Bipolar II Disorder: Symptoms, Course, and Response to Treatment

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The authors provide an overview of the diagnosis, course, and treatment of bipolar II disorder, a distinct subtype that is often misdiagnosed as unipolar depression or bipolar I disorder. They discuss research suggesting that underdiagnosis of bipolar II disorder reflects a failure to identify subthreshold expression of mania (hypomania). The course of bipolar II disorder is different from that of bipolar I disorder or unipolar depression, with distinct differences in rates of recovery, clinical features, and number of episodes. The risk of suicide appears to be particularly elevated. High rates of comorbid disorders have been reported, including substance abuse or dependence, anxiety disorders, and personality disorders. Few definitive studies exist on which to base conclusions about the differential efficacy of various treatment strategies in bipolar II disorder and bipolar I disorder. Preliminary studies suggest that the newer anticonvulsants may be of benefit for patients with bipolar II disorder, while other data suggest that there may be a greater role for antidepressant medications. (*Psychiatric Services* 52:358–361, 2001)

The term bipolar II was first used about 30 years ago to differentiate patients with recurrent depressive episodes and hypomania from those with classic bipolar disorder—bipolar I, with both depressive and manic episodes—and from those with recurrent major depression (1). Bipolar II disorder is recognized as a distinct subtype in the *DSM-IV* classification (2). The concept of a trichotomy of mood disorders—bipolar I, bipolar II, and unipolar major depression—has been supported by studies that found distinct patterns of symptoms and familial inheritance for bipolar II disorder (3). Preliminary imaging (4) and biochemical (5) studies that have separately examined subjects with bipolar I and bipolar II disorders have found differences in these groups that further support the view of bipolar II disorder as a discrete diagnostic entity.

This paper provides an overview of the diagnosis, course, and treatment of bipolar II disorder.

Diagnosis of bipolar II disorder

Despite its inclusion as a diagnostic entity in both the *DSM* and *ICD* classification manuals, the diagnosis appears to be underused. Cassano and colleagues (3) have recently argued that the underdiagnosis of bipolar II disorder reflects a failure to identify subthreshold expression of mania. They suggest that likely reasons for this failure are that patients' experience of mild mania may be ego-syntonic, that such experiences may not be associated with patients' subjective distress, and that these experiences are therefore not viewed as requiring intervention by either the patient or the clinician. According to *DSM-IV*, hypomania can be distinguished from mania because patients with hypomania do not experience psychosis, hospitalization, or marked impairment in functioning.

Akiskal and associates (6) have also suggested that hypomania is especially likely to be missed if it occurs in patients who experience atypical depression, despite the fact that patients with bipolar II disorder may be more likely than patients with unipolar depression to have atypical depressions (7,8). Furthermore, it has been repeatedly noted that bipolar II disorder occurs along a spectrum of severity (9,10), which makes establishing the lower limit of severity difficult. Finally, chronic mood instability is frequently diagnosed as personality disorder (11,12) or, in adolescents, as attention-deficit disorder (13).

The failure to recognize bipolar II disorder is not likely to be the result of phenomenological instability in patients. Indeed, bipolar II disorder appears to be diagnostically stable (14,15). In one study only 4 percent of patients with bipolar II disorder developed a manic episode over a two-year follow-up period (16), suggesting that patients do not fluctuate between diagnostic categories. Furthermore, although the cross-sectional reliability of the bipolar II diagnosis has been controversial (17), evidence suggests that diagnosis becomes more reliable when the diagnostician is clinically trained (18–20).

Symptoms and illness course

The results of some studies support the notion that bipolar II disorder is intermediate between unipolar depression and bipolar I disorder with respect to illness course. Research

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has found distinct differences in rates of recovery (14,21), clinical features (22), and number of episodes (23). Other aspects of illness course, such as age at onset, may (19) or may not differentiate patient groups. A recent study of outpatients found no differences in age at onset between 45 patients with bipolar I disorder and 141 with bipolar II disorder (24). We examined data from 138 patients with bipolar I disorder or bipolar II disorder and did not find clear differences in age at onset, symptom levels, or outcome during one to four years of follow-up (unpublished data, MacQueen GM, Young LT, Marriott M, et al, 2000). These findings are consistent with those of Coryell and colleagues (21), who found that patients with bipolar I disorder and those with bipolar II disorder had comparable degrees of psychosocial disability over the course of five years of follow-up, despite differences between the groups in the frequency and severity of manic symptoms.

In the aggregate, available data appear to suggest, not surprisingly, that patients with bipolar II disorder may differ from those with bipolar I disorder in the characteristic that distinguishes them diagnostically—that is, expression of mania. A tendency toward a mild expression of mania or a more severe expression may run in families (5,25); however, the two tendencies may not translate into substantive differences in the expression or frequency of depression or in overall functional outcome associated with the illness.

The number of episodes of depression in bipolar disorder may be a stronger predictor of psychosocial outcome than mania (26). Data supporting this thesis are consistent with the notion that outcome in bipolar I disorder and bipolar II disorder are not substantively different if intensity of mania is the primary variable that distinguishes these subtypes, particularly given data suggesting that patients with bipolar II disorder have more frequent episodes of depression (27,28).

One clinical feature that has consistently appeared to differentiate patients with bipolar II disorder from those with bipolar I disorder or unipolar depression is the risk of suicide, which appears to be elevated in this group (1,29,30). In a recent review, Rihmer and Pestality (31) summarized the results of studies in which lifetime rates of suicide attempts were analyzed separately for patients with bipolar I disorder, bipolar II disorder, and unipolar depression (16,19,25,28,32,33). Risk of suicide was higher for patients with bipolar depression than for those with unipolar depression. The risk was significantly higher for those with bipolar II disorder; when the results of all the studies were combined, 24 percent of patients with bipolar II disorder had experienced suicidal ideation or a suicide attempt, compared with 17 percent of the patients with bipolar I disorder.

The results from individual studies on the relative suicide risk of patients with bipolar I disorder and bipolar II disorder have been somewhat inconsistent. The inconsistency may be partly attributable to differences in the populations studied; two studies included only inpatients (1,33) and another excluded patients with a comorbid substance use or anxiety disorder (19). A high suicide risk for patients with bipolar II disorder was reported by Bulik and associates (34), who found a higher rate of bipolar II disorder among depressed patients who attempted suicide (19 percent) than among depressed patients who did not attempt suicide (9 percent).

Among studies of completed suicides, only two have separately reported the presence of bipolar I disorder, bipolar II disorder, and unipolar depression in the samples. In one study, 46 of 100 consecutive suicide victims had bipolar II disorder, while only one had bipolar I disorder and 53 had unipolar depression. In a Swedish sample of 25 suicide victims, nine had bipolar II disorder, two had bipolar I disorder, and 14 had unipolar depression. Because bipolar II disorder is much less prevalent than unipolar depression in the population, these data suggest a clear elevation in the risk of suicide among patients with bipolar II disorder, but not among those with bipolar I disorder.

One explanation for the high rate of attempted suicide among patients with bipolar II disorder may be that the diagnosis is often missed, and consequently patients are ineffectively treated. Ghaemi and colleagues (35) have shown that bipolar disorder was misdiagnosed in as many as 31 of 85 patients (37 percent) who were seen after a first episode of mania or hypomania. Misdiagnosis frequently leads to prescription of antidepressants in the absence of mood stabilizers, which may exacerbate a rapid-cycling course.

Failure to diagnose bipolar II disorder has been found to be associated with delayed treatment among women. In a study of more than 300 patients, Baldessarini and coauthors (36) reported a delay of 11 years from the onset of illness among women patients to treatment with lithium, compared with 6.9 years among men with bipolar I disorder. Of note in that study is that 53 percent of suicide attempts occurred within five years of the onset of illness, and the risk was substantially lower for patients adequately treated with lithium (36).

Rates of comorbidity are another aspect of illness that appears to differentiate bipolar II disorder from bipolar I disorder. High rates of comorbid disorders have been reported among patients with bipolar II disorder (37,38), including substance abuse or dependence (25,39), anxiety disorders (40), and personality disorders (11,12). Young and associates (41) noted high rates of comorbid anxiety in patients with bipolar disorder, including a subsample of patients with bipolar II disorder; however, it was unclear whether this association was an artifact of referral to a tertiary care center.

Angst and colleagues (42) reported a similarly strong association between bipolar II disorder and anxiety in a community sample. Perugi and associates (43) suggested that understanding the temperamental dysregulation that may underlie bipolar II disorder (6) may provide a framework for understanding why anxiety disorders such as social phobia and obsessive-compulsive disorder may occur at high rates among patients with bipolar II disorder. Like Himmelhoch (44), they suggested that the temperamental inhibition or con-

straint that characterizes social phobia and obsessive-compulsive disorder lies at one end of a continuum that has the disinhibited behavior of bipolar II disorder hypomania at the other end.

Although bipolar II disorder may often be misdiagnosed as personality disorder, a recent study of private-practice patients concluded that bipolar II disorder was easily distinguished from borderline personality disorder with the Structured Clinical Interview for DSM-IV Axis I and II Disorders (45). This finding suggests that the difficulty in distinguishing bipolar II disorder from personality disorder is not attributable to diagnostic overlap but is perhaps more likely to result when past history is not obtained in a structured manner.

Rates of comorbid psychiatric illness may account for much of the reported variance in the course and outcome of bipolar II disorder. Several studies have found that differences between patients with bipolar I disorder and those with bipolar II disorder diminish when comorbidity is excluded (19,40,46,47). In fact, in our own recent studies (cited above), which excluded patients with current substance abuse, the patients with bipolar I disorder were notably similar to those with bipolar II disorder on markers of course and outcome.

Treatment responsiveness

Among the most relevant of clinical questions is whether patients with bipolar II disorder differ from those with bipolar I disorder in responsiveness to treatment. Few studies have examined this issue. One recent study found that patients with bipolar II disorder were equally likely to respond to either prophylactic lithium or carbamazepine during a two-and-a-half-year follow-up period in which hospitalizations, recurrences, subclinical recurrences, concomitant medications, and side effects were assessed (48). A small, nonsignificant trend was noted in favor of carbamazepine. This finding was notable because it contrasts with the findings of another study of patients with bipolar I disorder that showed a better response to lithium than to carbamazepine (49). It is difficult to know whether the absence of observed differences was attributable to the small sample size—28 lithium-treated patients and 29 carbamazepine-treated patients (48).

As newer anticonvulsants are studied for efficacy among patients with bipolar disorder, data are beginning to emerge on the efficacy of these agents for patients with bipolar II disorder. Preliminary data suggest that lamotrigine may be efficacious for patients with bipolar II disorder, especially rapid-cycling patients (50), but data are available on only small samples of patients. Data also suggest that lamotrigine may be efficacious for the depressed phase of bipolar disorder (51). However, in the largest published study to include patients with bipolar II disorder, these patients constituted only 15 percent of the overall sample (11 patients), and their response rates were not reported separately.

The role of antidepressant medication in the treatment of bipolar disorder is controversial (52). The largest study of selective serotonin reuptake inhibitors in the treatment of patients with depression associated with bipolar II disorder examined the efficacy of fluoxetine monotherapy among 89 patients with bipolar II disorder, 89 age- and gender-matched patients with unipolar depression and 661 unmatched patients with unipolar depression (53). Fluoxetine was effective in both short-term treatment of the depressive episode and in relapse prevention for patients in remission over a one-year follow-up period. Among patients with bipolar II disorder, 3.8 percent became manic or hypomanic during the treatment phase, and 2 percent became manic or hypomanic during the relapse-prevention phase. Thus fluoxetine appeared both safe and efficacious in the treatment and prevention of depression in patients with bipolar II disorder.

In another study of fluoxetine monotherapy for 16 patients with bipolar II disorder, 13 patients responded, and only three patients showed evidence of needing to be switched to another medication during an extended treatment period (up to 80 weeks) (54). In a recent review, Thase and Sachs (55) concluded that "the decision to use concurrent mood stabilization during treatment of bipolar II depression must be made on a case by case basis with age of onset, cycle length, past history of rapid cycling, patient gender, and prior frequency and severity of hypomania important considerations."

In summary, few definitive studies are available on which to base conclusions about the differential efficacy of various treatment strategies in bipolar II disorder and bipolar I disorder. Preliminary studies suggest that the newer anticonvulsants may be of benefit for this group, and other data suggest that there may be a greater role for antidepressant medications for patients with bipolar II disorder. Treatment studies that include a discrete group of patients with bipolar II disorder are clearly needed. ♦

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