6 Bipolar Disorders

The bipolar disorders include bipolar disorder type I, commonly referred to as manic depression, bipolar type II disorder, and cyclothymia. Historically, we considered these mood disorders to be on a continuum with depressive disorders—hence the concept of polarity, with depression at one end and mania the other. Since the 1980s and the introduction of DSM-III, we separated the bipolar disorders from depressive disorders mainly because the disorders have different epidemiologic characteristics, courses, and treatments. However, at various times experts in mood disorders have reconsidered this separation, noting that many patients with major depressive disorder have past episodes of at least some manic symptoms. Many authorities see considerable continuity between recurrent depressive and bipolar disorders. There continues to be widespread discussion and debate about the bipolar spectrum, which incorporates classic bipolar disorder, bipolar II, and recurrent depressions.

THE CLINICAL PRESENTATION

Manic Episodes

Manic patients are excited, talkative, sometimes amusing, and frequently hyperactive. Their speech is usually rapid and loud and challenging to interrupt. It is commonly referred to as *pressured,* appearing as if driven by some unknown urgency. Pressured speech is considered a hallmark of mania.

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 someone prevents a patient from some unrealistic plan. Patients often exhibit a change of predominant mood from euphoria early in the course of the illness to later irritability. 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.

Manic patients describe rapid thoughts, as inferred from their speech. As the manic state increases, their speech contains puns, jokes, rhymes, or plays on words. They may seem clever, even brilliant. Manic patients are often easily distracted, and their cognitive functioning in the manic state is unrestrained, with an accelerated flow of ideas. At a still higher 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 incoherent and indistinguishable from that of a person with schizophrenia.

The manic patient's thought content includes themes of self-confidence and self-aggrandizement.

At times, manic patients are grossly psychotic and disorganized and require physical restraints and the intramuscular injection of sedating drugs.

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

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 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 psychiatrist 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.)

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.

We know less about the cognitive deficits associated with bipolar disorder than such chronic disorders like schizophrenia. However, there is some evidence to suggest they share some common deficits.

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. Their disinhibition may result in other examples of poor judgment, such as making phone calls during inappropriate times of the day. Pathologic 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 sometimes preoccupied with 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.

About 75 percent of all manic patients are assaultive or threatening at some time. Manic patients are at increased risk for suicide. However, the most significant risk seems to be when bipolar patients are depressed. Manic patients often drink alcohol excessively, perhaps in an attempt to self-medicate.

Depressive Episodes

The depressive episodes in bipolar disorder are similar to those described for depressive disorders. Many experts in the field feel that there are qualitative differences in the depressive episodes experienced by bipolar patients, and researchers have attempted to find reliable differences between bipolar I disorder depressive episodes and episodes of major depressive disorder, but the differences are elusive. Although the data are inconsistent and controversial, some clinicians report that the depressed patients who we later diagnose as having bipolar disorder often have hypersomnia, psychomotor retardation, psychotic symptoms, a history of postpartum episodes, a family history of bipolar I disorder, and a history of antidepressant-induced hypomania. Table 6-1 lists some differences between the depressive disorder seen in bipolar disorder and major depression.

Table 6-1
Differentiating Characteristics of Bipolar and Unipolar Depressions

	Bipolar	Unipolar
History of mania or hypomania (definitional)	Yes	No
Temperament and personality	Cyclothymic and extroverted	Dysthymic and introverted
Sex ratio	Equal	More women than men
Age of onset	Teens, 20s, and 30s	30s, 40s, and 50s
Postpartum episodes	More common	Less common
Onset of episode	Often abrupt	More insidious
Number of episodes	Numerous	Fewer
Duration of episode	3–6 mo	3–12 mo
Psychomotor activity	Retardation > agitation	Agitation > retardation
Sleep	Hypersomnia > insomnia	Insomnia > hypersomnia
Family History		
Bipolar disorder	Yes	±
Unipolar disorder	Yes	Yes
Alcoholism	Yes	Yes
Pharmacologic Response		
Most antidepressants	Induce hypomania–mania	±
Lithium carbonate	Prophylaxis	±

Bipolar Disorder in Children and Adolescents

It is easy to misdiagnose mania in adolescents as a conduct disorder, 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 we can see many of these symptoms in healthy adolescents, severe or persistent symptoms should cause clinicians to consider bipolar I disorder in the differential diagnosis.

DIAGNOSIS

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 do not meet the criteria for a manic episode. Cyclothymia and dysthymia are disorders that represent less severe forms of bipolar disorder and major depression, respectively.

Bipolar I Disorder

Bipolar I patients have at least one manic episode. It is what most people mean when they refer to bipolar as a disorder. Table 6-2 compares the different approaches to diagnosing bipolar I disorder.

Table 6-2
Bipolar I Disorder

	Bipolar I Disorder	
	DSM-5	**ICD-10**
Name	Bipolar I Disorder	Bipolar Affective Disorder ****NOTE:*** ICD-10 does not distinguish between Bipolar I and II, requiring only history of discrete episodes of mania, hypomania and/or depression, with episodes demarcated by switches in mood/affect.
Duration	• Manic episode: 1 wk+ • Hypomanic episode: 4 days+ • Major depressive episode: 2 wk+	
Symptoms	**Manic or hypomanic episodes** • Abnormally ↑ or irritable mood (required) • Grandiose thoughts • ↓ Need for sleep • Pressured speech • Racing and expansive thoughts • Distractibility • Hyperactivity • Impulsivity/high-risk activities **Depressive episodes** • Similar to that for major depressive disorder	• History of episodes of mania, hypomania and/or depression • Switches in mood/affect **Mania** • Abnormally ↑ or irritable mood (required) • ↑ Activity • ↑ Talkativeness • Flight of ideas/racing thoughts • Social disinhibition • ↓ Need for sleep • Grandiose thoughts • Distractibility • Impulsivity/recklessness • Hypersexuality **Hypomania** • Abnormally ↑ mood (required) • Psychomotor agitation • ↑ Talkativeness • Poor concentration/distractibility • ↓ Need for sleep • Hypersexuality • Impulsivity or ↑ spending • Over-familiarity **Depressive episode** • Depressed mood • Loss of interest or pleasure • Decreased energy *Additional symptoms:* • Low self-esteem • Excessive guilt or shame • Recurrent thoughts of death or suicide • Poor concentration • Psychomotor changes • Sleep disturbance • Change in appetite and/or weight
Required number of symptoms	At least 1 manic episode • Abnormally ↑ or irritable mood (required) ≥3 of the other symptoms (4 if irritable mood)	**Bipolar affective disorder, current episode hypomanic** • Hypomania • History of a prior affective episode (manic, hypomanic, depressed, mixed) **Bipolar affective disorder, current episode manic** • Mania • History of prior affective episode (manic, hypomanic, depressed, mixed) **Bipolar disorder, current episode mild/moderate/severe depression** • Depressive episode • History of prior affective episode (manic, hypomanic, depressed, mixed) **Bipolar disorder, current episode mixed** • Mixture or rapid alternation of hypomanic, manic and/or depressive symptoms • History of prior affective episode (manic, hypomanic, depressed, mixed)
Exclusions (not better explained by):	Drug abuse Medication effect Other medical condition Other psychiatric illness	Psychoactive substance use Another mental disorder

(*continued*)

Table 6-2
Bipolar I Disorder (*Continued*)

	Bipolar I Disorder	
	DSM-5	**ICD-10**
Psychosocial Impact	**Manic episode:** impaired functioning or needing hospitalization **Hypomanic episode:** No impairment or need for hospitalization **Depressive episode:** marked distress and/or psychosocial impairment	
Symptom Specifiers	**With mixed features:** • Either depressive or manic/hypomanic episode • Additional symptoms of depressive or manic/hypomanic period (not full criteria) **With rapid cycling:** • ≥4 mood episodes in 1 yr • ≥2-mo period of partial/full remission between episodes **With melancholic features:** Similar to that for major depressive disorder **With atypical features:** Similar to that for major depressive disorder **With anxious distress:** ≥2 symptoms among the following: • Feeling tense • Restlessness • Difficulty with concentration due to worrying • ↑ fear without cause • Fear of loss of control **With mood-congruent psychotic features** **With mood-incongruent psychotic features** **With catatonia**	**Current episode hypomanic** **Current episode manic without psychotic symptoms** **Current episode manic with psychotic symptoms** **mood congruent** **mood incongruent** **Current episode of depression** **Current episode mixed** **Currently in remission**—no symptoms. History of previous episodes.
Severity Specifiers	**Mild—**minimal symptoms, no to minimal impairment and/or distress **Moderate—**moderate symptomatology and impairment **Severe—**maximal symptoms, marked distress and impairment	**For current episode of depression** **Mild:** 2–3 symptoms **Moderate:** ≥4 symptoms, including ≥2 among loss of pleasure, depressed mood, and low energy **Severe:** symptoms are marked and distressing, suicidal thoughts are common **without psychotic symptoms** **with psychotic symptoms** **mood congruent** **mood incongruent**
Course Specifiers	**With peripartum onset:** • Episode occurs during pregnancy or within 4 wk after delivery **With seasonal pattern** • Pattern present for ≥2 yr **In partial remission** **In full remission**	

Patients with this disorder may have a single or recurrent episode. We consider manic episodes as distinct when they are separated by at least 2 months without significant symptoms of mania or hypomania. The episodes should not be due to another apparent cause, such as medication (including an antidepressant).

Bipolar II Disorder

Bipolar patients have hypomania rather than mania—manic-type symptoms that are not as severe or as impairing as full mania. Table 6-3 compares the different approaches to diagnosing bipolar II disorder.

It is easy to confuse other disorders, including dramatic but normal moods, with hypomania. For example, some patients with depression may be thrilled and very euphoric once emerging from a depressive episode. Many medications, including antidepressants, can induce hypomanic symptoms. The diagnostic approaches attempt to help distinguish hypomania from these other causes of a heightened mood.

Diagnostic Specifiers

Rapid Cycling. Some patients experience frequent manic episodes. When a patient has at least four such episodes in a year, we diagnose them with the rapid cycling subtype of bipolar I

Table 6-3
Bipolar II Disorder

	Bipolar II Disorder	
	DSM-5	**ICD-10**
Name	Bipolar II Disorder	Bipolar Affective Disorder *__NOTE:__ ICD-10 does not distinguish between Bipolar I and II, requiring only history of discrete episodes of mania, hypomania and/or depression, with episodes demarcated by switches in mood/affect.
Duration	See Table 6-2 for hypomanic and depressive episodes	See Table 6-2
Symptoms	**Hypomanic episodes** (see Table 6-2) **Depressive episodes** (see Table 6-2)	See Table 6-2
Required number of symptoms	≥1 hypomanic episode ≥1 depressive episode	
Exclusions (not better explained by):	Drug abuse Medication effect Other medical condition Another psychiatric illness Diagnose bipolar I if h/o manic episode	Psychoactive substance use Better explained by another mental disorder
Psychosocial Impact	• Hypomanic episode: NO marked impairment in functioning and NO hospitalization necessitated • Depressive episode: marked distress and/or impairment in psychosocial functioning	
Symptom Specifiers	**Current episode (see Table 6-2 for definitions)** **Depressed** **Hypomanic** **With anxious distress** **With mixed features** **With rapid cycling** **With melancholic features** **With atypical features** **With mood-congruent psychotic features** **With mood-incongruent psychotic features** **With catatonia**	See Table 6-2
Severity Specifiers	**Mild—**minimal symptoms, no to minimal impairment and/or distress **Moderate—**moderate symptomatology and impairment **Severe—**maximal symptoms, marked distress and impairment (note, impairment occurs during depressive episode)	See Table 6-2
Course Specifiers	**With peripartum onset—**see Table 6-2 **With seasonal pattern—**see Table 6-2 **In partial remission** **In full remission**	

disorder. 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 provoke rapid cycling.

With Seasonal Pattern. As with depressive disorders, mania can occur primarily during certain seasons. Some studies have found a higher prevalence of manic episodes in the spring and summer months. However, available research is most convincing for the seasonality of depressive episodes.

With Peripartum Onset. Mania occurring after pregnancy is a critical issue given the potential risk to the child.

Catatonia. 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. They are associated with depressive episodes, however.

Other Bipolar Disorders

Cyclothymia. Cyclothymic disorder has also been appreciated clinically for some time as a less severe form of bipolar disorder. Patients with cyclothymic disorder have at least 2 years of frequently occurring hypomanic symptoms that cannot fit the diagnosis of a manic episode and of depressive symptoms that cannot fit the diagnosis of a major depressive episode. Table 6-4 compares the different approaches to diagnosing cyclothymia.

Table 6-4
Cyclothymic Disorder

	Cyclothymic Disorder	
	DSM-5	**ICD-10**
Name	Cyclothymic Disorder	Cyclothymia
Duration	≥2 yr (≥1 for children) with depressive and hypomanic symptoms present ≥50% of the time	2-yr w/ periods of depression and elevated mood, without ever meeting criteria for a depressive episode or manic episode
Symptoms	Hypomanic episodes (see Table 6-2) Depressive episodes (see Table 6-2)	Unstable moods, many periods of depression or mild elation which are insufficient to be called hypomania or mild major depressive disorder
Required number of symptoms	Symptoms of hypomania and depression present, without ever meeting full criteria for a depressive episode or manic episode	Several episodes, symptoms are insufficient for a diagnosis of hypomania, major depression or another bipolar affective disorder
Exclusions (not better explained by):	• Substance use • Medication effect • Other medical condition • Other mental illness (i.e., Bipolar I or II)	Bipolar affective disorder (though history of bipolar affective disorder may be present)
Psychosocial Impact	Marked distress or impairment in areas of functioning	
Symptom Specifiers	**With anxious distress:** including at least two symptoms among feeling tense, restlessness, difficulty with concentration due to worrying, excessive fear without identifiable cause, fear of loss of control	Affective personality disorder Cycloid personality Cyclothymic personality

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.

DIFFERENTIAL DIAGNOSIS

When a patient with bipolar I disorder has a depressive episode, the differential diagnosis is the same as that for a patient with major depressive disorder. However, when a patient is manic, there is a broad differential, including other mood disorders, psychiatric disorders, medical disorders, and substances. We list some of these in Table 6-5.

Psychotic Disorders

It can be tough to distinguish a manic episode from the acute psychosis of a patient experiencing a psychotic episode. Although challenging, 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 heightened mood, rapid speech, and hyperactivity weighs toward mania. Mania often begins rapidly and is a marked change from previous behavior. Family history is also helpful.

When evaluating patients with catatonia, clinicians should look carefully for a history of manic or depressive episodes and a family history of mood disorders. There is an unfortunate tendency to misdiagnose manic symptoms in persons from minority groups (mainly Black and Hispanic) as schizophrenic symptoms.

Personality Disorders

Hypomania can frequently be confused with the mood lability of personality disorders, particularly borderline personality disorder.

Table 6-5
Differential Diagnosis of Mania

Medical
AIDS/HIV
Delirium
Hyperthyroidism
Postencephalitic syndrome
Substance induced
Antidepressant-induced mania
Steroid-induced mania
Amphetamine-induced mania
Cocaine-induced mania
Phencyclidine-induced mania
Alcohol intoxication
L-Dopa–induced mania
Bronchodilator-induced mania
Decongestant-induced mania
Psychiatric
Atypical psychosis
Bipolar disorder
Catatonic schizophrenia
Schizoaffective disorder

Patients with a 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.

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

Medical Conditions

In contrast to depressive symptoms, which are present in almost all psychiatric disorders, manic symptoms are more distinctive. However, a wide range of medical disorders and substances can cause manic symptoms. Antidepressant treatment can also be associated with the precipitation of mania in some patients.

COMORBIDITY

Whereas men more frequently present with substance use disorders, women more frequently present with comorbid anxiety and eating disorders. In general, patients with bipolar disorder more frequently show comorbidity of substance use and anxiety disorders than do patients with unipolar major depression. In the Epidemiologic 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.

Although cyclothymic disorder is sometimes diagnosed retrospectively in patients with bipolar I disorder, no identified personality traits are associated explicitly with 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 the treatment progresses (Fig. 6-1).

Onset

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.

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 incidence of bipolar I disorder in children and adolescents is about 1 percent, and the onset can be as early as age 8 years.

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.

Duration

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. Depressive episodes are generally similar to those for depressive disorders.

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 are classified as rapid cyclers.

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.

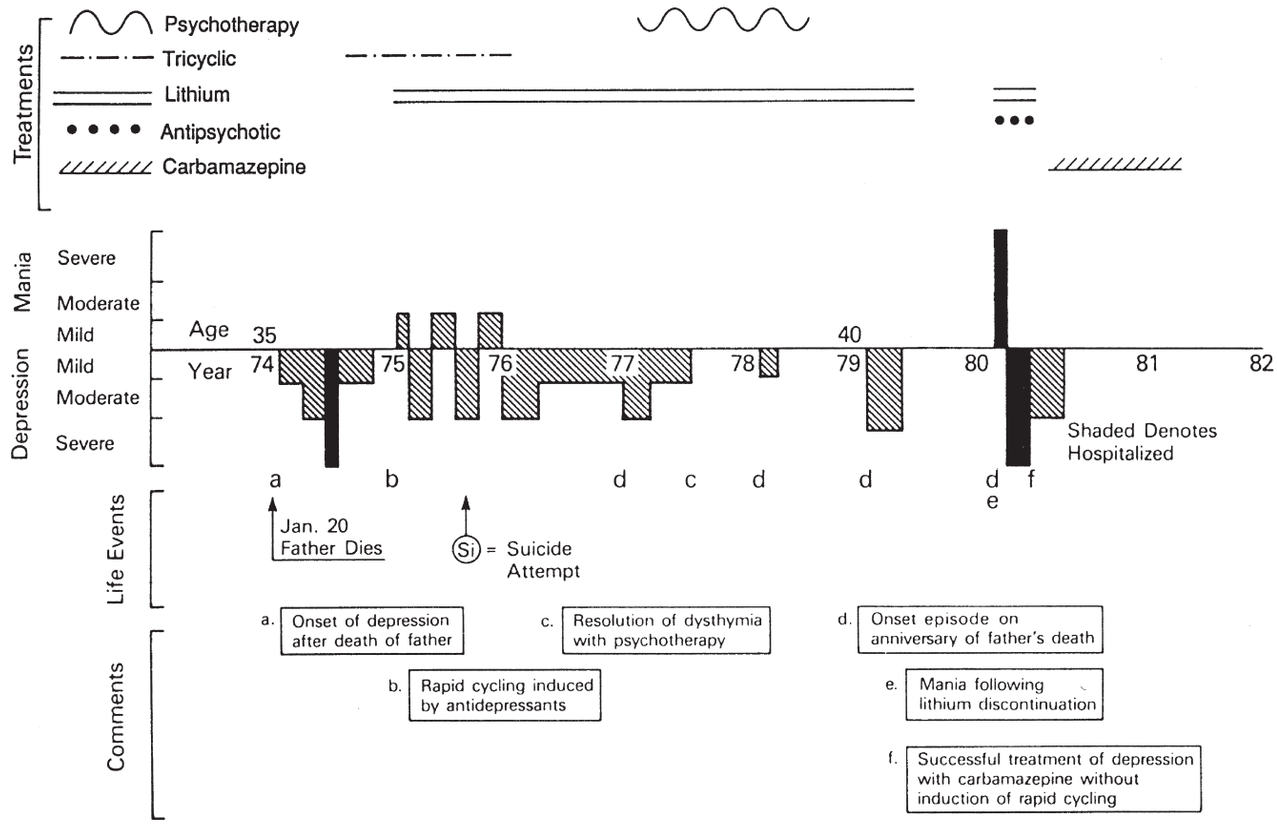

FIGURE 6-1
Graphing the course of a mood disorder. Prototype of a life chart. (Courtesy of Robert M. Post, M.D.)

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. 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 2 to 30 manic episodes, although the mean number is about 9. About 40 percent of all patients have more than 10 episodes. On long-term 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.

Prognostic Indicators

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 to a poor prognosis. A short duration of manic episodes, advanced age of onset, few suicidal thoughts, and few coexisting psychiatric or medical problems predict a better outcome.

TREATMENT APPROACH

Hospitalization

It is best to treat patients with severe mania in the hospital where aggressive dosing is possible, and it is possible to achieve an adequate response relatively quickly. Manic patients may test the limits of ward rules, shift responsibility for their acts onto others, or exploit the weaknesses of others, and they can create conflicts among staff members.

Choosing a Treatment

Medications are the treatments of choice for patients with bipolar disorders. However, psychotherapies can offer an essential adjunct to treatment.

Somatic Treatments

Pharmacotherapy

GENERAL CLINICAL GUIDELINES. We can divide the pharmacologic treatment of bipolar disorders into acute and maintenance phases. Bipolar treatment, however, also involves the formulation of different strategies for the patient who is experiencing mania or

Table 6-6
Recommendations for Pharmacologic Treatment of Acute Mania

First line	Monotherapy: lithium, divalproex, divalproex ER, olanzapine, risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, asenapine, paliperidone ER, cariprazine Adjunctive therapy with lithium or divalproex: risperidone, quetiapine, olanzapine, aripiprazole, asenapine
Second line	Monotherapy: carbamazepine, carbamazepine ER, ECT, haloperidol Combination therapy: lithium + divalproex
Third line	Monotherapy: chlorpromazine, clozapine, tamoxifen Combination therapy: lithium or divalproex + haloperidol, lithium + carbamazepine, adjunctive tamoxifen
Not recommended	Monotherapy: gabapentin, topiramate, lamotrigine, verapamil, tiagabine Combination therapy: risperidone + carbamazepine, olanzapine + carbamazepine

ECT, electroconvulsive therapy; XR or ER, extended release.
Modified from CANMAT/ISBD Guidelines.

hypomania or depression. Lithium and its augmentation by antidepressants, antipsychotics, and benzodiazepines have been the principal approach to the illness. However, three anticonvulsant mood stabilizers—carbamazepine, valproate, and lamotrigine—are commonly used options, as well as a series of atypical antipsychotics. Often, it is necessary to try different medications before finding an optimal treatment. Furthermore, although one strives for monotherapy, in the case of bipolar disorder, polypharmacy is common.

Table 6-6 lists some recommended medications for treating acute mania.

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, we must medicate patients when we need to protect themselves and others from harm.

INITIAL MEDICATION SELECTION. Figure 6-2 diagrams a strategy for selecting and preparing a bipolar patient for pharmacotherapy.

Acute Mania. The treatment of acute mania, or hypomania, usually is the most straightforward phase to treat. We can use agents alone or in combination to bring the patient down from a high.

Lithium Carbonate. Lithium carbonate is considered the prototypical mood stabilizer. However, because the onset of antimanic action with lithium can be slow, we often supplement it in the early phases of treatment by atypical antipsychotics, mood-stabilizing 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.

Anticonvulsants. Valproate (valproic acid or divalproex sodium) 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. Normal dose levels of valproic acid are 750 to 2,500 mg/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. Some laboratory testing is required during valproate treatment.

Carbamazepine has been used worldwide for decades as a first-line treatment for acute mania. The FDA approved it for acute mania in the United States in 2004. Typical doses of carbamazepine to treat acute mania range between 600 and 1,800 mg/day associated with blood levels of between 4 and 12 μg/mL. The keto congener of carbamazepine, oxcarbazepine, is better tolerated than carbamazepine, but the data for its efficacy are conflicting. A Cochrane review concluded there is insufficient evidence for this medication in acute mania.

Antipsychotics. The FDA approved many of the atypical antipsychotics for use in bipolar disorder. We list them in Table 6-7. Compared with older agents, such as haloperidol and chlorpromazine, atypical antipsychotics have a lesser liability for excitatory postsynaptic potential and tardive dyskinesia; many do not increase prolactin. However, many of them have the risk of weight gain with its associated medical problems. Some patients, however, require maintenance treatment with antipsychotic medication.

Acute Bipolar Depression

Lithium. There is limited evidence for lithium in bipolar depression. Early studies were promising, but later placebo-controlled studies did not confirm lithium's efficacy. More extensive studies that included lithium did suggest that lithium was at least as useful as other mood stabilizers for bipolar depression.

Anticonvulsants. The most promising anticonvulsant has been lamotrigine, which has several reasonable studies showing efficacy for bipolar depression. Its major limitation is that it must be titrated gradually to prevent a severe skin rash. Evidence for valproate and other anticonvulsants is limited. Gabapentin and levetiracetam appear to be ineffective.

Antipsychotics. Several of the atypical antipsychotics have shown efficacy for bipolar depression. Quetiapine has the best evidence. It appears that quetiapine, in a modest dose (300 mg/day), is sufficient to improve symptoms. Olanzapine, lurasidone, and cariprazine also have positive studies, and the FDA approved lurasidone for this indication. Ziprasidone and aripiprazole do not appear to be effective.

Antidepressants. It remains controversial whether antidepressants are useful for the depressive phase of bipolar disorder. This is particularly true in patients with rapid cycling and mixed states. They seem to be less effective than for major depressive disorder and may induce cycling, mania, or hypomania. The risk of inducing mania seems highest for tricyclic antidepressants, monoamine oxidase inhibitors, and perhaps the serotonin norepinephrine reuptake inhibitors such as venlafaxine. Most experts agree that antidepressants are not appropriate as monotherapy for patients with bipolar disorder.

Whether we can use them as adjuncts is also controversial. Some antidepressants have some evidence of efficacy for adjunctive therapy, such as fluoxetine. On the whole, the available evidence suggests they may have some usefulness when combined with a mood stabilizer.

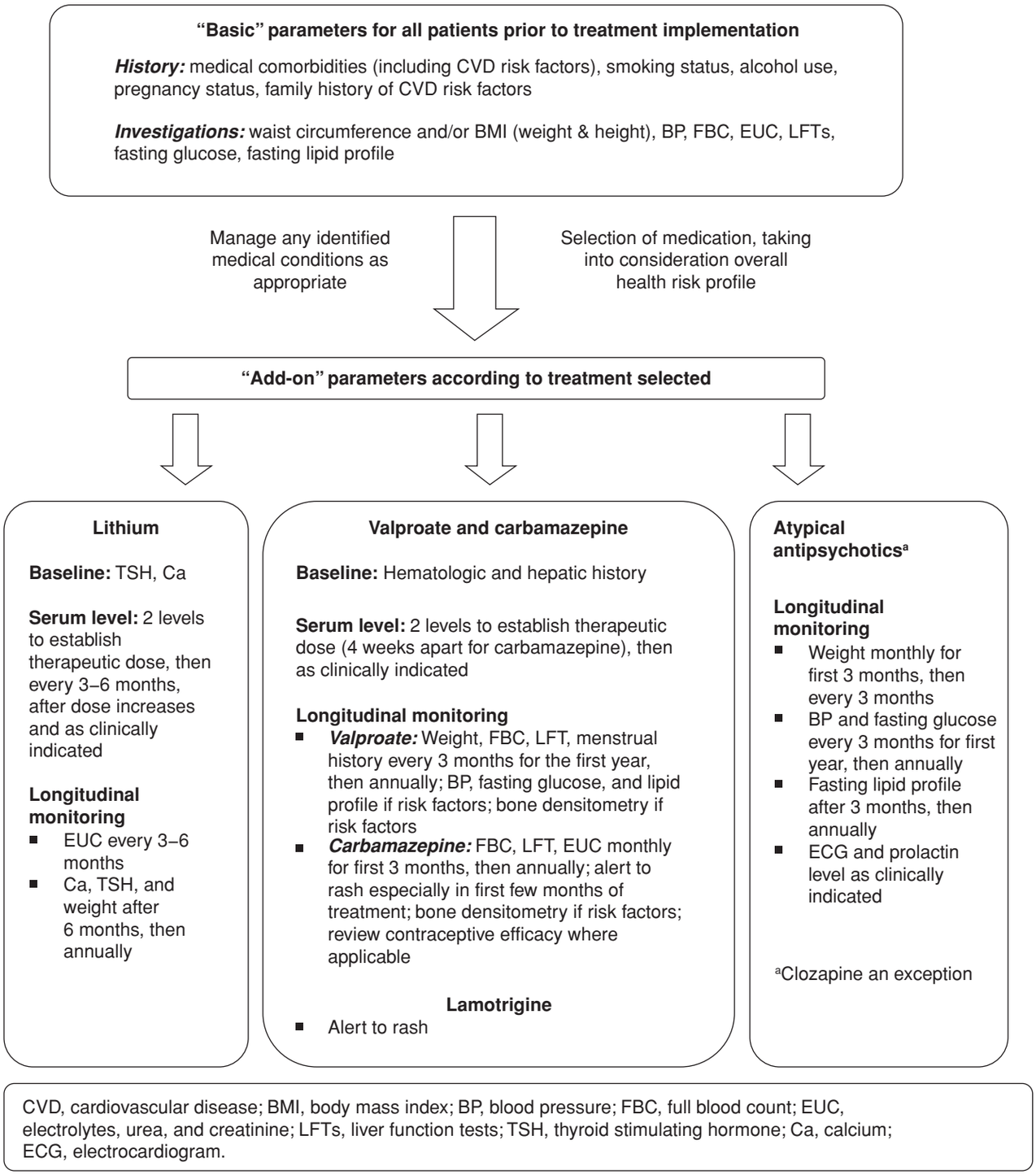

FIGURE 6-2
Recommendations for treatment monitoring in bipolar disorder. (Used with permission from ISBD safety monitoring guidelines.)

Electroconvulsive Therapy. 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 strong suicidal tendency presents as a medical emergency.

Other Agents. Various clinicians and researchers have tried many other agents in an attempt to find more options for treatment. Most studies have not been promising. Dopamine agonists, including modafinil and armodafinil, have some preliminary evidence. Omega-3-fatty acid adjunctive therapy has conflicting evidence. N-acetylcysteine (a glutathione precursor) has some preliminary evidence. Ketamine and other glutamatergic modulators may have a role in treatment-resistant patients.

Table 6-7
Atypical Antipsychotics for Bipolar Disorder: Efficacy Summary and Dose Ranges

		Efficacy					
				Prophylaxis			
Drug	Dose Range (mg)	Acute Mania	Acute Bipolar Depression	Mood Episodes	Mania	Depression	Comments
Olanzapine	5–20	Yes	Yes (see comments)	Yes	Yes	Yes	Improvement was seen mostly in sleep, appetite, and inner tension but not in core depressive symptoms Magnitude of benefit for depression less than for mania
Risperidone	1–6	Yes	No data	Yes	Yes	No	Prophylactic efficacy was demonstrated with Risperdal Consta but no studies with oral risperidone
Quetiapine	300–800	Yes	Yes	Yes	Yes	Yes	For bipolar depression, 300 mg/day is as effective as 600 mg/day (see text for guidance) Appears to have equal efficacy in preventing both mania and depression
Ziprasidone	80–160	Yes	No	Yes	Yes	No	Prophylaxis demonstrated for adjunctive therapy but no data for monotherapy
Aripiprazole	15–30	Yes	No	Yes	Yes	No	
Paliperidone	6–12	Yes	No data	Yes	Yes	No	Less effective than olanzapine in preventing mood episodes
Asenapine	10–20	Yes	No data	Yes	Yes	Yes	Numerically fewer patients in the asenapine group had relapse of manic and depressive episodes but the differences were not significant
Lurasidone	40–120	No data	Yes	Studies underway	Studies underway	Studies underway	Effective in depressed patients with mixed features
Cariprazine	3–12	Yes	Yes	No data	No data	No data	For bipolar depression, 1.5–3 mg/day is recommended, while for mania, up to 12 mg/day is appropriate

DURATION AND PROPHYLAXIS

Maintenance Treatment. 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 for the long-term treatment of patients with bipolar disorder. For patients treated with long-term lithium, thyroid supplementation is often necessary to treat lithium-induced hypothyroidism.

Lamotrigine has prophylactic antidepressant and, potentially, mood-stabilizing properties. Lamotrigine appears to be superior at the acute and prophylactic treatment of the depressive phase of illness compared to the manic.

ACUTE TREATMENT FAILURES. Most patients will respond to treatment within 2 weeks. When they do not respond, we should consider using a different approach. When patients do not respond to initial treatment, it makes sense to try another first-line treatment as there are several from which to choose. Most patients will respond to one of these treatments, at least during their manic phase; depression may be more difficult.

SELECTING SECOND TREATMENT OPTIONS. In the rare case that first-line treatment fails, other options include haloperidol, carbamazepine, and combination treatment with lithium and valproate. If those fail, other antipsychotics could be considered.

Other Somatic Treatments. In addition to ECT (discussed above), transcranial magnetic stimulation and magnetic seizure therapy have limited, although promising, data.

Psychosocial Therapy

Psychotherapy can be a crucial adjunct for patients. The goals of this therapy include helping treatment adherence, promoting stability, and avoiding risk factors for the disorder. Cognitive-behavioral therapy, interpersonal and social rhythm therapy, and family focused therapy are all reasonable therapies to use. Table 6-8 summarizes psychotherapeutic treatments for bipolar disorder, including the presumed underlying mechanism and sample interventions.

Table 6-8
Efficacious Psychotherapeutic Treatments for Bipolar Disorder

Treatment	Conceptualization of Disorder Etiology	Sample Interventions
Cognitive-behavioral therapy	Biologic vulnerability interacting with stress Skills deficits limit ability to manage symptoms	Identify and challenge automatic thoughts that interfere with treatment adherence Engage in rewarding activities that provide increased routine and stability Practice communication skills with providers
Interpersonal and social rhythm therapy	Interpersonal vulnerabilities arising from early attachment and learned relationship patterns, plus disruption of social rhythms	Develop awareness of patterns in primary relationships and the therapeutic relationship Track and stabilize social rhythms Interpersonal skills training Communication analysis
Family-focused therapy	Biologic vulnerability exacerbated by negative expressed emotion in family environment	Education regarding the disorder, including precipitants, risk factors, and effective treatment Establish relapse prevention plan, agreed upon by all involved family members Communication skills training Problem-solving skills training

THE EPIDEMIOLOGY OF THE DISORDER(S)

Incidence and Prevalence

We show the US prevalence rates of different clinical forms of bipolar disorder in Figure 6-3. The annual incidence of bipolar illness is usually estimated to be less than 1 percent. Worldwide it is estimated to vary from 0.3 to 1.2 percent by country. However, it is difficult to estimate because it is easy to miss milder forms of bipolar disorder.

Sex

In contrast to major depressive disorder, bipolar I disorder has a roughly 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 having the rapid cycling subtype of bipolar I disorder.

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 overall prevalence of bipolar disorder in adolescents is similar to adults. However, it increases with age; that is, the prevalence is about 2 percent in 13- and 14-year-olds, but it doubles by age 18.

Other Factors

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.

There is a higher than average incidence of bipolar I disorder in upper socioeconomic groups. Bipolar I disorder is more common in persons who did not graduate from college than in college graduates. This may also reflect the relatively early age of onset for the disorder.

THE NEUROBIOLOGY OF THE DISORDER

Similar to the depressive disorders, the most consistent abnormality observed in bipolar disorders is an increased frequency of abnormal hyperintensities in subcortical regions, such as periventricular regions, the basal ganglia, and the thalamus. We find this more commonly in bipolar I disorder than in depressed adults. These hyperintensities likely reflect the deleterious neurodegenerative effects of recurrent episodes.

Our Understanding of the Genetics of Bipolar Disorder

Studies of Inheritance Patterns. A family history of bipolar disorder conveys a higher risk for mood disorders in general and, specifically, a much greater risk for bipolar disorder. Unipolar depression is typically the most common form of mood disorder in families of bipolar probands. One large study found a threefold increase in the rate of bipolar disorder and a twofold increase in unipolar disorder in the biologic relatives of bipolar probands. First-degree relatives have an approximately 10-fold risk of developing the disorder. Twin studies suggest that the heritability is between 0.7 and 0.8.

Genetic Studies. Linkage studies have historically implicated several regions, most notably chromosomes 18q and 22q. Several linkage studies have found evidence for the involvement of specific genes in clinical subtypes. For example, the linkage evidence on 18q mainly derived from bipolar II–bipolar II sibling pairs and families that had panic symptoms.

GWAS studies report an ever-growing list of associated loci. Current evidence suggests a pattern of polygenic risk—many susceptible loci, each with a small effect that contributes to the disorder. These genes do not appear to be specific to bipolar disorder but rather overlap with other severe psychiatric disorders, particularly schizophrenia. Studies have tended to focus on genes that could give clues to etiology, such as genes involved in neurodevelopment, or genes encoding for voltage-dependent calcium channels.

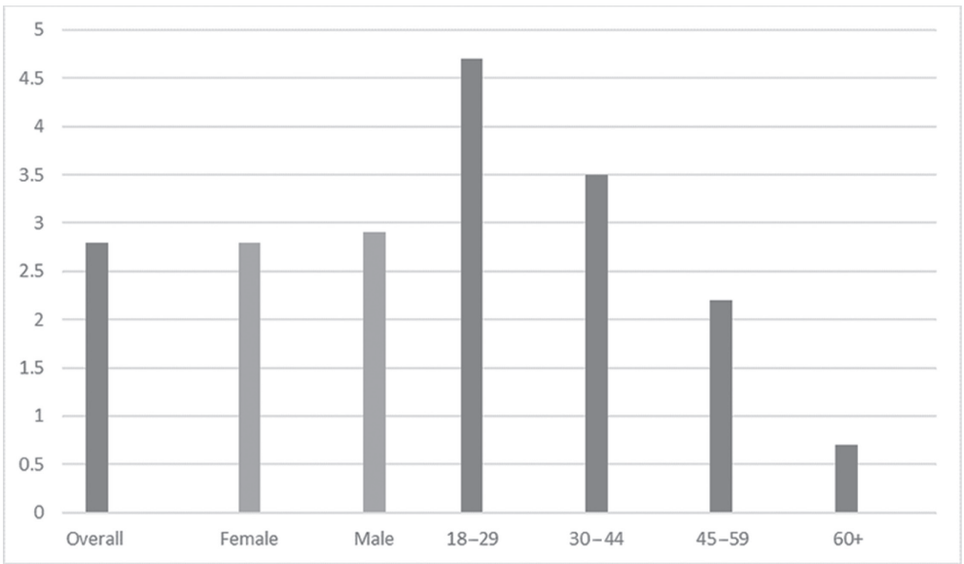

FIGURE 6-3
Past year prevalence of bipolar disorder in US Adults. (Data from the National Comorbidity Survey Replication [2001–2003].)

Perhaps the most important finding from genetic studies is that of the many genes found to be associated with bipolar disorder, most of them are also associated with schizophrenia.

Pathologic Imaging Findings

Structural Imaging. Individual studies have reported various areas of the brain with variations in gray matter volume, including the striatum, thalamus, amygdala, hippocampus, and pituitary—potentially meaningful findings as these are traditionally regions of interest in this disorder given their presumed functions. However, many of these are small studies with findings with conflicting results. At least one meta-analysis concluded that the evidence taken as a whole did not support morphologic differences in these areas.

There have been some consistent structural findings in other brain regions, including the inferior frontal gyrus, left insula, cerebellum, and left orbitofrontal gyrus, which are seen both in affected individuals and first-degree relatives. Although the significance of these findings is not well understood, many of these areas seem involved in emotional regulation, and the inferior frontal gyrus may have a particular role in executive function, particularly response inhibition. In several cases, the differences are of increased thickness in bipolar patients, suggesting that these brain changes may represent compensatory reactions to the disorder rather than etiologic risk factors.

Functional Imaging. There are fewer fMRI or PET studies than there are MRI studies; the majority examine the brain during the performance of various cognitive or emotional tasks and suggest either increased or decreased activations along various circuits. Consistent findings include abnormalities along a network that includes the superior and medial frontal cortex and insula, which showed increased activation compared with controls. As many of the areas are involved in executive functioning and working memory, this appears to be consistent with neuropsychological studies of the disorder. Other areas may show decreased activation, including the amygdala, basal ganglion, and limbic system. These findings may be evidence for downregulation of specific circuits, perhaps in response to the abnormal activity in the other circuits.

Inflammatory Markers

Some inflammatory markers, most notably interleukin-6, are elevated in bipolar patients. Markers of inflammation may be particularly evident during adolescence and become less evident in adulthood.

Other Neurochemical Findings. Some studies have found alterations in brain-derived neurotrophic factor, and in at least one study, this alteration may predict lithium responsiveness. Similarly, some studies of measures of oxidative stress in bipolar patients showed abnormalities that related to lithium response, however these findings are preliminary.

Assessment of the hypothalamic–pituitary–adrenal (HPA) axis suggests a dysregulated system, as evidenced by increased ACTH and cortisol levels in bipolar patients. However, these findings appear only to occur after individuals become symptomatic, suggesting that this is a result of the disorder.

THE PSYCHOLOGY OF THE DISORDER

Psychological studies have focused on neuropsychological findings, particularly of cognitive deficits associated with the disorder. Most commonly reported are deficits of executive functioning and verbal memory and learning. A variety of other related deficits, including deficits of cognitive flexibility, psychomotor speed, and attention, are also reported, although not consistently. Response inhibition is the executive function focused on the ability to prevent one's impulsive response to a situation when such a response would be inappropriate in the environmental context. This inhibition is often deficient in bipolar patients, as well as in first-degree relatives without bipolar disorder. It is particularly deficient in individuals who have bipolar disorder with psychotic features. Other executive function deficits include general impulsivity and risk-taking behavior. We see some of these same deficits with schizophrenia. However, they are less severe in schizophrenia and less likely to be recognized before the disorder appears. It may be that the cognitive deficits are indicative of a broader disorder that crosses traditional diagnostic lines and represents a spectrum of disorders defined by psychotic symptoms.

ETIOLOGY

Biologic Theories

As noted, several pathologic findings point at specific disrupted systems in the brain, particularly areas involved in the regulation of emotions and executive functioning. What remains unclear are which findings are the results of the disorder and which are causative. For example, the significant disruptions seen in the HPA axis in patients with bipolar disorder seem to represent a neurobiologic scar that is seen only after symptoms occur.

As discussed above, converging evidence suggests that calcium signaling may be, at least in part, implicated in the disorder. The genetic abnormalities found in genes associated with voltage-gated calcium channels noted above, as well as the clinical observation that certain drugs have mechanisms of action involving calcium channels (e.g., antiepileptic drugs) lend support for such a theory. Furthermore, preclinical cellular studies show some evidence for increased intracellular calcium signaling in the neurons of bipolar patients. The evidence for calcium channel abnormalities in high risk but asymptomatic individuals, as well as first-degree relatives of patients with the disorder, suggests that this may be involved in the etiology of the disorder.

Neurodevelopment likely plays a role as well, like schizophrenia, and the fact that immunologic markers are more prevalent in bipolar individuals during adolescence than adulthood appears to support a developmental etiology for the disorder.

Psychosocial Theories

Most psychodynamic theories of mania view manic episodes as a defense against underlying depression.

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.)

However, such approaches to understanding bipolar disorder have become less accepted as the biologic evidence has mounted. The role of the environment, particularly psychosocial stress, is likely crucial in the etiology. Karl Abraham, for example, believed that the manic episodes might 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 excessive 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. Melanie Klein also viewed mania as a defensive reaction to depression, using manic defenses such as omnipotence, in which the person develops delusions of grandeur.

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