CHAPTER 1

An Overview of Bipolar Disorder and Its Diagnosis

Descriptions of mania and melancholia date back to the time of Hippocrates (circa 400 BC). The Greek physician Aretaeus (second century AD) is credited with being the first to suggest that mania was intimately connected with melancholia and to note the many forms of manic-depressive illness (Maneros & Goodwin, 2005):

> The development of mania is really a worsening of the disease [melancholia], rather than a change into another disease . . . the sadness [of melancholics] became better after various lengths of time and changed into happiness; the patients then develop a mania. (p. 6)
>
> Some patients with mania . . . laugh, play, dance day and night, and stroll through the market, sometimes with a garland on their head, as they had won a game . . . But others fly into a rage. The manifestations of mania are countless. (p. 5)

The idea that mania and depression are two manifestations of the same illness was written about extensively by French clinicians in the mid-nineteenth century. Jean-Pierre Falret introduced the term *folie circulaire* and Jules Baillarger the term *la folie a double forme* to describe the alternation of manic and depressive episodes that are the hallmark of classic bipolar disorder (Pichot, 2004). In 1854, Falret predicted that many depressed patients would eventually be recognized as actually belonging to the bipolar spectrum (Akiskal et al., 2006a). Many of the manifestations of bipolar spectrum illness that have been the subject of recent clinical attention were described by these French doctors (Haustgen, 1995).

The German psychiatrist Emil Kraepelin built on the work of the French and made careful long-term observations of a large number of manic-depressive patients during the late nineteenth and early twentieth centuries. In his 1921 edition

of *Manic-Depressive Insanity and Paranoia,* he concluded, as had Falret before him, that many forms of depression are actually expressions of bipolar illness:

> Manic-depressive insanity . . . includes on the one hand the whole domain of so-called periodic and circular insanity, on the other hand simple mania, *the greater part of the morbid states termed melancholia* and also a not inconsiderable number of cases of [confusional or delirious insanity]. (p. 1; emphasis added)

It is clear, as well, from the following that Kraepelin was a proponent of the spectrum model:

> . . . we include here certain slight and slightest colorings of mood, some of them periodic, some of them continuously morbid, which on the one hand are to be regarded as the rudiment of more severe disorders, on the other hand pass without sharp boundary into the domain of personal predisposition. In the course of the years I have become more and more convinced that all of the above-mentioned states only represent manifestations of a single morbid process. (p. 1)

The idea that patients with both mania and melancholia might have an illness different from those patients who suffered with just melancholia did not begin to take shape until the last half of the twentieth century. A German physician, Karl Leonhard, came up with the concept of a monopolar-bipolar dichotomy. This distinction received some validation in the late 1960s when research showed there were clinical, familial, and course features that differentiated the two (Vieta et al., 2005). The separation of unipolar from bipolar disorder was not formally accepted, however, until the publication of the third edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* in 1980.

There were categories for cyclothymia and atypical bipolar disorder in the *DSM-III,* but bipolar disorders not meeting criteria for bipolar I were often considered unipolar variants and treated as such. A number of studies have found many patients initially diagnosed with unipolar depression in a variety of settings actually have, upon closer examination, a bipolar disorder (e.g., Ghaemi et al., 2000; Hirschfeld et al., 2003; Lish et al., 1994; Manning et al., 1998). In the study by Ghaemi, 56 percent of subjects diagnosed initially with unipolar depression were subsequently found to have a bipolar spectrum illness upon more careful examination.

Some psychiatrists are now suggesting that the unipolar-bipolar distinction may be a false dichotomy and are urging a return to the unitary view of depression and mania. The effectiveness of treatments such as lithium, quetiapine, and electroconvulsive therapy in both the manic and depressive phases of the illness supports this view.

Even if the distinction between unipolar and bipolar disorder has some validity at the extremes (alternating manic and depressive episodes at one extreme and pure depression without manic or hypomanic episodes at the other), careful observation has revealed there are many patients in between these extremes who appear to belong to a broader spectrum of bipolar illness than that defined by

the *DSM* criteria. In 1990, Goodwin and Jamison wrote that ". . . there is evidence individual patients exhibit varying degrees of loading for mania or depression—evidence that strongly suggests a continuum or spectrum model [of mood disorders]" (p. 70). A tendency to mood instability or mania may be expressed more readily when the patient is given antidepressants—something that has been happening increasingly since the debut of Prozac in the United States in 1989. A 5-year study of prescription claim information from a random sample of two million commercially insured patients under the age of 18 found that the use of antidepressants increased 49 percent from 1998 to 2002. For children ages 5 and under, the study revealed there was a 100 percent increase in use of antidepressants in girls and a 64 percent increase in use in boys (Delate et al., 2004).

Hagop Akiskal and a number of other psychiatric researchers (e.g., J. Angst, F. Benazzi, S. Ghaemi, F. Goodwin, A. Koukopolous, A. Marneros, G. Perugi) have revitalized and extended Kraeplin's ideas about the bipolar spectrum. They have written extensively on the connections between many forms of depression and bipolar disorder, the phenomenology of the bipolar spectrum illnesses, the misdiagnosis of bipolar disorder as unipolar depression, the problems of antidepressant monotherapy in bipolar depression, the temperamental foundations from which full-blown mood episodes later emerge, and how disorders such as substance abuse, cluster B personality disorders, and a number of impulse control problems are associated with bipolar illness. We may well be coming full circle back to the idea of a unitary manic-depressive illness.

The *DSM-IV-TR*

The *Diagnostic and Statistical Manual of Mental Disorders—DSM-IV-TR* (American Psychiatric Association, 2000)—describes four types of mood episodes (Table 1.1), which "cannot be diagnosed as separate entities [but] serve as the building blocks" (p. 345) for the mood disorder diagnoses, including the bipolar disorders.

A *major depressive episode* in adults is defined in the *DSM-IV-TR* as the presence of five or more of the following symptoms: depressed mood, loss of pleasure, changes in appetite and weight, insomnia or oversleeping (hypersomnia), psychomotor agitation or retardation, fatigue, feelings of worthlessness or excessive guilt, trouble concentrating or indecisiveness, suicidal ideation or recurrent thoughts of death. At least one of the symptoms has to be either (a) depressed mood or (b) loss of interest or pleasure. In addition, the *DSM-IV-TR* requires that "the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning" (p. 356).

TABLE 1.1

***DSM-IV-TR* Mood Episodes**

- Major depressive
- Manic
- Mixed
- Hypomanic

A *manic episode* in an adult is defined in the

DSM-IV-TR by "a distinct period of abnormally and persistently elevated, explosive, or irritable mood lasting at least 1 week (or any duration if hospitalization is necessary)" (p. 357). Three or more of the following symptoms (four if the mood is only irritable) must have persisted for at least one week and "been present to a significant degree" (p. 357): inflated self-esteem or grandiosity, decreased need for sleep, increased talkativeness or pressure to keep talking, flight of ideas or subjective experience that thoughts are racing, distractibility, increase in goal-directed activity (socially, at work or school, or sexually) or psychomotor agitation, excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, foolish business investments). In addition, the *DSM-IV-TR* requires that "the mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features" (p. 357).

A *mixed episode*, according to *DSM-IV-TR* criteria, is diagnosed when an individual meets criteria both for a manic episode and a major depressive episode nearly every day for at least a 1-week period. As is the case for a manic episode, the *DSM-IV-TR* also requires that a mixed episode "is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features" (pp. 362–363). As opposed to the euphoria and grandiosity seen in pure mania, mixed mania includes symptoms such as severe anxiety, agitation, hostility, irritable mood, somatic complaints, expressions of extreme distress, and cognitive impairment (Goldberg et al., 2000). I will describe mixed episodes in more detail later in this chapter.

A *hypomanic episode* is defined in the *DSM-IV-TR* as a distinct period of persistently elevated, expansive, or irritable mood lasting at least 4 days. This mood must be clearly different from the usual nondepressed mood. During the period of mood disturbance, three or more (four if the mood is only irritable) of the symptoms described previously for a manic episode have been present to a significant degree, have produced an unequivocal and uncharacteristic change in functioning, are observable by others, are not severe enough to cause marked impairment in functioning or hospitalization, and are not associated with psychotic features. Table 1.2 lists the *DSM-IV-TR* subtypes of bipolar disorder.

TABLE 1.2

***DSM-IV-TR* Bipolar Disorder Categories**

- Bipolar I
- Bipolar II
- Cyclothymia
- Bipolar Disorder NOS (Not Otherwise Specified)

Bipolar I disorder in adults is characterized by episodes of major depression and mania. An individual may receive the diagnosis of bipolar I disorder in the *DSM-IV-TR* only if he or she currently has or has had at least one manic or

mixed episode. The current episode of bipolar I disorder, for those who have had a previous manic or mixed episode, may be described as hypomanic, manic, mixed, or depressed.

Bipolar II disorder is the second category listed in the *DSM-IV-TR* classification of bipolar disorders. In adults, it is characterized by episodes of major depression and hypomania. The most recent or current episode may be described as either hypomanic or depressed. The third category of bipolar disorder in *DSM-IV-TR* is *cyclothymia*. In adults, it is defined as the presence, over at least a 2-year period, of numerous hypomanic and depressive episodes that cause clinically significant distress or impairment of functioning. The person must not have been without the symptoms for 2 months and the depressions cannot meet diagnostic criteria for a major depressive episode during the first 2 years of the illness. After the initial 2 years, a diagnosis of both cyclothymia and bipolar I disorder is given if the person develops a manic episode, and a diagnosis of both cyclothymia and bipolar II disorder is given if the person develops symptoms of depression that meet diagnostic criteria for a major depressive episode.

The final *DSM-IV-TR* bipolar disorder category is *Bipolar Disorder Not Otherwise Specified*. This category is for mood disorders with bipolar features that do not meet criteria for any of the other three categories.

DSM-IV-TR Mood Disorder Symptom and Course "Specifiers"

The *DSM-IV-TR* lists a number of terms that may be used to describe the current symptom picture and the course of a mood disorder. These terms are referred to as specifiers. Five are key in understanding the symptoms and course of bipolar spectrum illnesses. These are listed in Table 1.3.

Psychotic Features

The presence of false beliefs (delusions) or false perceptions (hallucinations) does not necessarily imply a diagnosis of schizophrenia. As many as two-thirds of bipolar patients in a manic episode have delusions or hallucinations (Goodwin & Jamison, 1990). Bipolar patients in mixed and depressive phases of the illness may also have delusions or hallucinations. There are two types of psychotic features: mood-congruent and mood incongruent.

TABLE 1.3

Key *DSM-IV-TR* Symptom and Course Specifiers

- Psychotic features
- Rapid cycling
- Atypical features
- Seasonal pattern
- Postpartum onset

Mood-Congruent Psychotic Features According to the *DSM-IV-TR*, mood-congruent psychotic features are delusions or hallucinations "whose content is entirely consistent with either the typical depressive themes of personal inadequacy, guilt, disease, death, nihilism or deserved pun-

ishment" (p. 413) or "the typical manic themes of inflated worth, power, knowledge, identity or special relationship to a deity or famous person" (p. 415). An example of a depressive delusion of disease, for example, is the belief that one's insides are rotting. A belief one is Jesus Christ is an example of a manic delusion of grandiosity. A depressive hallucination would be hearing death's footsteps in the house each night. Hearing a voice telling you that you have been chosen by God to save the world is a manic hallucination. Hallucinations are typically auditory. Visual or olfactory hallucinations should prompt a search for organic illness.

Mood-Incongruent Psychotic Features Mood-incongruent psychotic features are delusions or hallucinations that do not have typical depressive or manic themes. Mood-incongruent psychotic symptoms, according to the *DSM-IV-TR*, include the belief that one is being harassed, harmed, or targeted for harm by some person or organization (delusions of persecution), the experience that the thoughts of others are being inserted into one's mind (thought insertion), the experience that one's thoughts are being sent out to others or that others can perceive one's thoughts (thought broadcasting), and the belief one's mind or body is being controlled by others or some outside force (delusions of control).

The depressive or manic content of mood-congruent psychotic features may prompt clinicians to consider a mood disorder diagnosis, but mood-incongruent psychotic features often lead clinicians to quickly and mistakenly diagnose schizophrenia. Bipolar patients can, however, have mood-incongruent psychotic features.

Rapid-Cycling

DSM-IV-TR defines rapid-cycling as "at least four episodes of mood disturbance in the previous 12 months that meet criteria for a Major Depressive, Manic, Mixed, or Hypomanic Episode" (p. 428). Episodes must be separated "by partial or full remission for at least 2 months" or there must be "a switch to an episode of opposite mood episode" (p. 428). Patients with bipolar disorder may cycle much more often than four times a year, especially when exposed to antidepressants. Cycling can even occur on or within the same day, especially in children with bipolar disorder. This is referred to as *ultradian cycling*. I will discuss rapid-cycling in more detail later in this chapter.

Atypical Features

A depressed patient who loses his or her appetite, who has middle-of-the-night or early morning awakening, and whose mood is not reactive (his or her mood does not improve temporarily in response to positive events) is said to have typical symptoms of depression. *DSM-IV-TR* defines another set of symptoms as *atypical*. The term *atypical* does not imply unusual or rare. Atypical symptoms are common, especially in nonpsychotic, mildly to moderately depressed, female outpatients. A patient is said to have atypical symptoms when, during the most recent

2 weeks of a major depressive episode, his or her mood improves temporarily in response to positive events and when he or she has two or more of the following symptoms: increased need for sleep (hypersomnia); increased appetite or significant weight gain; heavy, leaden feelings in the arms and legs (leaden paralysis); and a "long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment" (American Psychiatric Association, 2000, p. 422).

Depression with hypersomnia had the highest specificity for the diagnosis of bipolar II disorder of any of the atypical symptoms in a study by Benazzi and Rihmer (2000). However, clinicians should keep in mind that bipolar patients, when more severely depressed, may have the middle-of-the-night awakening typically seen in severely depressed unipolar patients (Goodwin & Jamison, 1990).

Seasonal Pattern

Patients who oversleep, crave carbohydrates, gain weight, and become lethargic in the fall and winter and then become more energetic in the summer are said to have seasonal affective disorder (SAD). A substantial number of patients with SAD have bipolar illness (Goodwin & Jamison, 1990; Rosenthal & Wehr, 1987). A small percentage of patients with SAD have summer depressions and winter euthymia or hypomania.

The *DSM-IV-TR* notes that the prevalence of the seasonal pattern increases with higher latitudes. Levitt and Boyle (2002) presented data showing there was no evidence to support an increase in prevalence with increasing latitude. However, their data was based on a survey of individuals spread across only eight degrees of latitude. The *DSM-IV-TR* also indicates that women make up 60 to 90 percent of individuals with a seasonal pattern of depression.

Postpartum Onset

The *DSM-IV-TR* defines postpartum onset of depression as a depressive episode that begins within 4 weeks of giving birth to a child. Postpartum mood episodes with psychotic features occur in 1 in 500 to 1 in 1,000 deliveries but occur more frequently in women with previous postpartum episodes, a prior history of mood disorder, and especially in women with a history of bipolar I disorder. They may also occur more frequently in women with a family history of bipolar disorder (American Psychiatric Association, 2000).

There is a strong association between postpartum psychosis and bipolar disorder (Chaudron & Pies, 2003). A woman seeking help for depression who has a history of postpartum psychosis should be suspected of having bipolar disorder.

Problems with the *DSM-IV-TR* Classification of Bipolar Disorders

Akiskal (1996) and others such as Benazzi (2006b), Angst et al. (2003), and Ghaemi et al. (2006) have pointed out that there are a number of problems with

the *DSM-IV-TR* classification of bipolar disorders that lead to the under-diagnosis of bipolar spectrum illnesses. As Vieta et al. (2005) suggest, "current diagnostic criteria lack the sensitivity to detect the full range of conditions within the bipolar spectrum" (p. 89).

Shortcomings of the *DSM-IV-TR* classification of bipolar disorders include the following:

1. The *DSM-IV-TR* contains no criteria for differentiating unipolar from bipolar depression. More specifically, differences in symptoms (phenomenology), course and family history between the two are not described.
2. An episode may only be labeled *mixed* in *DSM-IV-TR* if the patient's symptoms meet the full criteria for both depression and mania. However, it is not uncommon, especially in outpatient practice, for clinicians to see patients with a major depressive episode who also have only a few manic symptoms. Benazzi (2001) has found that the presence of three hypomanic symptoms (agitation, irritability, and racing or crowded thoughts) clearly differentiates bipolar from unipolar patients. Agitated depression has typically been considered a unipolar variant. Koukopoulos and Koukopoulos (1999) have argued persuasively that agitated depression is, in fact, a type of mixed state.
3. *DSM-IV-TR* requires 4-day duration for an activated state to be considered a hypomanic episode. But Angst et al. (2003) have documented that the mean duration of hypomanic episodes is 1 to 3 days.
4. The sharp demarcation of Axis II personality disorders in general and antisocial, narcissistic, and borderline personality disorders in particular from Axis I mood disorders may not be warranted (Akiskal et al., 2006b). The fluidity of the boundaries between Axis I and Axis II was demonstrated in 1980 when depressive personality disorder was reclassified as an Axis I disorder and labeled dysthymia. The disorder had been thought to originate from trauma in the oral stage of development and the dynamic interplay between subsequent hostile impulses and the superego (Goldberg, 1975). But a number of lines of evidence indicated that depressive personality disorder had, in spite of its chronic course, a close biological connection to episodic major depressive disorder.
5. The *DSM-IV-TR* requirements for a diagnosis of atypical depression are overly strict. *DSM-IV-TR* requires that a patient have mood reactivity (mood improves in response to positive events) if his or her symptoms are to be labeled atypical. Benazzi (2005) asserts there is little empirical support for this requirement. He describes the study by Angst et al. (2002), which found that mood reactivity is no more important for the diagnosis of atypical depression than any of the other atypical features. A clinician's

index of suspicion for a bipolar depression should be raised if the patient is oversleeping, even if mood reactivity is not present.

6. *DSM-IV-TR* requires that an individual have a euphoric or irritable mood to be labeled hypomanic. But periods of overactive behavior and increased productivity are more reliable markers of hypomania (Akiskal, 2005). They are more easily remembered by the patient and his or her family than a change in mood.
7. *DSM-IV-TR* acknowledges that "some evidence suggests that there may be a bipolar 'diathesis' in individuals who develop manic- or hypomanic- or mixed-like episodes following somatic treatment for depression" (p. 359). But, as of now, in the absence of a previous history of mania or hypomania, manic patients who develop manic, hypomanic, or mixed episodes with somatic antidepressant treatments are not considered bipolar. Akiskal and Pinto (1999), however, have found that individuals with antidepressant-induced hypomania very often go on to develop spontaneous hypomania. Angst et al. (2003) discuss a number of other "minor forms" of bipolar disorder. Table 1.4 lists several of these minor or atypical forms of bipolar disorder. They are atypical in the sense that individuals with these forms have no prior history of hypomania.

The problem with widening the diagnostic criteria for bipolar disorder, of course, is the loss of specificity and the danger of overdiagnosis. As sensitivity to the subtle manifestations of bipolar disorder increases, specificity of the diagnosis decreases. While the risk of overdiagnosis should be kept in mind, clinicians need to be aware that the risk of misdiagnosis of bipolar depression as unipolar depression poses substantially greater potential for harm. Treatment of bipolar depression with antidepressants runs a number of serious risks including the induction of hypomania, mixed states, or rapid cycling or the worsening of preexisting agitation and rapid cycling.

TABLE 1.4

Atypical Forms of Bipolar Disorder (No History of Hypomania)

- Antidepressant-induced hypomania or mixed states
- Depression in a child, adolescent, or young adult with a family history of bipolar disorder
- Depression in an individual with a premorbid hyperthymic temperament
- Brief, frequent, recurrent depressions
- Agitated depression

Epidemiology, Phenomenology, and Course of Bipolar Spectrum Disorders

Bipolar disorder with manic episodes (bipolar I disorder) lies at one of the extremes of the bipolar spectrum and occurs in two percent of the U.S. population (Grant et al., 2005). It is far from being the most common form of bipolar disorder. The universe of bipolar disorders (bipolar I, bipolar II, cyclothymia, and the rest of the bipolar spectrum) has been found to make up as much as 6.4 percent of the U.S. population (Judd & Akiskal, 2003). Pini et al. (2005) conducted a literature search, supplemented by a survey of experts along with selected reanalyses of existing data from epidemiological studies, to determine the prevalence of bipolar disorders in the European Union. They estimated a 6 percent prevalence rate of bipolar spectrum illnesses in Europeans. A report from Swiss researchers indicated a nearly 11 percent prevalence of individuals with soft bipolar disorder in a 20-year prospective community cohort study of young adults (Angst et al., 2003).

The percentage of the population with bipolar illness appears to be increasing and the age of onset decreasing. One factor may be a molecular genetic phenomenon known as trinucleotide repeat expansion. Trinucleotide repeats (TNRs) are parts of DNA that contain the same trinucleotide sequence repeated many times. If the repeat occurs in a gene, the number of trinucleotide repeats will increase and may result in disease. Genes with TNRs have been implicated in the etiology of bipolar disorder (Lange & McInnis, 2002; McInnis et al., 1993).

Other possible factors causing increased prevalence and decreased age of onset include increased exposure to light at night, environmental toxins, increased substance abuse, increased use of antidepressants, decreased omega-3 fatty acid intake, or psychosocial stress on children from the increasing divorce rate. Severe childhood adversity has been associated with earlier onset of bipolar disorder and greater recurrence (Dienes et al., 2006).

One reason for the misdiagnosis of bipolar patients is that they typically spend a great deal more time depressed than they do manic or hypomanic. Bipolar I patients are symptomatic about 45 percent of their lives. They spend about two-thirds of this time in the depressive phase of their illness (Judd et al., 2002). If a clinician is not familiar with the symptoms that suggest bipolar as opposed to unipolar depression or does not probe for a history of hypomania, he or she will arrive at the wrong diagnosis (see Figure 1.1).

Depression at first episode predicts more depressive episodes in the course of the illness (Perlis et al., 2005). Turvey et al. (1999) reported that, in a cohort of bipolar patients, those whose illness began with depression had higher overall morbidity over a 15-year follow up than those with a manic onset. Studies differ on what percentage of patients with bipolar illness have depression as opposed to mania as a first episode, but Roy-Byrne et al. (1985) reported that 60 percent of 71 patients had a depressive first episode. Perugi et al. (2000) found that among 320 bipolar patients, 50 percent had a depressive first episode, 25 percent had a manic first episode, and 25 percent had a mixed first episode.

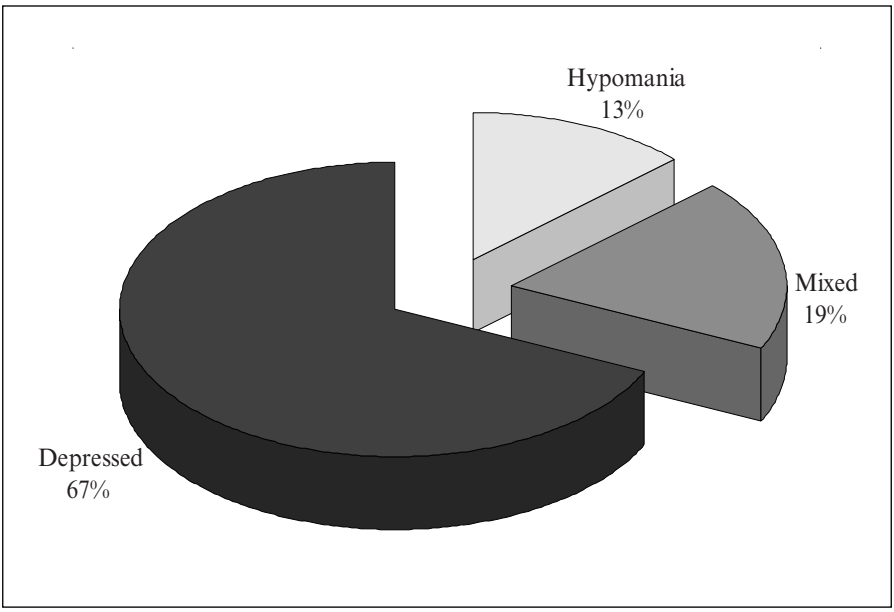

Figure 1.1 *Bipolar I Disorder: Symptoms during Time Ill (146 patients over 12.8 years)*

There have been studies on several other dimensions of bipolar illness, as well. Goodwin and Jamison (1990) note, for example, that research on the course of bipolar illness has shown that, as episodes recur, they tend to occur closer together (cycle length decreases, frequency increases). In addition, they report that initial episodes are often triggered by some well-defined psychosocial or biological stress (work, childbirth), whereas later episodes require less stress. Kraepelin (1921) wrote:

> The kind and duration of the attacks and the intervals by no means remain the same in the individual case but may frequently change, so that the case must be reckoned always to new forms. (p. 139)

Given the variety of expressions of bipolar illness (phenotypes) seen in outpatient practice today and the course-altering influence of the antidepressants so many patients have been exposed to, it would seem even more difficult for a clinician to predict the course of any particular patient's illness. However, patients will often ask about the prognosis for their illness. Perhaps the best and most critical information that can be given is that the illness is recurrent and that, without aggressive treatment, it is likely to adversely affect quality of life and impair functioning. Untreated bipolar illness can also shorten an individual's life span. This is not due solely to suicide. All-cause mortality is twice as high for individuals with bipolar illness as for the general population (Keller, 2004).

According to data by Tohen et al. (2003), 98 percent of patients recovered from their manic episode within 2 to 4 years of first hospitalization, but 57 percent of them switched to a depressive episode or had another manic episode during

that period. Patients with mixed episodes tend to make slower recoveries and have shorter time to relapse than pure manic patients (Keller et al., 1993). In a group of bipolar I patients hospitalized with mania, those who had above-median Hamilton-Depression rating scale depression scores (i.e., were in a mixed state) were only half as likely to recover and did so much later than those with lower scores (Chengappa et al., 2005).

Although 98 percent of patients recovered symptomatically from their manic episodes in the Tohen et al (2003) study, only 43 percent achieved functional recovery. Clinicians should be aware that functional recovery very often lags symptomatic recovery for many bipolar patients. Keller et al. (1993) found that, on average, 80 percent of bipolar patients relapse after 5 years. According to O'Connell et al. (1991), predictors of relapse included a depression to mania course, a family history of mania, and nonadherence to medication.

An individual patient's chances for stability can be increased, however, if he or she works closely with a prescriber to find the right combination of medications; maintains stable social and biological rhythms (especially sleep habits); learns how to calmly solve interpersonal problems; and avoids alcohol, drugs, and caffeine. Scott et al. (2006), in a review of published, randomized controlled studies of psychological therapies for bipolar patients, found that adjunctive psychotherapy reduces relapse rates compared to standard psychiatric care. Table 1.5 summarizes key phenomenologic and course features of bipolar I disorder.

TABLE 1.5

Bipolar I Disorder: Phenomenology and Course

- There is a 10-year gap between first symptoms and correct diagnosis (Ghaemi et al., 2000).
- BP I patients spend 45 percent of their lives ill (Judd et al., 2002).
- Well intervals between episodes tend to decrease with time (Goodwin & Jamison, 1990).
- Functional recovery substantially lags symptomatic recovery (Tohen et al., 2003).
- More rapid onset and offset of symptoms than in unipolar depression (Bowden, 1993).
- BP I patients spend considerably more time depressed than manic (Judd et. al., 2002).
- Earlier age of onset for bipolar disorder than for unipolar disorder (Ghaemi et al., 2006).
- About 30 to 40 percent of BP I patients have mixed episodes (Akiskal et al., 2000).

Bipolar II Disorder

Although first described by Dunner in 1976, bipolar II disorder did not become an officially recognized diagnosis until the publication of *DSM-IV* in 1994. The excited phase of bipolar II disorder may be less intense than in bipolar I, but bipolar II illness is quite debilitating, largely because of the depressive phase of the illness. In fact, there is some evidence bipolar II disorder causes more family dysfunction than bipolar I disorder (Coryell et al., 1985).

Akiskal et al. (1995) have found that bipolar II patients have more mood instability between major episodes than bipolar I patients. Patients with bipolar II disorder have a background temperament that is basically cyclothymic. Akiskal and his colleagues believe that this temperamental profile may be the defining characteristic of bipolar II illness rather than the hypomanic episodes emphasized in *DSM-IV-TR*.

Bipolar II patients spend 93 percent of the time they are ill in the depressive phase of their illness, compared to only 2 percent of the time they are ill in the hypomanic phase and 4 percent in mixed phases (Judd et al., 2003b). See Figure 1.2.

In adults, bipolar II disorder is a fairly stable diagnosis. Relatively few adult bipolar II patients go on to develop manic episodes (Coryell et al., 1995). Children with bipolar II, on the other hand, have a more unstable course. About

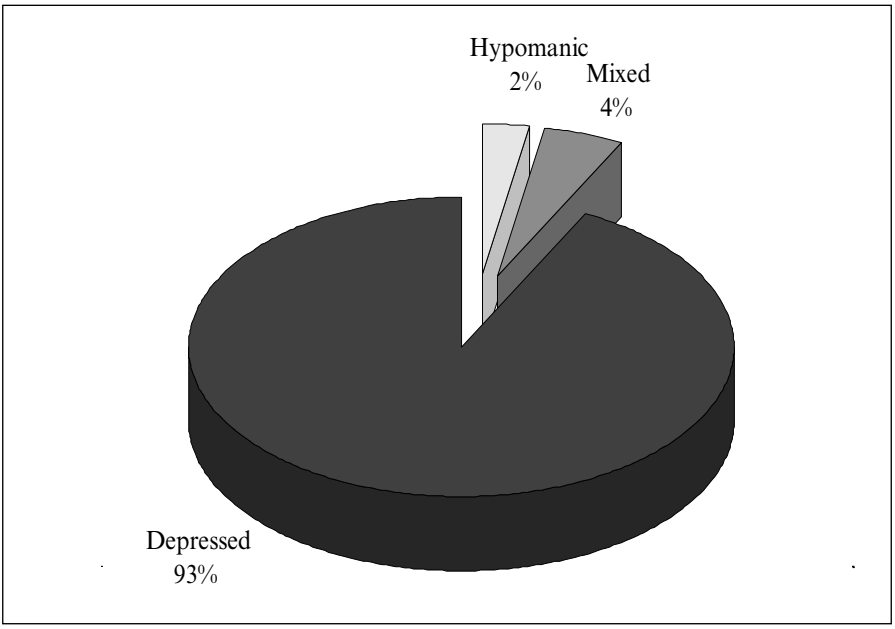

Figure 1.2 *Bipolar II Disorder: Symptoms during Illness (86 patients over 13.4 years)*
Source: Data from Judd et al. (2003b).

20 percent of bipolar II children convert to bipolar I over time (Birmaher et al., 2006).

A clinician may need to look for more than a family history of bipolar illness to validate a suspected diagnosis of bipolar II disorder. While Benazzi (2004) found that bipolar II was the most common diagnosis in family members of bipolar II patients, Joyce et al. (2004) found that only seven percent of bipolar II patients had a family history of bipolar II disorder. Another seven percent had a family history of bipolar I disorder. Forty-two percent, however, had relatives with depression. Family histories that suggest bipolar II disorder and other bipolar spectrum illnesses will be discussed in detail in the next chapter. However, an example of what clinicians might look for is a family history of creativity and achievement. Several studies have found a high rate of creativity among relatives of patients with bipolar II disorder (Coryell et al., 1989; Simeonova et al., 2005). Hypomania can be adaptive, leading to superior functioning and achievement in the arts, politics, sales, business, and the entertainment industry. Table 1.6 lists reported differences between bipolar I and bipolar II disorder.

TABLE 1.6

Reported Differences between Bipolar I (BP I) and Bipolar II (BP II) Disorder

- BP II patients spend much more time depressed than BP I patients (Judd et al., 2003b).[a]
- Higher episode frequency, more rapid-cycling (Ayuso-Gutierrez & Ramos-Brieva, 1982; Baldessarini et al., 2000) in BP II patients.
- Less psychotic features in BP II patients (Vieta et al., 2005).
- BP II patients are less often hospitalized than BP I patients (Vieta et al., 2005).
- BP II patients have more interepisode moodiness (Akiskal et al., 1995).
- Higher rates of divorce, separation, and interpersonal conflicts (Coryell et al., 1985; Rihmer, 2002) in BP II patients.
- BP II patients have shorter duration of episodes (Coryell et al., 1985; Rihmer, 2002).
- Higher rate of anxiety disorders in BP II patients (Judd et al., 2003a).
- Higher rate of attempted and completed suicide in BP II patients (Rhimer & Pestality, 1999).[a]

[a]Contrary data exist.

Cyclothymia

Cyclothymia is a term first used by Karl Ludwig Kahlbaum in 1882 to refer to a mild form of "cyclical insanity" (Howland & Thase, 1993). It is a heterogeneous group of disorders that are typically of early onset, chronic, and without intervening euthymic periods. They are little studied, except by Akiskal (Akiskal, 1996; Akiskal et al., 1977). Estimates of prevalence vary widely and are probably unreliable due, in part, to varied diagnostic criteria, levels of expertise in diagnosing the disorder, and the population studied. Patients with cyclothymia had more relatives with bipolar disorders than controls in a study by Depue et al. (1981). The depressive episodes are generally characterized by hypersomnia (Akiskal et al., 1977). Cyclothymia is probably best viewed as a temperament out of which can grow more severe mood episodes (Akiskal et al., 1979; Kraepelin, 1921, 1921). Because many patients with this temperament go on to develop more pronounced mood episodes, it is a very unstable diagnosis (Akiskal et al., 1979). Dysthymia might be a form of cyclothymia according to Akiskal (1996). He cites as evidence the early age of onset, atypical symptoms, and family histories of bipolar disorder seen in some dysthymic patients.

Mixed States

About 30 to 40 percent of bipolar I patients have mixed episodes (Akiskal et al., 2000; Swann, 1995). Nearly 49 percent of depressed bipolar II patients had three or more hypomanic symptoms (Benazzi, 2000). Mixed episodes are those in which a patient has both depressive and manic symptoms at the same time. Some mixed episodes may be a transition state that occurs as a person switches from depression to mania. Many, however, are discrete episodes. In a systematic retrospective examination of a large sample of bipolar I patients, Perugi et al. (2000) found that 50 percent of patients had an initial episode of illness that was depressive, 25 percent had a manic episode, and 25 percent had a mixed episode.

Akiskal (1992) believes that mixed states are more than just the simultaneous occurrence of symptoms of opposite polarity. He has proposed the novel idea that mixed states occur when a manic episode or a major depressive episode is superimposed on a premorbid temperament of the opposite polarity. For instance, a manic or hypomanic episode that occurs in a person with a depressive temperament or dysthymia produces the mixed state referred to as dysphoric mania or hypomania. McElroy et al. (1992), in a review of the studies on dysphoric mania available at the time, concluded that dysphoric mania may be more severe and more likely to be associated with suicidality, a younger age at onset, a longer duration of illness, higher rates of personal and familial depression, concomitant alcohol or sedative-hypnotic abuse, and poorer outcome than euphoric mania.

Depressive mixed states or agitated depressions, which are very common in

outpatient practice, may come about when a depressive episode occurs in an individual who has what is referred to as a hyperthymic temperament. (A nonepisodic, habitual way of functioning characterized by extroversion, exuberance, optimism, overconfidence, high energy, and a reduced need for sleep.) Patients with depressive mixed states can be identified by one or more of the following: restlessness, hypersexuality, racing thoughts, and pressured speech. Patients with depressive mixed states usually have fewer episodes of longer duration and more interepisode symptoms than patients with pure mania.

Rapid Cycling

The *DSM-IV-TR* states that rapid cycling occurs in 5 to 15 percent of patients with bipolar disorder. Akiskal et al. (2000) estimated a 20 percent or less rate of rapid cycling in bipolar patients. This is the rate that was found in a study of the first 500 patients enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD; Schneck et al., 2004). Coryell (2005) estimated a 16 percent rate. But Kupka et al. (2005), in a 1-year, prospective study of 539 outpatients with bipolar I disorder ($N = 419$), bipolar II disorder ($N = 104$), and bipolar disorder not otherwise specified ($N = 16$), reported a 38 percent rate of rapid cycling. The high rate may be due to the large number of very ill patients in that study.

Papadimitriou et al. (2005) state that patients with rapid cycling usually suffer from bipolar II disorder. It is not clear if rapid cycling is genetically determined. There is no increased rate of rapid cycling in the families of patients with rapid cycling compared to the families of nonrapid cycling. Thus, rapid cycling appears to be a temporary phase in the illness, not a separate entity (Kilzieh & Akiskal, 1999). Elhaj and Calabrese (2005) suggest that early onset rapid cycling might have a genetic component, however. Subclinical hypothyroidism, substance abuse, and disturbances in circadian biological and social rhythms might contribute to rapid cycling, according to Papadimitriou and his colleagues.

The role of thyroid dysfunction in rapid cycling and mixed states is not clear. There are studies that indicate there is a higher rate of thyroid dysfunction in mixed and rapid-cycling patients (e.g., Bauer et al., 1990; Oomen et al., 1996; Zarate et al., 1997), but there are also studies that do not find such a relationship (Joffe et al., 1994; Post et al., 1989). However, there is enough evidence of a relationship to warrant investigation of thyroid hormone status in individual patients with rapid cycling and mixed states.

In the Kupka study, patients with rapid cycling more frequently had a history of childhood physical and/or sexual abuse and drug abuse. The average time spent manic/hypomanic increased as a function of episode frequency, but the average time spent depressed was comparable in patients with one episode and in those with more than one episode.

The *DSM-IV-TR* indicates that 70 to 90 percent of rapid-cycling patients are

women. In the STEP-BD study, rapid-cycling patients were indeed more likely to be women, although this gender difference was somewhat more pronounced among bipolar I patients than bipolar II patients. In addition, rapid-cycling bipolar patients experienced onset of their illness at a younger age, were more often depressed at study entry, and had poorer global functioning in the year before study entry than nonrapid-cycling patients.

As cycle frequency increases, the number of adult patients experiencing that frequency of cycling decreases (Goodwin & Jamison, 1990). There has apparently been an increase in cycle frequency since 1960 (Wolpert et al., 1990). This may be due, in part, to increased substance abuse or the increased use of antidepressant medication in bipolar patients.

Women and Bipolar Disorder

The studies on phenomenology of bipolar disorder in women have recently been expertly reviewed by McElroy et al. (2006). Following is a summary of their most clinically relevant findings supplemented by studies reported since the publication of their review.

Women suffer from depressive disorders at about twice the rate of men. The incidence of bipolar I disorder, however, is equal in men and women. The data on sex distribution in bipolar II disorder are contradictory, with some studies showing a preponderance of women and some showing equal distribution of the sexes. No studies indicate a preponderance of males. Data from the first 500 patients in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) showed BP II was more common in women (Baldassano et al., 2005). Benazzi (2006a) found 67 percent of 374 bipolar II private practice outpatients were women.

Men more often have a manic or hypomanic onset of their illness, an earlier age of onset, and longer duration of manic episodes than women, whereas women more often have a depressive onset of their illness. Epidemiologic studies have shown that mixed and depressive symptoms are more common in women than men (Grant et al., 2005). Among the first 500 STEP-BD patients, women were not found to have a higher number of lifetime episodes of depression, however. Given the number of epidemiologic studies showing that they do, this result has to be questioned.

Kennedy et al. (2005) investigated gender differences in age at onset and incidence of first-episode mania and bipolar disorder in all adults in a portion of southeast London, England, over a 35-year period. Men had an earlier age of onset of mania. In addition, there was an association between antisocial behavior in childhood and an early onset of bipolar disorder. Grigoroiu-Serbanescu et al. (2005), however, found that the presence of a family history of bipolar disorder had a strong influence on age of onset, at least in females. They investigated the effect of the interaction between gender and family history on age of onset of bipolar disorder in 264 Romanian bipolar I patients. Bipolar women with a fam-

ily history of bipolar disorder had an earlier age of onset than bipolar women without a family history of bipolar illness. (The authors cited a study done on a German sample that had a similar same finding.) Females without a family history of bipolar disorder had a later onset than males with no family history of bipolar illness.

Studies suggest women have more narrowly defined mixed states (full syndrome mania and full syndrome depression), atypical symptoms (especially overeating and weight gain), and rapid cycling then men. The sex distribution appears more equal for less strictly defined mixed states (mania with a few depression symptoms and depression with a few manic symptoms). Although the *DSM-IV-TR* indicates that 70 to 90 percent of rapid cyclers are women, Kupka et al. (2005), in a 1-year, prospective study of 539 outpatients with bipolar I disorder ($N = 419$), bipolar II disorder ($N = 104$), and bipolar disorder not otherwise specified ($N = 16$) found that the proportion of women with rapid cycling was greater than the proportion of men with rapid cycling only among patients with eight or more episodes per year.

The STEP-BD (Baldassano et al., 2005) and other studies have found that, in general, women with bipolar disorder are saddled with a great deal of comorbidity. Women are more vulnerable to thyroid dysfunction than men and even mild thyroid dysfunction can adversely affect the course of mood disorders (Hendrick et al., 1998). Women are more likely to report a history of sexual abuse, which may be a factor leading to greater comorbidity.

Bipolar men more often abuse substances than bipolar women. Still, bipolar women abuse substances much more often than women in the general population (Frye et al., 2003). Baldassano et al. (2005) also found that men were more likely to have a history of legal problems than women. Friedman et al. (2005) found that among a group of rapid-cycling bipolar disorder patients who were substance abusers, men were more likely to have a criminal history. Both Frye and Friedman note that although women with bipolar disorder are less likely to have a criminal history than their male counterparts (Baldassano et al., 2005), they were more likely to have a criminal history than were women in the general population.

In a nationally representative, community mental health survey of over 36,000 Canadian individuals, female bipolar subjects were significantly more likely than male subjects to be prescribed an antidepressant medication (OR = 1.99, $p = .01$), even in the absence of higher frequency of recent depressions (Schaffer et al., 2006). This is of some concern since women may be more prone to the cycle-inducing effects of antidepressants (Leibenluft, 1997).

Bipolar disorder symptoms may worsen premenstrually, and the postpartum period is a time of high risk for first onset of mood and psychotic episodes for women in general, but especially so for women who are bipolar. Women with bipolar disorder often relapse to depressive, manic, and mixed episodes in subsequent pregnancies. The presence of mood symptoms during pregnancy is

associated with postpartum mood episodes. The rate of postpartum psychosis in women with bipolar disorder was reported in one study to be between 20 and 30 percent. Bipolar women who have a family history of postpartum psychosis are at higher risk of postnatal episodes than bipolar women without such a family history. Antidepressants are not the treatment of choice for all women with postpartum depression, especially if they have a family history of bipolar illness. Sharma (2006) described three women with postpartum depression who were treated with antidepressants. None of the three had a past history of psychiatric illness but in each case there was a family history of bipolar (BP) disorder. Treatment with antidepressants resulted in a mixed episode, cycle acceleration, and a postpartum psychosis. Discontinuation of antidepressants and treatment with mood stabilizers and atypical antipsychotics resulted in remission and sustained improvement.

Women are likely to be at some increased risk for unipolar depression during the perimenopause (Rasgon et al., 2005). The risk for increased mood instability for bipolar women who are perimenopausal or postmenopausal seem less clear. Some studies have shown greater mood instability during these periods for a minority of women with bipolar disorder, especially if they are not on hormone replacement therapy.

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