with such an early onset is associated with a poor prognosis. Manic symptoms are common in older persons, although the range of causes is broad and includes nonpsychiatric medical conditions, dementia, and delirium, as well as bipolar I disorder. The onset of true bipolar I disorder in older persons is relatively uncommon. Prognosis. Patients with bipolar I disorder have a poorer prognosis than do patients with major depressive disorder. About 40 to 50 percent of patients with bipolar I disorder may have a second manic episode within 2 years of the first episode. Although lithium prophylaxis improves the course and prognosis of bipolar I disorder, probably only 50 to 60 percent of patients achieve significant control of their symptoms with lithium. One 4-year follow-up study of patients with bipolar I disorder found that a premorbid poor occupational status, alcohol dependence, psychotic features, depressive features, interepisode depressive features, and male gender were all factors that contributed a poor prognosis. Short duration of manic episodes, advanced age of onset, few suicidal thoughts, and few coexisting psychiatric or medical problems predict a better outcome. About 7 percent of patients with bipolar I disorder do not have a recurrence of symptoms; 45 percent have more than one episode, and 40 percent have a chronic disorder. Patients may have from two to 30 manic episodes, although the mean number is about nine. About 40 percent of all patients have more than ten episodes. On longterm follow-up, 15 percent of all patients with bipolar I disorder are well, 45 percent are well but have multiple relapses, 30 percent are in partial remission, and 10 percent are chronically ill. One third of all patients with bipolar I disorder have chronic symptoms and evidence of significant social decline. Bipolar II Disorder The course and prognosis of bipolar II disorder indicate that the diagnosis is stable because there is a high likelihood that patients with bipolar II disorder will have the same diagnosis up to 5 years later. Bipolar II disorder is a chronic disease that warrants long-term treatment strategies. TREATMENT Treatment of patients with mood disorders should be directed toward several goals. First, the patient’s safety must be guaranteed. Second, a complete diagnostic evaluation

of the patient is necessary. Third, a treatment plan that addresses not only the immediate symptoms but also the patient’s prospective well-being should be initiated. Although current treatment emphasizes pharmacotherapy and psychotherapy addressed to the individual patient, stressful life events are also associated with increases in relapse rates. Thus, treatment should address the number and severity of stressors in patients’ lives. Overall, the treatment of mood disorders is rewarding for psychiatrists. Specific treatments are now available for both manic and depressive episodes, and data indicate that prophylactic treatment is also effective. Because the prognosis for each episode is good, optimism is always warranted and is welcomed by both the patient and the patient’s family. Mood disorders are chronic, however, and the psychiatrist must educate the patient and the family about future treatment strategies. Hospitalization The first and most critical decision a physician must make is whether to hospitalize a patient or attempt outpatient treatment. Clear indications for hospitalization are the risk of suicide or homicide, a patient’s grossly reduced ability to get food and shelter, and the need for diagnostic procedures. A history of rapidly progressing symptoms and the rupture of a patient’s usual support systems are also indications for hospitalization. A physician may safely treat mild depression or hypomania in the office if he or she evaluates the patient frequently. Clinical signs of impaired judgment, weight loss, or insomnia should be minimal. The patient’s support system should be strong, neither overinvolved nor withdrawing from the patient. Any adverse changes in the patient’s symptoms or

behavior or the attitude of the patient’s support system may suffice to warrant hospitalization. Patients with mood disorders are often unwilling to enter a hospital voluntarily and may have to be involuntarily committed. These patients often cannot make decisions because of their slowed thinking, negative Weltanschauung (world view), and hopelessness. Patients who are manic often have such a complete lack of insight into their disorder that hospitalization seems absolutely absurd to them. Psychosocial Therapy Although most studies indicate—and most clinicians and researchers believe—that a combination of psychotherapy and pharmacotherapy is the most effective treatment for major depressive disorder, some data suggest another view: Either pharmacotherapy or psychotherapy alone is effective, at least in patients with mild major depressive episodes, and the regular use of combined therapy adds to the cost of treatment and exposes patients to unnecessary adverse effects. Three types of short-term psychotherapies—cognitive therapy, interpersonal therapy, and behavior therapy—have been studied to determine their efficacy in the treatment of major depressive disorder. Although its efficacy in treating major depressive disorder is not as well researched as these three therapies, psychoanalytically oriented

psychotherapy has long been used for depressive disorders, and many clinicians use the technique as their primary method. What differentiates the three short-term psychotherapy methods from the psychoanalytically oriented approach are the active and directive roles of the therapist, the directly recognizable goals, and the end points for short-term therapy. Accumulating evidence is encouraging about the efficacy of dynamic therapy. In a randomized, controlled trial comparing psychodynamic therapy with cognitive behavior therapy, the outcome of the depressed patients was the same in the two treatments. The National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program found the following predictors of response to various treatments: low social dysfunction suggested a good response to interpersonal therapy, low cognitive dysfunction suggested a good response to cognitive-behavioral therapy and pharmacotherapy, high work dysfunction suggested a good response to pharmacotherapy, and high depression severity suggested a good response to interpersonal therapy and pharmacotherapy. Cognitive Therapy. Cognitive therapy, originally developed by Aaron Beck, focuses on the cognitive distortions postulated to be present in major depressive disorder. Such distortions include selective attention to the negative aspects of circumstances and unrealistically morbid inferences about consequences. For example, apathy and low energy result from a patient’s expectation of failure in all areas. The goal of cognitive therapy is to alleviate depressive episodes and prevent their recurrence by helping patients identify and test negative cognitions; develop alternative, flexible, and positive ways of thinking; and rehearse new cognitive and behavioral responses. Studies have shown that cognitive therapy is effective in the treatment of major depressive disorder. Most studies found that cognitive therapy is equal in efficacy to pharmacotherapy and is associated with fewer adverse effects and better follow-up than pharmacotherapy. Some of the best controlled studies have indicated that the combination of cognitive therapy and pharmacotherapy is more efficacious than either therapy alone, although other studies have not found that additive effect. At least one study, the NIMH Treatment of Depression Collaborative Research Program, found that pharmacotherapy, either alone or with psychotherapy, may be the treatment of choice for patients with severe major depressive episodes. Interpersonal Therapy. Interpersonal therapy, developed by Gerald Klerman, focuses on one or two of a patient’s current interpersonal problems. This therapy is based on two assumptions. First, current interpersonal problems are likely to have their roots in early

dysfunctional relationships. Second, current interpersonal problems are likely to be involved in precipitating or perpetuating the current depressive symptoms. Controlled trials have indicated that interpersonal therapy is effective in the treatment of major depressive disorder and, not surprisingly, may be specifically helpful in addressing interpersonal problems. Some studies indicate that interpersonal therapy may be the most effective method for severe major depressive episodes when the

treatment choice is psychotherapy alone. The interpersonal therapy program usually consists of 12 to 16 weekly sessions and is characterized by an active therapeutic approach. Intrapsychic phenomena, such as defense mechanisms and internal conflicts, are not addressed. Discrete behaviors—such as lack of assertiveness, impaired social skills, and distorted thinking—may be addressed but only in the context of their meaning in, or their effect on, interpersonal relationships. Behavior Therapy. Behavior therapy is based on the hypothesis that maladaptive behavioral patterns result in a person's receiving little positive feedback and perhaps outright rejection from society. By addressing maladaptive behaviors in therapy, patients learn to function in the world in such a way that they receive positive reinforcement. Behavior therapy for major depressive disorder has not yet been the subject of many controlled studies. The limited data indicate that it is an effective treatment for major depressive disorder. Psychoanalytically Oriented Therapy. The psychoanalytic approach to mood disorders is based on psychoanalytic theories about depression and mania. The goal of psychoanalytic psychotherapy is to effect a change in a patient's personality structure or character, not simply to alleviate symptoms. Improvements in interpersonal trust, capacity for intimacy, coping mechanisms, the capacity to grieve, and the ability to experience a wide range of emotions are some of the aims of psychoanalytic therapy. Treatment often requires the patient to experience periods of heightened anxiety and distress during the course of therapy, which may continue for several years. Family Therapy. Family therapy is not generally viewed as a primary therapy for the treatment of major depressive disorder, but increasing evidence indicates that helping a patient with a mood disorder to reduce and cope with stress can lessen the chance of a relapse. Family therapy is indicated if the disorder jeopardizes a patient's marriage or family functioning or if the mood disorder is promoted or maintained by the family situation. Family therapy examines the role of the mood-disordered member in the overall psychological well-being of the whole family; it also examines the role of the entire family in the maintenance of the patient's symptoms. Patients with mood disorders have a high rate of divorce, and about 50 percent of all spouses report that they would not have married or had children if they had known that the patient was going to develop a mood disorder. Vagal Nerve Stimulation Experimental stimulation of the vagus nerve in several studies designed for the treatment of epilepsy found that patients showed improved mood. This observation led to the use of left vagal nerve stimulation (VNS) using an electronic device implanted in the skin, similar to a cardiac pacemaker. Preliminary studies have shown that a number

of patients with chronic, recurrent major depressive disorder went into remission when treated with VNS. The mechanism of action of VNS to account for improvement is unknown. The vagus nerve connects to the enteric nervous system and, when stimulated, may cause release of peptides that act as neurotransmitters. Extensive clinical trials are being conducted to determine the efficacy of VNS. Transcranial Magnetic Stimulation Transcranial magnetic stimulation (TMS) shows promise as a treatment for depression. It involves the use of very short pulses of magnetic energy to stimulate nerve cells in the brain. It is specifically indicated for the treatment of depression in adult patients

who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode. Repetitive transcranial magnetic stimulation (rTMS) produces focal secondary electrical stimulation of targeted cortical regions. It is nonconvulsive, requires no anesthesia, has a safe side effect profile, and is not associated with cognitive side effects. The patients do not require anesthesia or sedation and remain awake and alert. It is a 40-minute outpatient procedure that is prescribed by a psychiatrist and performed in a psychiatrist's office. The treatment is typically administered daily for 4 to 6 weeks. The most common adverse event related to treatment was scalp pain or discomfort. TMS therapy is contraindicated in patients with implanted metallic devices or nonremovable metallic objects in or around the head. Sleep Deprivation Mood disorders are characterized by sleep disturbance. Mania tends to be characterized by a decreased need for sleep, but depression can be associated with either hypersomnia or insomnia. Sleep deprivation may precipitate mania in patients with bipolar I disorder and temporarily relieve depression in those who have unipolar depression. Approximately 60 percent of patients with depressive disorders exhibit significant but transient benefits from total sleep deprivation. The positive results are typically reversed by the next night of sleep. Several strategies have been used in an attempt to achieve a more sustained response to sleep deprivation. One method used serial total sleep deprivation with a day or two of normal sleep in between. This method does not achieve a sustained antidepressant response because the depression tends to return with normal sleep cycles. Another approach used phase delay in the time patients go to sleep each night, or partial sleep deprivation. In this method, patients may stay awake from 2 AM to 10 PM daily. Up to 50 percent of patients get same-day antidepressant effects from partial sleep deprivation, but this benefit also tends to wear off in time. In some reports, however, serial partial sleep deprivation has been used successfully to treat insomnia associated with depression. The third, and probably most effective, strategy combines sleep deprivation with pharmacological treatment of depression. A number of studies

have suggested that total and partial sleep deprivation followed by immediate treatment with an antidepressant or lithium (Eskalith) sustains the antidepressant effects of sleep deprivation. Likewise, several reports have suggested that sleep deprivation accelerates the response to antidepressants, including fluoxetine (Prozac) and nortriptyline (Aventyl, Pamelor). Sleep deprivation has also been noted to improve premenstrual dysphoria. (Premenstrual dysphoric disorder, which is classified as a depressive disorder in DSM-5, is discussed in detail in Section 26.1, Psychiatry and Reproductive Medicine.) Phototherapy Phototherapy (light therapy) was introduced in 1984 as a treatment for SAD (mood disorder with seasonal pattern). In this disorder, patients typically experience depression as the photoperiod of the day decreases with advancing winter. Women represent at least 75 percent of all patients with seasonal depression, and the mean age of presentation is 40 years. Patients rarely present older than the age of 55 years with seasonal affective disorder. Phototherapy typically involves exposing the affected patient to bright light in the range of 1,500 to 10,000 lux or more, typically with a light box that sits on a table or desk. Patients sit in front of the box for approximately 1 to 2 hours before dawn each day, although some patients may also benefit from exposure after dusk. Alternatively, some manufacturers have developed light visors, with a light source built into the brim of the hat. These light visors allow mobility, but recent controlled studies have questioned the use of this type of light exposure. Trials have typically lasted 1 week, but longer treatment durations may be associated with greater response. Phototherapy tends to be well tolerated. Newer light sources tend to use lower light intensities and come equipped with filters; patients are instructed not to look directly at the light

source. As with any effective antidepressant, phototherapy, on rare occasions, has been implicated in switching some depressed patients into mania or hypomania. In addition to seasonal depression, the other major indication for phototherapy may be in sleep disorders. Phototherapy has been used to decrease the irritability and diminished functioning associated with shift work. Sleep disorders in geriatric patients have reportedly improved with exposure to bright light during the day. Likewise, some evidence suggests that jet lag might respond to light therapy. Preliminary data indicate that phototherapy may benefit some patients with OCD that has a seasonal variation. Pharmacotherapy After a diagnosis has been established, a pharmacological treatment strategy can be formulated. Accurate diagnosis is crucial because unipolar and bipolar spectrum disorders require different treatment regimens. The objective of pharmacologic treatment is symptom remission, not just symptom reduction. Patients with residual symptoms, as opposed to full remission, are more likely to experience a relapse or recurrence of mood episodes and to experience ongoing

impairment of daily functioning. Major Depressive Disorder. The use of specific pharmacotherapy approximately doubles the chances that a depressed patient will recover in 1 month. All currently available antidepressants may take up to 3 to 4 weeks to exert significant therapeutic effects, although they may begin to show their effects earlier. Choice of antidepressants is determined by the side effect profile least objectionable to a given patient’s physical status, temperament, and lifestyle. That numerous classes of antidepressants (Table 8.110) are available, many with different mechanisms of action, represents indirect evidence for heterogeneity of putative biochemical lesions. Although the first antidepressant drugs, the monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), are still in use, newer compounds have made the treatment of depression more “clinician and patient friendly.” Table 8.1-10 Antidepressant Medications

GENERAL CLINICAL GUIDELINES. The most common clinical mistake leading to an

unsuccessful trial of an antidepressant drug is the use of too low a dosage for too short a time. Unless adverse events prevent it, the dosage of an antidepressant should be raised to the maximum recommended level and maintained at that level for at least 4 or 5 weeks before a drug trial is considered unsuccessful. Alternatively, if a patient is improving clinically on a low dosage of the drug, this dosage should not be raised unless clinical improvement stops before maximal benefit is obtained. When a patient does not begin to respond to appropriate dosages of a drug after 2 or 3 weeks, clinicians may decide to obtain a plasma concentration of the drug if the test is available for the particular drug being used. The test may indicate either noncompliance or particularly unusual pharmacokinetic disposition of the drug and may thereby suggest an alternative dosage. DURATION AND PROPHYLAXIS. Antidepressant treatment should be maintained for at least 6 months or the length of a previous episode, whichever is greater. Prophylactic treatment with antidepressants is effective in reducing the number and severity of recurrences. One study concluded that when episodes are less than 21/2 years apart, prophylactic treatment for 5 years is probably indicated. Another factor suggesting prophylactic treatment is the seriousness of previous depressive episodes. Episodes that have involved significant suicidal ideation or impairment of psychosocial functioning may indicate that clinicians should consider prophylactic treatment. When antidepressant treatment is stopped, the drug dose should be tapered gradually over 1 to 2 weeks, depending on the half-life of the particular compound. Several studies indicate that maintenance antidepressant medication appears to be safe and effective for the treatment of chronic depression. Prevention of new mood episodes (i.e., recurrences) is the aim of the

maintenance phase of treatment. Only patients with recurrent or chronic depressions are candidates for maintenance treatment. INITIAL MEDICATION SELECTION. The available antidepressants do not differ in overall efficacy, speed of response, or long-term effectiveness. Antidepressants, however, do differ in their pharmacology, drug–drug interactions, short- and long-term side effects, likelihood of discontinuation symptoms, and ease of dose adjustment. Failure to tolerate or to respond to one medication does not imply that other medications will also fail. Selection of the initial treatment depends on the chronicity of the condition, course of illness (a recurrent or chronic course is associated with increased likelihood of subsequent depressive symptoms without treatment), family history of illness and treatment response, symptom severity, concurrent general medical or other psychiatric conditions, prior treatment responses to other acute phase treatments, potential drug– drug interactions, and patient preference. In general, approximately 45 to 60 percent of all outpatients with uncomplicated (i.e., minimal psychiatric and general medical comorbidity), nonchronic, nonpsychotic major depressive disorder who begin treatment with medication respond (i.e., achieve at least a 50 percent reduction in baseline symptoms); however, only 35 to 50 percent achieve remission (i.e., the virtual absence

of depressive symptoms). TREATMENT OF DEPRESSIVE SUBTYPES. Clinical types of major depressive episodes may have varying responses to particular antidepressants or to drugs other than antidepressants. Patients with major depressive disorder with atypical features may preferentially respond to treatment with MAOIs or SSRIs. Antidepressants with dual action on both serotonergic and noradrenergic receptors demonstrate greater efficacy in melancholic depressions. Patients with seasonal winter depression can be treated with light therapy. Treatment of major depressive episodes with psychotic features may require a combination of an antidepressant and an atypical antipsychotic. Several studies have also shown that ECT is effective for this indication—perhaps more effective than pharmacotherapy. For those with atypical symptom features, strong evidence exists for the effectiveness of MAOIs. SSRIs and bupropion (Wellbutrin) are also of use in atypical depression. COMORBID DISORDERS. The concurrent presence of another disorder can affect initial treatment selection. For example, the successful treatment of OCD associated with depressive symptoms usually results in remission of the depression. Similarly, when panic disorder occurs with major depression, medications with demonstrated efficacy in both conditions are preferred (e.g., tricyclics and SSRIs). In general, the nonmood disorder dictates the choice of treatment in comorbid states. Concurrent substance abuse raises the possibility of a substance-induced mood disorder, which must be evaluated by history or by requiring abstinence for several weeks. Abstinence often results in remission of depressive symptoms in substanceinduced mood disorders. For those with continuing significant depressive symptoms, even with abstinence, an independent mood disorder is diagnosed and treated. General medical conditions are established risk factors in the development of depression. The presence of a major depressive episode is associated with increased morbidity or mortality of many general medical conditions (e.g., cardiovascular disease, diabetes, cerebrovascular disease, and cancer). THERAPEUTIC USE OF SIDE EFFECTS. Choosing more sedating antidepressants (e.g., amitriptyline [Elavil, Endep]) for more anxious, depressed patients or more activating agents (e.g., desipramine) for more psychomotor-retarded patients is not generally helpful. For example, any short-term benefits with paroxetine, mirtazapine, or amitriptyline (more sedating drugs) on symptoms of anxiety or insomnia may become liabilities over time. These drugs often continue to be sedating in the longer run, which can lead to patients prematurely discontinuing medication and increase the risk of relapse or recurrence. Some practitioners use adjunctive medications (e.g., sleeping pills or

anxiolytics) combined with antidepressants to provide more immediate symptom relief or to cover those side effects to which most patients ultimately adapt. A patient's prior treatment history is important because an earlier response typically predicts current response. A documented failure on a properly conducted trial of a particular antidepressant class (e.g., SSRIs, tricyclics, or MAOIs) suggests choosing an

agent from an alternative class. The history of a first-degree relative responding to a particular drug is associated with a good response to the same class of agents in the patient. ACUTE TREATMENT FAILURES. Patients may not respond to a medication, because (1) they cannot tolerate the side effects, even in the face of a good clinical response; (2) an idiosyncratic adverse event may occur; (3) the clinical response is not adequate; or (4) the wrong diagnosis has been made. Acute phase medication trials should last 4 to 6 weeks to determine if meaningful symptom reduction is attained. Most (but not all) patients who ultimately respond fully show at least a partial response (i.e., at least a 20 to 25 percent reduction in pretreatment depressive symptom severity) by week 4 if the dose is adequate during the initial weeks of treatment. Lack of a partial response by 4 to 6 weeks indicates that a treatment change is needed. Longer time periods—8 to 12 weeks or longer—are needed to define the ultimate degree of symptom reduction achievable with a medication. Approximately half of patients require a second medication treatment trial because the initial treatment is poorly tolerated or ineffective. SELECTING SECOND TREATMENT OPTIONS. When the initial treatment is unsuccessful, switching to an alternative treatment or augmenting the current treatment is a common option. The choice between switching from the initial single treatment to a new single treatment (as opposed to adding a second treatment to the first one) rests on the patient's prior treatment history, the degree of benefit achieved with the initial treatment, and patient preference. As a rule, switching rather than augmenting is preferred after an initial medication failure. On the other hand, augmentation strategies are helpful with patients who have gained some benefit from the initial treatment but who have not achieved remission. The best-documented augmentation strategies involve lithium (Eskalith) or thyroid hormone. A combination of an SSRI and bupropion (Wellbutrin) is also widely used. In fact, no combination strategy has been conclusively shown to be more effective than another. ECT is effective in psychotic and nonpsychotic forms of depression but is recommended generally only for repeatedly nonresponsive cases or in patients with very severe disorders. A new therapy involves the use of the anesthetic agent ketamine, which has been shown to be effective in treatment resistant depression. It has a mechanism of action that inhibits the postsynaptic glutamate binding protein N-methyl-Daspartate (NDMA) receptor. Because abnormalities in glutamatergic signaling have been implicated in major depressive disorder, this may account for its efficacy. Patients usually receive a single infusion of ketamine over a 30-minute period at a concentration of 0.5 mg/kg. A positive response is usually seen within 24 hours, and improved mood lasts for about 2 to 7 days. The most common side effects are dizziness, headache, and poor coordination, which are transitory. Dissociative symptoms, including hallucinations, may also occur. COMBINED TREATMENT. Medication and formal psychotherapy are often combined in practice. If physicians view mood disorders as fundamentally evolving from psychodynamic issues, their ambivalence about the use of drugs may result in a poor

response, noncompliance and probably inadequate dosages for too short a treatment period. Alternatively, if physicians ignore the psychosocial needs of a patient, the outcome of pharmacotherapy may be compromised. Several trials of a combination of pharmacotherapy and

psychotherapy for chronically depressed outpatients have shown a higher response and higher remission rates for the combination than for either treatment used alone. Bipolar Disorders. The pharmacological treatment of bipolar disorders is divided into both acute and maintenance phases. Bipolar treatment, however, also involves the formulation of different strategies for the patient who is experiencing mania or hypomania or depression. Lithium and its augmentation by antidepressants, antipsychotics, and benzodiazepines has been the major approach to the illness, but three anticonvulsant mood stabilizers—carbamazepine (Tegretol), valproate (Depakene), and lamotrigine (Lamictal)—have been added more recently, as well as a series of atypical antipsychotics, most of which are approved for the treatment of acute mania, one also for monotherapy of acute depression, and three for prophylactic treatment (Table 8.1-11). Each of these medications is associated with a unique side effect and safety profile, and no one drug is predictably effective for all patients. Often, it is necessary to try different medications before an optimal treatment is found. Table 8.1-11 Mechanistic Classes of Medications Used in Bipolar Illness: Preliminary Evidence of Spectrum of Efficacy in Mania or Depression

TREATMENT OF ACUTE MANIA. The treatment of acute mania, or hypomania, usually is the easiest phases of bipolar disorders to treat. Agents can be used alone or in combination to bring the patient down from a high. Patients with severe mania are best treated in the hospital where aggressive dosing is possible and an adequate response can be achieved within days or weeks. Adherence to treatment, however, is often a problem because patients with mania frequently lack insight into their illness and refuse to take medication. Because impaired judgment, impulsivity, and aggressiveness combine to put the patient or others at risk, many patients in the manic phase are medicated to protect themselves and others from harm. Lithium Carbonate. Lithium carbonate is considered the prototypical “mood stabilizer.” Yet because the onset of antimanic action with lithium can be slow, it usually is

supplemented in the early phases of treatment by atypical antipsychotics, moodstabilizing anticonvulsants, or high-potency benzodiazepines. Therapeutic lithium levels are between 0.6 and 1.2 mEq/L. The acute use of lithium has been limited in recent years by its unpredictable efficacy, problematic side effects, and the need for frequent laboratory tests. The introduction of newer drugs with more favorable side effects, lower toxicity, and less need for frequent laboratory testing has resulted in a decline in lithium use. For many patients, however, its clinical benefits can be remarkable. Valproate. Valproate (valproic acid [Depakene] or divalproex sodium [Depakote]) has surpassed lithium in use for acute mania. Unlike lithium, valproate is only indicated for acute mania, although most experts agree it also has prophylactic effects. Typical dose levels of valproic acid are 750 to 2,500 mg per day, achieving blood levels between 50 and 120 µg/mL. Rapid oral loading with 15 to 20 mg/kg of divalproex sodium from day 1 of treatment has been well tolerated and associated with a rapid onset of response. A number of laboratory tests are required during valproate treatment. Carbamazepine and Oxcarbazepine. Carbamazepine has been used worldwide for decades as a first-line treatment for acute mania but has only gained approval in the United States in 2004. Typical doses of carbamazepine to treat acute mania range between 600 and 1,800 mg per day associated with blood levels of between 4 and 12 µg/mL. The keto congener of carbamazepine, oxcarbazepine, may possess similar antimanic properties. Higher doses than those of carbamazepine are required because 1,500 mg of oxcarbazepine approximates 1,000 mg of carbamazepine. Clonazepam and Lorazepam. The high-potency benzodiazepine anticonvulsants used in acute mania include clonazepam (Klonopin) and lorazepam (Ativan). Both may be effective

and are widely used for adjunctive treatment of acute manic agitation, insomnia, aggression, and dysphoria, as well as panic. The safety and the benign side effect profile of these agents render them ideal adjuncts to lithium, carbamazepine, or valproate. Atypical and Typical Antipsychotics. All of the atypical antipsychotics—olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole—have demonstrated antimanic efficacy and are approved by the Food and Drug Administration for this indication. Compared with older agents, such as haloperidol (Haldol) and chlorpromazine (Thorazine), atypical antipsychotics have a lesser liability for excitatory postsynaptic potential and tardive dyskinesia; many do not increase prolactin. However, they have a wide range of substantial to no risk for weight gain with its associated problems of insulin resistance, diabetes, hyperlipidemia, hypercholesteremia, and cardiovascular impairment. Some patients, however, require maintenance treatment with an antipsychotic medication. TREATMENT OF ACUTE BIPOLAR DEPRESSION. The relative usefulness of standard antidepressants in bipolar illness, in general, and in rapid cycling and mixed states, in particular, remains controversial because of their propensity to induce cycling, mania,

or hypomania. Accordingly, antidepressant drugs are often enhanced by a mood stabilizer in the first-line treatment for a first or isolated episode of bipolar depression. A fixed combination of olanzapine and fluoxetine (Symbyax) has been shown to be effective in treating acute bipolar depression for an 8-week period without inducing a switch to mania or hypomania. Paradoxically, many patients who are bipolar in the depressed phase do not respond to treatment with standard antidepressants. In these instances, lamotrigine or low-dose ziprasidone (20 to 80 mg per day) may prove effective. Electroconvulsive therapy may also be useful for patients with bipolar depression who do not respond to lithium or other mood stabilizers and their adjuncts, particularly in cases in which intense suicidal tendency presents as a medical emergency. Other Agents. When standard treatments fail, other types of compounds may prove effective. The calcium channel antagonist verapamil (Calan, Isoptin) has acute antimanic efficacy. Gabapentin, topiramate, zonisamide, levetiracetam, and tiagabine have not been shown to have acute antimania effects, although some patients may benefit from a trial of these agents when standard therapies have failed. Lamotrigine does not possess acute antimanic properties but does help prevent recurrence of manic episodes. Small studies suggest the potential acute antimanic and prophylactic efficacy of phenytoin. ECT is effective in acute mania. Bilateral treatments are required because unilateral, nondominant treatments have been reported to be ineffective or even to exacerbate manic symptoms. ECT is reserved for patients with rare refractory mania and for patients with medical complications, as well as extreme exhaustion (malignant hyperthermia or lethal catatonia). MAINTENANCE TREATMENT OF BIPOLAR DISORDER. Preventing recurrences of mood episodes is the greatest challenge facing clinicians. Not only must the chosen regimen achieve its primary goal—sustained euthymia—but the medications should not produce unwanted side effects that affect functioning. Sedation, cognitive impairment, tremor, weight gain, and rash are some side effects that lead to treatment discontinuation. Lithium, carbamazepine, and valproic acid, alone or in combination, are the most widely used agents in the long-term treatment of patients with bipolar disorder. Lamotrigine has prophylactic antidepressant and, potentially, mood-stabilizing properties. Patients with bipolar I disorder depression taking lamotrigine exhibit a rate of switch into mania that is the same as the rate with placebo. Lamotrigine appears to have superior acute and prophylactic antidepressant properties compared with antimanic properties. Given that breakthrough depressions are a difficult problem during prophylaxis, lamotrigine has a unique therapeutic role. Very slow increases of lamotrigine help avoid the rare side effect of lethal rash. A dose of 200 mg

per day appears to be the average in many studies. The incidence of severe rash (i.e., StevensJohnson syndrome, a toxic epidermal necrolysis) is now thought to be approximately two in 10,000 adults and four in 10,000 children. Thyroid supplementation is frequently necessary during long-term treatment. Many patients treated with lithium develop hypothyroidism, and many patients with bipolar

disorder have idiopathic thyroid dysfunction. T3 (25 to 50 µg per day), because of its short half-life, is often recommended for acute augmentation strategies, but T4 is frequently used for long-term maintenance. In some centers, hypermetabolic doses of thyroid hormone are used. Data indicate improvement in both manic and depressive phases with hypermetabolic T4-augmenting strategies. Table 8.1-12 summarizes the principles of treatment of bipolar disorders. Table 8.1-12 Principles in the Treatment of Bipolar Disorders REFERENCES Akiskal HS. Mood disorders: Clinical features. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th edition. Philadelphia: Lippincott Williams & Wilkins; 2009:1693.

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2007;10:123. 8.2 Dysthymia and Cyclothymia DYSTHYMIA The most typical features of dysthymia, also known as persistent depressive disorder, is the presence of a depressed mood that lasts most of the day and is present almost continuously. There are associated feelings of inadequacy, guilt, irritability, and anger; withdrawal from society; loss of interest; and inactivity and lack of productivity. The term dysthymia, which means “ill humored,” was introduced in 1980. Before that time, most patients now classified as having dysthymia were classified as having depressive neurosis (also called neurotic depression). Dysthymia is distinguished from major depressive disorder by the fact that patients complain that they have always been depressed. Thus, most cases are of early onset, beginning in childhood or adolescence and certainly occurring 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. Although dysthymia can occur as a secondary complication of other psychiatric disorders, the core concept of dysthymia refers to a subaffective or subclinical depressive disorder with (1) low-grade chronicity for at least 2 years; (2) insidious onset, with origin often in childhood or adolescence; and (3) a persistent or intermittent course. The family history of patients with dysthymia is typically replete with both depressive and bipolar disorders, which is one of the more robust findings supporting its link to primary mood disorder. Epidemiology Dysthymia is common among the general population and affects 5 to 6 percent of all persons. It is seen among patients in general psychiatric clinics, where it affects between half and one-third of all patients. No gender differences are seen for incidence rates. The disorder is more common in women younger than 64 years of age than in men of any age and is more common among unmarried and young persons and in those with low incomes. Dysthymia frequently coexists with other mental disorders, particularly major depressive disorder, and in persons with major depressive disorder, there is less likelihood of full remission between episodes. The patients may also have coexisting anxiety disorders (especially panic disorder), substance abuse, and borderline personality disorder. The disorder is more common among those with first-degree relatives with major depressive disorder. Patients with dysthymia are likely to be taking a wide range of psychiatric medications, including antidepressants, antimanic agents such as lithium (Eskalith) and carbamazepine (Tegretol), and sedative-hypnotics. Etiology Biological Factors. The biological basis for the symptoms of dysthymia and major depressive disorder are similar, but the biological bases for the underlying pathophysiology in the two disorders differ. SLEEP STUDIES. Decreased rapid eye movement (REM) latency and increased REM density are two state markers of depression in major depressive disorder that also occur in a significant proportion of patients with dysthymia. NEUROENDOCRINE STUDIES. The two most studied neuroendocrine axes in major depressive disorder and dysthymia are the adrenal axis and the thyroid axis, which have been tested by using the dexamethasone-suppression test (DST) and the thyrotropin-releasing hormone (TRH)-stimulation test, respectively. Although the results of studies are not absolutely consistent, most indicate that patients with dysthymia are less likely to have abnormal results on a DST than are patients with major depressive disorder.

Psychosocial Factors. Psychodynamic theories about the development of dysthymia posit that the disorder results from personality and ego development and culminates in difficulty adapting to adolescence and young adulthood. Karl Abraham, for example, thought that the conflicts of depression center on oral- and anal-sadistic traits. Anal traits include excessive orderliness, guilt,

and concern for others; they are postulated to be a defense against preoccupation with anal matter and with disorganization, hostility, and self-preoccupation. A major defense mechanism used is reaction formation. Low self-esteem, anhedonia, and introversion are often associated with the depressive character. FREUD. In Mourning and Melancholia, Sigmund Freud asserted that an interpersonal disappointment early in life can cause a vulnerability to depression that leads to ambivalent love relationships as an adult; real or threatened losses in adult life then trigger depression. Persons susceptible to depression are orally dependent and require constant narcissistic gratification. When deprived of love, affection, and care, they become clinically depressed; when they experience a real loss, they internalize or introject the lost object and turn their anger on it and thus on themselves. COGNITIVE THEORY. The cognitive theory of depression also applies to dysthymia. It holds that a disparity between actual and fantasized situations leads to diminished self-esteem and a sense of helplessness. The success of cognitive therapy in the treatment of some patients with dysthymia may provide some support for the theoretical model. Diagnosis and Clinical Features The DSM-5 diagnosis criteria for dysthymia (Table 8.2-1) stipulate the presence of a depressed mood most of the time for at least 2 years (or 1 year for children and adolescents). To meet the diagnostic criteria, a patient should not have symptoms that are better accounted for as major depressive disorder and should never have had a manic or hypomanic episode. DSM-5 allows clinicians to specify whether the onset was early (before age 21 years) or late (age 21 years or older). DSM-5 also allows specification of atypical features in dysthymia. Table 8.2-1 DSM-5 Diagnostic Criteria for Dysthymia

The profile of dysthymia 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 disturbances in appetite and libido are uncharacteristic, and psychomotor agitation or retardation is not observed. This all translates into a depression with attenuated symptomatology. Subtle endogenous features are observed, however, including inertia, lethargy, and anhedonia that are characteristically worse in

the morning. Because patients presenting clinically often fluctuate in and out of a major depression, the core DSM-5 criteria for dysthymia tend to emphasize vegetative dysfunction; however, cognitive symptoms are often present. Dysthymia is quite heterogeneous. Anxiety is not a necessary part of its clinical picture, yet dysthymia is often diagnosed in patients with anxiety and phobic disorders. That clinical situation is sometimes diagnosed as mixed anxiety depressive disorder. For greater operational clarity, it is best to restrict dysthymia to a primary disorder, one that cannot be explained by another psychiatric disorder. The essential features of such primary dysthymia include habitual gloom, brooding, lack of joy in life, and preoccupation with inadequacy. Dysthymia then is best characterized as long-standing, fluctuating, low-grade depression, experienced as part of the habitual self and representing an accentuation of traits observed in the depressive temperament (Table 8.2-2). The clinical picture of dysthymia is varied, with some patients proceeding to major depression and others manifesting the pathology largely at the personality level. Table 8.2-2 Attributes, Assets, and Liabilities of Depressive and Hyperthymic Temperaments 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. (Courtesy of HS Akiskal, M.D.) Dysthymic Variants. Dysthymia is common 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 World Health Organization (WHO) conference, this condition aggravates the prognosis of the underlying neurological disease and therefore deserves pharmacotherapy. 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 dysthymia presenting clinically as adults tend to pursue a chronic unipolar course that may or may not be complicated by major depression. They rarely develop spontaneous hypomania or mania. When treated with antidepressants, however, some of them may develop brief hypomanic switches that typically disappear when the antidepressant dose is decreased. Differential Diagnosis The differential diagnosis for dysthymia is essentially identical to that for major depressive disorder. Many substances and medical illnesses can cause chronic depressive symptoms. Two disorders are particularly important to consider in the differential diagnosis of dysthymia—minor depressive disorder and recurrent brief depressive disorder. Minor Depressive Disorder. Minor depressive disorder (discussed in Section 8.1) is characterized by episodes of depressive symptoms that are less severe than those seen in major depressive disorder. The difference between dysthymia and minor depressive disorder is primarily the episodic nature of the symptoms in the latter. Between episodes, patients with minor depressive disorder have a euthymic mood, but patients with dysthymia have virtually no euthymic periods. Recurrent Brief Depressive Disorder. Recurrent brief depressive disorder (discussed in Section 8.1) is characterized by brief periods (less than 2 weeks) during which depressive episodes are present. Patients with the disorder would meet the diagnostic criteria for major depressive disorder if their episodes lasted longer. Patients

with recurrent brief depressive disorder differ from patients with dysthymia on two counts: They have an episodic disorder, and their symptoms are more severe. Double Depression. An estimated 40 percent of patients with major depressive disorder also meet the criteria for dysthymia, a combination often referred to as double depression. Available data support the conclusion that patients with double depression have a poorer prognosis than patients with only major depressive disorder. The treatment of patients with double depression should be directed toward both disorders because the resolution of the symptoms of major depressive episode still leaves these patients with significant psychiatric impairment. Alcohol and Substance Abuse. Patients with dysthymia commonly meet the diagnostic criteria for a substance-related disorder. This comorbidity can be logical; patients with dysthymia tend to develop coping methods for their chronically depressed state that involve substance abuse. Therefore, they are likely to use alcohol, stimulants such as cocaine, or marijuana, the choice perhaps depending primarily on a patient’s social context. The presence of a comorbid diagnosis of substance abuse presents a diagnostic

dilemma for clinicians; the long-term use of many substances can result in a symptom picture indistinguishable from that of dysthymia. Course and Prognosis About 50 percent of patients with dysthymia experience an insidious onset of symptoms before age 25 years. Despite the early onset, patients often suffer with the symptoms for a decade before seeking psychiatric help and may consider early-onset dysthymia simply part of life. Patients with an early onset of symptoms are at risk for either major depressive disorder or bipolar I disorder in the course of their disorder. Studies of patients with the diagnosis of dysthymia indicate that about 20 percent progressed to major depressive disorder, 15 percent to bipolar II disorder, and fewer than 5 percent to bipolar I disorder. The prognosis for patients with dysthymia varies. Antidepressive agents and specific types of psychotherapies (e.g., cognitive and behavior therapies) have positive effects on the course and prognosis of dysthymia. The available data about previously available treatments indicate that only 10 to 15 percent of patients are in remission 1 year after the initial diagnosis. About 25 percent of all patients with dysthymia never attain a complete recovery. Overall, however, the prognosis is good with treatment. Treatment Historically, patients with dysthymia either received no treatment or were seen as candidates for long-term, insight-oriented psychotherapy. Contemporary data offer the most objective support for cognitive therapy, behavior therapy, and pharmacotherapy. The combination of pharmacotherapy and some form of psychotherapy may be the most effective treatment for the disorder.

Cognitive Therapy. Cognitive therapy is a technique in which patients are taught new ways of thinking and behaving to replace faulty negative attitudes about themselves, the world, and the future. It is a short-term therapy program oriented toward current problems and their resolution. Behavior Therapy. Behavior therapy for depressive disorders is based on the theory that depression is caused by a loss of positive reinforcement as a result of separation, death, or sudden environmental change. The various treatment methods focus on specific goals to increase activity, to provide pleasant experiences, and to teach patients how to relax. Altering personal behavior in depressed patients is believed to be the most effective way to change the associated depressed thoughts and feelings. Behavior therapy is often used to treat the learned helplessness of some patients who seem to meet every life challenge with a sense of impotence. Insight-Oriented (Psychoanalytic) Psychotherapy. Individual insightoriented psychotherapy is the most common treatment method for dysthymia, and many clinicians consider it the treatment of choice. The psychotherapeutic approach attempts to relate the development and maintenance of depressive symptoms and maladaptive personality features to unresolved conflicts from early childhood. Insight into depressive equivalents (e.g., substance abuse) or into childhood disappointments as antecedents to adult depression can be gained through treatment. Ambivalent current relationships with parents, friends, and others in the patient’s current life are examined. Patients’ understanding of how they try to gratify an excessive need for outside approval to counter low self-esteem and a harsh superego is an important goal of this therapy. Interpersonal Therapy. In interpersonal therapy for depressive disorders, a patient’s current interpersonal experiences and ways of coping with stress are examined to reduce depressive symptoms and to improve self-esteem. Interpersonal therapy lasts for about 12 to 16 weekly sessions and can be combined with antidepressant medication. Family and Group Therapies. Family therapy may help both the patient and the patient’s family deal with the symptoms of the disorder, especially when a biologically based subaffective syndrome seems to be present. Group therapy may help withdrawn patients learn new ways to overcome their interpersonal problems in social situations. Pharmacotherapy. Because of long-standing and commonly held theoretical beliefs that dysthymia is primarily a

psychologically determined disorder, many clinicians avoid prescribing antidepressants for patients; however, many studies have shown therapeutic success with antidepressants. The data generally indicate that selective serotonin reuptake inhibitors (SSRIs) venlafaxine and bupropion are an effective treatment for patients with dysthymia. Monoamine oxidase inhibitors (MAOIs) are effective in a subgroup of patients with the disorder, a group who may also respond

to the judicious use of amphetamines. Hospitalization. Hospitalization is usually not indicated for patients with dysthymia, but particularly severe symptoms, marked social or professional incapacitation, the need for extensive diagnostic procedures, and suicidal ideation are all indications for hospitalization. CYCLOTHYMIC DISORDER Cyclothymic disorder is symptomatically a mild form of bipolar II disorder, characterized by episodes of hypomania and mild depression. In DSM-5, cyclothymic disorder is defined as a “chronic, fluctuating mood disturbance” with many periods of hypomania and of depression. The disorder is differentiated from bipolar II disorder, which is characterized by the presence of major (not minor) depressive and hypomanic episodes. As with dysthymia, the inclusion of cyclothymic disorder with the mood disorders implies a relation, probably biological, to bipolar I disorder. Some psychiatrists, however, consider cyclothymic disorder to have no biological component and to result from chaotic object relations early in life. Contemporary conceptualization of cyclothymic disorder is based to some extent on the observations of Emil Kraepelin and Kurt Schneider that one-third to two-thirds of patients with mood disorders exhibit personality disorders. Kraepelin described four types of personality disorders: depressive (gloomy), manic (cheerful and uninhibited), irritable (labile and explosive), and cyclothymic. He described the irritable personality as simultaneously depressive and manic and the cyclothymic personality as the alternation of the depressive and manic personalities. Epidemiology Patients with cyclothymic disorder may constitute from 3 to 5 percent of all psychiatric outpatients, perhaps particularly those with significant complaints about marital and interpersonal difficulties. In the general population, the lifetime prevalence of cyclothymic disorder is estimated to be about 1 percent. This figure is probably lower than the actual prevalence because, as with patients with bipolar I disorder, the patients may not be aware that they have a psychiatric problem. Cyclothymic disorder, as with dysthymia, frequently coexists with borderline personality disorder. An estimated 10 percent of outpatients and 20 percent of inpatients with borderline personality disorder have a coexisting diagnosis of cyclothymic disorder. The female-to-male ratio in cyclothymic disorder is about 3 to 2, and 50 to 75 percent of all patients have an onset between ages 15 and 25 years. Families of persons with cyclothymic disorder often contain members with substance-related disorder. Etiology As with dysthymia, controversy exists about whether cyclothymic disorder is related to

the mood disorders, either biologically or psychologically. Some researchers have postulated that cyclothymic disorder has a closer relation to borderline personality disorder than to the mood disorders. Despite these controversies, the preponderance of biological and genetic data favors the idea of cyclothymic disorder as a bona fide mood disorder. Biological Factors. About 30 percent of all patients with cyclothymic disorder have positive family histories for bipolar I disorder; this rate is similar to the rate for patients with bipolar I disorder. Moreover, the pedigrees of families with bipolar I disorder often contain generations of patients with bipolar I disorder linked by a generation with cyclothymic disorder. Conversely, the prevalence of cyclothymic disorder in the relatives of patients with bipolar I disorder is much higher than the prevalence of cyclothymic disorder either in the relatives of patients with other mental disorders or in persons who are

mentally healthy. The observations that about one-third of patients with cyclothymic disorder subsequently have major mood disorders, that they are particularly sensitive to antidepressant-induced hypomania, and that about 60 percent respond to lithium add further support to the idea of cyclothymic disorder as a mild or attenuated form of bipolar II disorder. Psychosocial Factors. Most psychodynamic theories postulate that the development of cyclothymic disorder lies in traumas and fixations during the oral stage of infant development. Freud hypothesized that the cyclothymic state is the ego's attempt to overcome a harsh and punitive superego. Hypomania is explained psychodynamically as the lack of self-criticism and an absence of inhibitions occurring when a depressed person throws off the burden of an overly harsh superego. The major defense mechanism in hypomania is denial, by which the patient avoids external problems and internal feelings of depression. Patients with cyclothymic disorder are characterized by periods of depression alternating with periods of hypomania. Psychoanalytic exploration reveals that such patients defend themselves against underlying depressive themes with their euphoric or hypomanic periods. Hypomania is frequently triggered by a profound interpersonal loss. The false euphoria generated in such instances is a patient's way to deny dependence on love objects and simultaneously disavowing any aggression or destructiveness that may have contributed to the loss of the loved person. Diagnosis and Clinical Features Although many patients seek psychiatric help for depression, their problems are often related to the chaos that their manic episodes have caused. Clinicians must consider a diagnosis of cyclothymic disorder when a patient appears with what may seem to be sociopathic behavioral problems. Marital difficulties and instability in relationships are common complaints because patients with cyclothymic disorder are often promiscuous and irritable while in manic and mixed states. Although there are anecdotal reports of

increased productivity and creativity when patients are hypomanic, most clinicians report that their patients become disorganized and ineffective in work and school during these periods. The DSM-5 diagnostic criteria for cyclothymic disorder stipulate that a patient has never met the criteria for a major depressive episode and did not meet the criteria for a manic episode during the first 2 years of the disturbance. The criteria also require the more or less constant presence of symptoms for 2 years (or 1 year for children and adolescents). Signs and Symptoms. The symptoms of cyclothymic disorder are identical to the symptoms of bipolar II disorder except that they are generally less severe. On occasion, however, the symptoms may be equally severe but of shorter duration than those seen in bipolar II disorder. About half of all patients with cyclothymic disorder have depression as their major symptom, and these patients are most likely to seek psychiatric help while depressed. Some patients with cyclothymic disorder have primarily hypomanic symptoms and are less likely to consult a psychiatrist than are primarily depressed patients. Almost all patients with cyclothymic disorder have periods of mixed symptoms with marked irritability. Most patients with cyclothymic disorder seen by psychiatrists have not succeeded in their professional and social lives as a result of their disorder, but a few have become high achievers who have worked especially long hours and have required little sleep. Some persons' ability to control the symptoms of the disorder successfully depends on multiple individual, social, and cultural attributes. The lives of most patients with cyclothymic disorder are difficult. The cycles of the disorder tend to be much shorter than those in bipolar I disorder. In cyclothymic disorder, the changes in mood are irregular and abrupt and sometimes occur within hours. The unpredictable nature of the mood changes produces great stress. Patients often feel that their moods are out of control. In irritable, mixed periods, they may become involved in unprovoked disagreements with friends, family, and coworkers. Mr. B, a 25-year-old single man, came for evaluation due to

irritability, insomnia, jumpiness, and excessive energy. He reported that such episodes lasted from a few days to a few weeks and alternated with longer periods of feeling hopeless, dejected, and worn out with thoughts of suicide. Mr. B reported having been this way for as long as he could remember. He had never been treated for his symptoms. He denied using drugs and said he had “only the occasional drink to relax.” As a child, Mr. B went from one foster family to another and was an irresponsible and trouble-making child. He frequently ran away from home, was absent from school, and committed minor crimes. He ran away from his last foster family at the age of 16 years and drifted ever since, taking occasional odd jobs. When he became restless at one location or job, he quickly moved on to the next. He did not have close friends because he would form and end friendships quickly.

Substance Abuse. Alcohol abuse and other substance abuse are common in patients with cyclothymic disorder, who use substances either to self-medicate (with alcohol, benzodiazepines, and marijuana) or to achieve even further stimulation (with cocaine, amphetamines, and hallucinogens) when they are manic. About 5 to 10 percent of all patients with cyclothymic disorder have substance dependence. Persons with this disorder often have a history of multiple geographical moves, involvements in religious cults, and dilettantism. Differential Diagnosis When a diagnosis of cyclothymic disorder is under consideration, all the possible medical and substance-related causes of depression and mania, such as seizures and particular substances (cocaine, amphetamine, and steroids), must be considered. Borderline, antisocial, histrionic, and narcissistic personality disorders should also be considered in the differential diagnosis. Attention-deficit/hyperactivity disorder (ADHD) can be difficult to differentiate from cyclothymic disorder in children and adolescents. A trial of stimulants helps most patients with ADHD and exacerbates the symptoms of most patients with cyclothymic disorder. The diagnostic category of bipolar II disorder (discussed in Section 8.1) is characterized by the combination of major depressive and hypomanic episodes. Course and Prognosis Some patients with cyclothymic disorder are characterized as having been sensitive, hyperactive, or moody as young children. The onset of frank symptoms of cyclothymic disorder often occurs insidiously in the teens or early 20s. The emergence of symptoms at that time hinders a person’s performance in school and the ability to establish friendships with peers. The reactions of patients to such a disorder vary; patients with adaptive coping strategies or ego defenses have better outcomes than patients with poor coping strategies. About one-third of all patients with cyclothymic disorder develop a major mood disorder, most often bipolar II disorder. Treatment Biological Therapy. The mood stabilizers and antimanic drugs are the first line of treatment for patients with cyclothymic disorder. Although the experimental data are limited to studies with lithium, other antimanic agents—for example, carbamazepine and valproate (Depakene)—are reported to be effective. Dosages and plasma concentrations of these agents should be the same as those in bipolar I disorder. Antidepressant treatment of depressed patients with cyclothymic disorder should be done with caution because these patients have increased susceptibility to antidepressantinduced hypomanic or manic episodes. About 40 to 50 percent of all patients with cyclothymic disorder who are treated with antidepressants experience such episodes.

Psychosocial Therapy. Psychotherapy for patients with cyclothymic disorder is best directed toward increasing patients’ awareness of their condition and helping them develop coping mechanisms for their mood swings. Therapists usually need to help patients repair any damage, both work and family related, done during episodes of hypomania. Because of the long-term nature of cyclothymic disorder, patients often require lifelong treatment. Family and group therapies may be supportive,

educational, and therapeutic for patients and for those involved in their lives. The psychiatrist conducting psychotherapy is able to evaluate the degree of cyclothymia and so provide an early-warning system to prevent full-blown manic attacks before they occur. REFERENCES Epperson C. Premenstrual dysphoric disorder and the brain. Am J Psychiatry. 2013;170(3):248–252. Fava GA, Rafanelli C, Tomba E, Guidi J, Grandi S. The sequential combination of cognitive behavioral treatment and wellbeing therapy in cyclothymic disorder. Psychother Psychosom. 2011;80:136. Gitlin M, Frye MA. Maintenance therapies in bipolar disorders. Bipolar Disord. 2012;14(s2):51. Helseth V, Samet S, Johnsen J, Bramness JG, Waal H. Independent or substance-induced mental disorders? An investigation of comorbidity in an acute psychiatric unit. J Dual Diagn. 2013;9(1):78–86. Huprich SK, DeFife J, Westen D. Refining a complex diagnostic construct: Subtyping Dysthymia with the Shedler–Westen Assessment Procedure-II. J Affect Disord. 2014;152:186–192. Khazaal Y, Gex-Fabry M, Nallet A, et al. Affective temperaments in alcohol and opiate addictions. Psychiatr Q. 2013;84(4):429–438.. Mechri A, Kerkeni N, Touati I, Bacha M, Gassab L. Association between cyclothymic temperament and clinical predictors of bipolarity in recurrent depressive patients. J Affect Disord. 2011;132:285. Parker G, McCraw S, Fletcher K. Cyclothymia. Depress Anxiety. 2012;29:487. Perugi G, Popovic D. Practical management of cyclothymia. In: Young AH, Ferrier IN, Michalak EE, eds. Practical Management of Bipolar Disorders. New York: Cambridge University Press; 2010:139. Post RM, Altshuler LL. Mood disorders: Treatment of bipolar disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th edition. Vol. 2. Philadelphia: Lippincott Williams & Wilkins; 2009:1743. Rubio JM, Olfson M, Villegas L, Perez-Fuentes G, Wang S, Blanco C. Quality of life following remission of mental disorders: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2013;74(5):e445–e450. Serretti A, Chiesa A, Calati R, et al. Influence of family history of major depression, bipolar disorder, and suicide on clinical features in patients with major depression and bipolar disorder. Eur Arch Psychiatry Clin Neurosci. 2013;263(2):93–103. Tomba E, Rafanelli C, Grandi S, Guidi J, Fava GA. Clinical configuration of cyclothymic disturbances. J Affect Disord. 2012;139:244. Totterdell P, Kellett S, Mansell W. Cognitive behavioural therapy for cyclothymia: Cognitive regulatory control as a mediator of mood change. Behav Cogn Psychother. 2012;40:412. Vaingankar JA, Rekhi G, Subramaniam M, Abdin E, Chong SA. Age of onset of life-time mental disorders and treatment contact. Social Psychiatry and Psychiatric Epidemiology. 2013;48(5):835–843. Van Meter AR, Youngstrom EA, Findling RL. Cyclothymic disorder: A critical review. Clin Psychol Rev. 2012;32:229.