

# Improving the Course of Illness and Promoting Continuation of Treatment of Bipolar Disorder

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The course and characteristics of the different types of bipolar disorder have profound implications for its long-term prognosis and treatment. Patients with bipolar I disorder are symptomatically ill nearly half the time and have a high probability of relapse. Bipolar II disorder is more chronic, more depressive, and associated with more neuroticism and emotional instability between episodes than bipolar I. Impaired psychosocial functioning and a high risk for suicide are common to all types of bipolar disorder. The illness can be stabilized through pharmacotherapy and by patients maintaining orderly patterns of life activities and using psychotherapy, psychoeducation, and mood charting. Adherence to pharmacotherapy increases the duration of remission. Physicians can help improve adherence by selecting medications with simple dosage regimens and educating patients and families about the disorder and what to expect from medications.

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The naturalistic course and characteristics of bipolar disorder in its various manifestations have important long-term prognostic and therapeutic implications. The 20-year Collaborative Depression Study (CDS)<sup>1</sup> by the National Institute of Mental Health has helped clarify distinctions among bipolar I disorder, bipolar II disorder, bipolar disorder not otherwise specified, and unipolar mania and depression, and it has elucidated the natural history of these disorders. Nevertheless, the complexity of bipolar disorder and its many manifestations have led to a broad variance in prevalence estimates, largely because clinical samples have included patients with the broad spectrum of bipolar disorder types, including mania, hypomania, recurrent and sporadic brief hypomania, depression, and cyclothymia (Table 1).

Bipolar disorder of all types often is accompanied by comorbid disorders, especially anxiety disorders (panic attacks, agoraphobia, social phobia, and obsessive-compulsive syndromes) and substance abuse (tobacco dependence, alcohol abuse, illicit drug use, and overuse of

prescription drugs). A study by Kessler et al.<sup>2</sup> concluded that 93% of patients with the euphoric-grandiose form of bipolar I disorder experience an anxiety disorder, and 71% have at least 1 form of substance abuse at some point in their lives. In addition, all types of bipolar disorder can have serious consequences. An estimated 7.1% to 20.3% of bipolar disorder patients have attempted suicide.<sup>3</sup>

## BIPOLAR I DISORDER

Adult bipolar I disorder is highly recurrent and chronic, particularly in patients with a mixed/cycling or depression-only polarity during the intake episode.<sup>4</sup> Greater severity of bipolar I disorder is associated with younger age at the index episode, longer duration of the index episode, mixed/cycling or cycling polarity, severity of depression, and comorbid psychosis or substance abuse, as well as social factors such as family discord and poor socioeconomic, educational, or occupational status.<sup>5,6</sup>

Patients with bipolar I disorder are likely to remain symptomatic for much of their lives, even when they are not experiencing an episode of mania, depression, or hypomania. In a cohort followed for a mean of 12.8 years by Judd and coworkers,<sup>4</sup> patients were symptomatically ill nearly half the time and had an extraordinarily high probability of relapse. Depressive symptoms occurred more than 3 times as often as manic symptoms in patients with bipolar I disorder. Depressive symptoms were present during 32% of the follow-up period, manic symptoms for 9%, and cycling or mixed/cycling symptomatology for 6%. Subsyndromal and minor depressive or dysthymic

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**Table 1. Lifetime Prevalence Rates of Bipolar Disorder<sup>a</sup>**

Diagnosis	No. of Studies	Range of Rates, %
Bipolar I disorder	13	0.0–1.7
Bipolar II disorder	9	0.2–3.0
Bipolar spectrum disorders	7	2.6–6.5

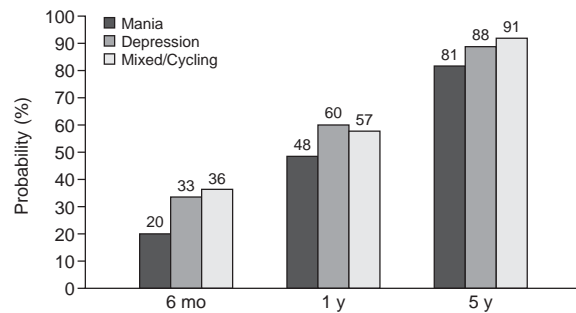
<sup>a</sup>Data from Angst.<sup>3</sup>

symptoms were more prevalent than episodes of major depression (22.9% vs. 8.9% of weeks during follow-up), and subsyndromal manic and hypomanic symptoms were 3 times more frequent than symptoms at the threshold of mania (7.0% vs. 2.3% of follow-up weeks).

The duration of bipolar I disorder episodes is closely linked to their polarity. Manic episodes persisted for 6 weeks, major depressive episodes for 12 weeks, and mixed/cycling episodes for 45 weeks.<sup>4,7</sup> A 10-year prospective follow-up<sup>8</sup> based on observations of intraindividual variability in episode length among a cohort of 131 bipolar disorder patients found that median cycle lengths during the first 5 years were similar to those during the subsequent 5 years. Episodes did not decrease systematically in length over time, as the researchers had expected at the initiation of the study. The lengths of cycles were unpredictable and were uncorrelated between the first 5 and second 5 years of the study.<sup>8</sup>

The great majority of patients relapse after recovering from an episode of bipolar I disorder. Factors that predict recurrence of bipolar I disorder include recovery from a mixed/cycling episode, depression-to-mania polarity shifts, episode recency, a family history of mania, and non-adherence to prescribed medications.<sup>9</sup> The probability of relapse varies with the type of episode and becomes greater as the length of time increases since the last episode. In a 5-year naturalistic study, Keller et al.<sup>10</sup> found that among people whose last episode was mixed/cycling, 36% relapsed after 6 months, 57% after 1 year, and 91% after 5 years. If the last episode was depressive, 33% of patients relapsed after 6 months, 60% after 1 year, and 88% after 5 years. For patients whose last episode was manic, 20% relapsed after 6 months, 48% after 1 year, and 81% after 5 years. About 80% of all patients with bipolar I disorder will relapse within 5 years of a previous episode (Figure 1).

A 10-year follow-up study found that as long as 7 years after recovery from the initial episode, the cumulative likelihood of recurrence is 80% for all bipolar I disorder patients and 66% for patients whose index episode was followed by at least 3 symptom-free years. Even with patients who have received sustained lithium prophylaxis, the likelihood of at least 1 recurrence exceeded 70% within 5 years of recovery.<sup>11</sup> Among relapsed patients, those with a mixed/cycling episode had the lowest cumulative probability of recovery and needed the longest time for recovery. The median times to recovery were 17 weeks for patients who had a mixed/cycling episode, 11 weeks for those with

**Figure 1. Cumulative Probability of Relapse in Adults With Bipolar I Disorder According to Polarity of the Last Episode (N = 172)<sup>a</sup>**

<sup>a</sup>Data from Keller et al.<sup>10</sup>

a pure depressive episode, and 6 weeks for patients who experienced a pure manic episode.<sup>10</sup>

The risk for suicide among individuals with bipolar I disorder is up to 30 times greater than that for the general population.<sup>12</sup> The suicide risk appears to be highest early in the course of bipolar I disorder. Mortality associated with other causes—both natural and unnatural—is approximately 2 times greater for people with the disorder than for the general population. In order, cardiovascular disease, suicide, and cancer are the 3 most frequent causes of death among patients with any type of bipolar disorder. All natural causes of death, except cancer and central nervous system diseases in men, are higher for people with one type of bipolar disorder.<sup>13</sup> The significant decrements in psychosocial functioning that result from bipolar I disorder include increased divorce rates (one study found that 57% of the marriages of all bipolar disorder patients ended in divorce; divorce occurred only after, and never before, the first episode of mania),<sup>14</sup> reduced functional capacity in virtually all domains, and a greater prevalence of alcohol and drug abuse.

## BIPOLAR II DISORDER

The distinction between bipolar I disorder and bipolar II disorder was first hypothesized in the mid-1980s and is now widely accepted. Prospective studies describing the long-term course of bipolar II disorder are limited largely to those of Angst et al. in the Zurich Cohort Study<sup>15</sup> and the CDS.<sup>1</sup>

Bipolar II disorder tends to be more chronic than bipolar I disorder. Bipolar II is overwhelmingly more depressive than bipolar I disorder with far more major and minor depressive episodes. As reported by the CDS, patients with bipolar II disorder experience fewer and less-severe manic episodes, although hypomanic symptoms also can have a deleterious impact on the patient. Bipolar II disorder is marked by significantly more neuroticism, shorter inter-

episode intervals of euthymia, and less emotional stability between episodes than bipolar I disorder. Patients with bipolar II disorder also tended to experience less severe acute intake episodes in the CDS. Rapid cycling is common in bipolar II disorder, with cycling episodes appearing to last more than 2 years in 20% of patients.<sup>1,15</sup> Rapid-cycling patients tend to be female and to exhibit depression, hypomania, or cycling between periods of depression and hypomania during the index episode.<sup>16</sup>

The serious consequences of bipolar II disorder are similar to those of bipolar I disorder: impaired function, decreased productivity, increased substance abuse, psychiatric and general medical comorbidity, and increased mortality, including a 10% to 15% rate of completed suicide.<sup>1,15</sup> In addition, patients with bipolar II disorder have a significantly higher lifetime prevalence of anxiety disorders in general (38% of bipolar II disorder patients reported experiencing anxiety, compared with 25% of the general population), and social and simple phobias specifically, than patients with bipolar I disorder.<sup>1</sup>

#### AGE-SPECIFIC RESEARCH

Few naturalistic/observational studies on the age-specific course of bipolar disorder have been undertaken. These include a single prospective, longitudinal study of childhood-onset illness,<sup>17</sup> 2 studies of adolescent-onset bipolar disorder,<sup>18,19</sup> and only 2 prospective studies that followed adults for longer than 20 years.<sup>4,20</sup>

Relatively few studies have been conducted on bipolar disorder in the elderly. One characteristic of bipolar disorder among elderly people is that mania frequently may not manifest for many years after an initial depressive episode. For elderly bipolar disorder patients whose initial episode was depressive, a mean latency period of more than 15 years before the first manic episode has been reported. Manic episodes also may be less severe in older patients. The frequency of cycles, however, appears to increase with age. Mortality rates in elderly people with bipolar disorder appear to be markedly higher than in those who do not have bipolar disorder, although the reasons for the excess mortality have not been studied.<sup>21</sup>

#### UNIPOLAR MANIA

Before the CDS, most experts doubted the existence of unipolar mania. Available data involve only a small number of patients who were observed for periods of up to 20 years.<sup>22</sup> Although unipolar mania is rare, the disorder's diagnostic validity was supported recently by Solomon and colleagues, who followed 27 subjects diagnosed with unipolar mania on study entry. None of these patients had a history of major depression before entering the study. Seven patients had no episodes of major depression during the 15- to 20-year follow-up. During a prospective follow-

up, 5 of those 7 patients experienced up to 8 episodes of hypomania lasting a total of 15 weeks.<sup>22</sup>

#### PROGNOSIS

Certain characteristics seem to be associated with a more favorable prognosis. Patients with the least complex medical and psychological make-up—those with fewer comorbidities and those not demonstrating mixed/cycling symptoms, for example—are more likely than others to achieve relatively good control of bipolar disorder. Regular patterns of sleep, nutrition, and social activities are very beneficial, as is involvement in emotionally or financially rewarding activities such as school or employment.

Both sleep deprivation and substance abuse can exacerbate mood disorders, and patients without those problems are more likely to attain better control of their disorder. A patient with clear insight into the nature and severity of his or her illness also has a better chance of maintaining prolonged remission. In contrast, ambivalence about the disease and its treatment can lead to compliance problems and treatment failure.<sup>12</sup>

#### TREATMENT

The recommended approach to the management of bipolar disorder is a combination of medication and psychological counseling, which should include some form of psychotherapy and patient education. Psychotherapy can include cognitive-behavioral therapy, psychoeducational groups, family-focused therapy (FFT), and interpersonal and social rhythm therapy. Central to stabilizing the illness is the establishment of a long-term, consistent, supportive environment between psychiatrist and patient that enables the patient to learn to accept the chronic nature of his or her illness and to integrate its care into daily life.<sup>12</sup>

Family-focused therapy is a behaviorally based program for patients and families that provides patient education and training in communication and problem-solving skills. Family-focused therapy may be an effective adjunct to pharmacotherapy. The efficacy of FFT was demonstrated in a 9-month trial with 101 bipolar disorder patients assigned to either FFT or 2 family education sessions and follow-up crisis management. Patients in the FFT group had fewer relapses, longer delays between relapses, and greater improvements in depressive, but not manic, symptoms. The most dramatic improvements were seen in families with high levels of expressed emotion.<sup>23</sup>

Mood charting is another valuable tool that patients can use to record the course of their illness, the sequence of episodes, the patterns of cycling, and the efficacy of prior treatments. Through mood charting, patients can assess their progress with each type of treatment. Mood charting can provide a reliable assessment of the severity of manic and depressive episodes, help guide the patient and physi-

cian more rapidly toward the right treatment modalities, and may help identify and improve outcomes in treatment-resistant bipolar depression. However, mood charting requires a time investment by patients and, therefore, may be underutilized because of time constraints.<sup>24–26</sup>

Because bipolar disorder is a chronic illness with a high probability of multiple episodes, its effective control requires lifelong therapy. Unfortunately, a high proportion of patients with bipolar disorder frequently do not follow their prescribed treatment regimens. Hospital admissions for acute mania have been significantly associated with noncompliance.<sup>27</sup> It often is difficult to determine the sequence of events leading to a recurrence of bipolar disorder—whether the breakthrough was a result of a patient's stopping medication or whether the illness broke through and became severe enough so that a patient then discontinued his medication. However, 50% to 66% of patients reportedly fail to comply with prescribed medications during the first year of treatment.<sup>15,28</sup> According to a study by Schumann et al., 53.9% of patients with bipolar disorder discontinue their prophylactic medication at some time. Of those patients, 43.2% halt treatment during the first 6 months of therapy.<sup>28</sup> The overall prevalence of nonadherence has been estimated between 20% and 66%.<sup>27</sup>

Many patients do not adhere to their prescribed treatment regimens because of the medications' adverse effects; therefore, initial treatment decisions should consider long-term tolerability of therapies. If a patient is intolerant of the side effects of the mood stabilizer lithium, for example, the physician should be prepared to switch to another mood stabilizer, such as valproate.<sup>29</sup> When adjusting dosage levels to manage side effects, physicians should follow precisely the guidelines in the package insert. In lithium maintenance therapy, medication dosages should be tapered slowly, because a sharp reduction in lithium dosage is linked to a high risk for symptom recurrence.<sup>30</sup>

### ENCOURAGING ADHERENCE

Nonadherence is so prevalent with bipolar disorder patients that clinicians should assume that their patients do not adhere fully to their medication regimens. A number of strategies are available to improve adherence. One strategy is, whenever possible, to select a medication with a rapid onset of action. Rapid onset may help reinforce adherence simply by causing a noticeably rapid abatement of symptoms. To the extent possible, physicians should keep dosage regimens simple, with a minimum number of daily doses. In addition, patients should be given realistic expectations about their medications' adverse effects.

Interventions are available to help control the side effects that lead to nonadherence. For example, atypical antipsychotics, which are used for acute mania and long-term maintenance, often are associated with weight gain, a major reason for nonadherence. A study of patients receiving

atypical antipsychotics showed that they lost at least 10 lb by exercising, consulting with a dietician, following self-directed diet plans, and setting weight-loss goals; exercise was the most critical element in maintaining weight loss.<sup>31</sup>

The involvement of family and friends in patient care can improve treatment outcomes by helping to keep the patient on his or her treatment regimen and improving his or her ability to identify symptoms of an impending relapse. In a study of family members' involvement in patients' care, integrated family and individual therapy that included psychoeducation for patients and their families increased relapse-free time and reduced depressive symptoms during 1 year of treatment compared with patients who received standard community care. Patients in both groups received mood-stabilizing medications.<sup>32</sup>

Patients and their family members or other caregivers should be educated about the disorder and the medications used to treat it. The different types of psychotherapy and family therapy can all improve adherence by reinforcing patient-physician bonds.

*Drug name:* lithium (Lithobid, Eskalith, and others).

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