Diagnosis and Management of Patients With Bipolar II Disorder

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Bipolar II disorder is frequently misdiagnosed as major depressive disorder. In particular, correct diagnosis of bipolar II disorder may be delayed by years due to the predominance of depressive symptoms and the relative subtlety of hypomania, which may manifest only briefly and without elevated mood. The prevalence of bipolar II disorder varies from 0.5% to about 5% depending on the criteria used. Diagnosis can be improved by using mood disorder questionnaires, systematic probing, and prospective mood diary charting. There is a dearth of research into treatment of bipolar disorder. The limited available evidence suggests that lithium and lamotrigine may have efficacy in preventing relapse of mood episodes. Acute bipolar II depression could be treated with a combination of a mood stabilizer plus an antidepressant or pramipexole and in rare cases with antidepressant monotherapy. Hypomania will likely respond to monotherapy with antimanic agents. Adjunctive psychosocial treatments may provide additional benefit in patients with bipolar II disorder.

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Although bipolar II disorder was first described by Dunner and colleagues in 1976,[1] it took nearly 2 decades before it was incorporated into the DSM-IV[2] in 1994. Like those with major depressive disorder (MDD, also called unipolar depression), patients with bipolar II disorder must have a current or past major depressive episode, but the essential feature that defines and distinguishes bipolar II disorder from unipolar depression is a current or past hypomanic episode. There is, however, controversy about the definitions of hypomania and bipolar II disorder. Therefore, it is not surprising that prevalence and rates of misdiagnosis vary between studies. This article will briefly review these data and provide some practical tips for the diagnosis and management of bipolar II disorder in clinical practice.

EPIDEMIOLOGY

The U.S. Epidemiologic Catchment Area database study[3] (N = 18,252) reported a prevalence of 0.5% for hypomania. Many researchers[4–6] have since argued that these figures represent a gross underestimation of the true prevalence of bipolar II disorder. In a 2003 reexamination of the Epidemiologic Catchment Area database, Judd and Akiskal[7] found the prevalence of bipolar spectrum disorders in the general population to be 6.4%. "Soft spectrum" bipolarity, referring to subsyndromal but dysfunctional levels of illness, accounted for 5.1% of these cases. Full-diagnosis bipolar I disorder accounted for 0.8% and full-diagnosis bipolar II disorder for 0.5% of the total. This reanalysis showed that patients with subsyndromal manic symptoms had significantly higher health service use, need for public assistance, and even suicidal behavior compared with those with no mental disorder.

Angst and colleagues,[8] using a modified definition of bipolar II disorder, reported that 5.3% of their cohort met "hard criteria" (hypomania with consequences) for bipolar II while another 5.7% met "soft criteria" (hypomanic symptoms without consequences) for the disorder, giving a total prevalence of 11%. Their data showed that the 2 bipolar II subgroups differed significantly from those with MDD but not from each other on a number of clinical validators, thus suggesting that the 2 groups of bipolar patients should be considered under a single category.

Researchers, including Angst et al.[8] and Judd et al.,[9] have also found in long-term studies that patients who have hypomanic symptoms for a short duration (e.g., 1–3 or 2–6 days) do not differ from those who have symptoms for a longer duration (e.g., ≥ 4 or ≥ 7 days) on a number of demographic and clinical features including age at onset, family history of mania or depression, symptom status over a longer term, and chronicity. These data are consistent with a recent recommendation made by an International Consensus Group[10] that suggested a 2-day symptomatic period for a diagnosis of hypomania. The apparent lack of distinction between the disorder with long and that with short hypomanic episodes is important because crite-

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Table 1. DSM-IV Criteria for a Hypomanic Episode[a]

The individual experiences a distinct period of persistently elevated, expansive, or irritable mood, lasting at least 4 days, that is clearly different from his or her usual nondepressed mood
The mood disturbance is accompanied by 3 of the following (4 if the mood is only irritable) to a significant degree:
Inflated self-esteem or grandiosity
Decreased need for sleep
Unusual or pressured talkativeness
Flight of ideas or the feeling that the mind is racing
Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli)
Increased goal-directed activity or psychomotor agitation
Excessive involvement in pleasurable activities (eg, buying sprees, sexual activity) without regard for unpleasant consequences
The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic
The disturbance in mood and the change in functioning are observable by others
The episode is not psychotic and not severe enough to cause marked impairment or to necessitate hospitalization
The symptoms are not due to the direct physiological effects of a substance or a general medical condition

[a]Adapted with permission from the American Psychiatric Association.[2]

ria from the DSM-IV for a hypomanic episode stipulate a duration of at least 4 days (Table 1).

For reasons like these, some experts have suggested that certain changes to the DSM-IV criteria for hypomania would better reflect the presentation and the prevalence of bipolar II and other bipolar spectrum disorders. One such change would be to remove duration criteria for hypomania when 3 or more hypomanic symptoms are present, which would emphasize change in functioning over duration of change. Further, including hyperactivity (i.e., increased goal-directed activity and/or psychomotor agitation) in the primary criteria would more clearly indicate that hypomania is not necessarily experienced as elevated or euphoric mood,[8] but may feel like a period of heightened urgency or productivity.

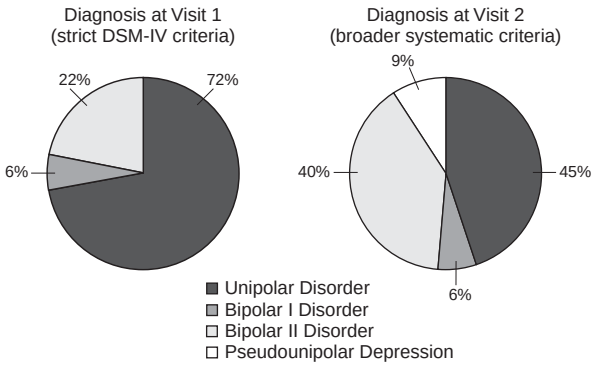
DIAGNOSIS

Misdiagnosis or Delayed Diagnosis

Depression is the predominant mood disturbance in bipolar II disorder, and individuals with bipolar symptomatology tend to seek help when in a depressed, rather than hypomanic, phase. It is therefore not uncommon for patients with bipolar II disorder to be misdiagnosed with MDD. This not only delays proper treatment but may expose patients to risks associated with inappropriate treatment, such as mood switching, cycling, mixed states, and possible treatment resistance.[11]

In a long-term follow-up of symptom status ratings of bipolar II patients over a number of years, Judd et al.[9] found that the frequency of depressive symptoms in bipolar II disorder exceeded the frequency of hypomanic symptoms by 39 times. Even when present, hypomania may be relatively subtle, further contributing to a delayed

Figure 1. Underrecognition of Hypomania in Patients With Major Depressive Episodes (N = 250)[a]



[a]Data from Hantouche et al.[11]

diagnosis. In the French multicenter study EPIDEP, reported by Hantouche et al.,[11] a systematic and specific search for hypomanic episodes among patients diagnosed with MDD revealed that many of these patients better fit the diagnosis of a bipolar spectrum disorder (Figure 1). Using a sample of 600 patients interviewed over 20 years, the Zurich study[8] found that diagnoses of MDD dropped from 21.3% to 17.1% when DSM-IV criteria for bipolar II disorder were applied and to 11.4% when "soft" criteria for bipolar II disorder were applied. In other studies, 27%[11] to 56%[12] of patients who were diagnosed with a bipolar disorder had been previously misdiagnosed with MDD. Such misdiagnosed patients did not necessarily lack a clear-cut history of bipolarity; 37% of depressed patients who had experienced a manic or hypomanic episode prior to their first visit to a health care provider were still diagnosed as having MDD.[13] In this population, 11.6 years elapsed between the first time the patient sought professional help and correct diagnosis of bipolar II disorder, about twice the time between presentation and correct diagnosis of bipolar I.

A preliminary report[14] on the first patients in the ongoing Canadian consortium on bipolar disorder prospective study of clinical characteristics and treatment outcome revealed an average gap of 14 years between onset of first depressive symptoms and correct diagnosis of bipolar I disorder, while the delay was 23 years for those with bipolar II disorder. Of note is the finding that patients with bipolar II disorder had an average of 6 depressive episodes in the previous 2 years, compared with 2 depressive episodes in the previous 2 years for patients with bipolar I.

Practical Tips for Diagnosis of Bipolar II Disorder

About 60% to 70% of patients with bipolar disorder will have a depressive episode as the first mood episode[15,16] and at some later stage may go on to develop hypomania or mania and thus meet the diagnostic criteria for a bipolar I or II disorder. Again, many patients with

bipolar II disorder seek help during a depressive rather than a hypomanic phase. Therefore, clinicians should be alert to bipolarity in any patient presenting with a depressive episode.

Correct and prompt diagnosis of bipolar II disorder can be facilitated by a number of steps initiated by the clinician. Recent research has shown that a mood disorder questionnaire improves detection of bipolar II disorder.[17] In clinical settings, patients could be asked to complete a mood disorder questionnaire while waiting to see the physician, and those who respond positively to 1 or more items could be probed in greater detail to elicit a previous history of hypomanic episodes. Indeed, studies[18,19] indicate that systematic probing for a previous history of hypomanic/manic symptoms increases the detection rate of bipolar II disorder. The symptoms of mania and hypomania should be explained to the patient. When possible and with patients' consent, family members or friends should be interviewed. Practical tips for recognizing past episodes of hypomania include taking a detailed history to detect indicators such as racing thoughts, periods of overactivity and decreased need for sleep, risk-taking, and out-of-character behavior followed by shame or regret once the episode has ended. Hypomanic episodes often precede or immediately follow depressive episodes; therefore, careful attention should be paid to ascertaining behavioral changes during those periods. Younger age at onset, a family history of bipolarity, and the presence of reverse vegetative symptoms such as hypersomnia and hyperphagia during depression indicate a greater likelihood that the patient has a bipolar spectrum disorder.[20,21] In cases where the index of suspicion is high, prospective mood ratings using a customized mood diary and assessing/interviewing the patient on days when mood and behavioral symptoms rate in the hypomanic range may help confirm a diagnosis of bipolar II disorder.

TREATMENT

To date, no large, randomized, double-blind, placebo-controlled trials have enrolled patients with only bipolar II disorder, so there is little research evidence to guide clinicians in providing optimal treatment for this common disorder. Most of the available data come from open-label studies, post hoc analyses, or research that combined populations of patients with bipolar I and bipolar II disorders. These data have been critically reviewed in a previous publication.[22] Below is a brief overview of clinical management of various phases of bipolar II disorder.

Management of Hypomania

Lithium, valproate, carbamazepine, and the atypical antipsychotics (aripiprazole, risperidone, olanzapine, quetiapine, and ziprasidone) have proven efficacy in double-blind placebo-controlled trials for the treatment of acute mania[23,24] without a propensity to switch patients into depression. Although no double-blind placebo-controlled trials have specifically examined the efficacy of any of these agents for the treatment of hypomania in bipolar II disorder, clinical experience indicates that all of the above-listed agents are effective in treating hypomania, both as monotherapy and in combination with one another. This statement is consistent with the findings of an open-label study[25] that reported the efficacy of risperidone as monotherapy or in combination with lithium or valproate in treating hypomanic symptoms in patients with bipolar II disorder.

In clinical practice, patients usually continue with the treatment that worked in the acute phase. Hence, when choosing treatment for acute hypomania, it may be more appropriate to choose those treatments that have some evidence of efficacy in maintenance treatment. Since lithium is the only medication with evidence of efficacy in maintenance treatment of bipolar II disorder (see Maintenance Treatment section), lithium could be considered the first-line treatment for patients who are taking no medication at the time of presentation with hypomania. If a patient is already taking lithium or another antimanic agent, then that medication should be optimized before considering other options. Although there are no data on such, a switch to another antimanic agent or a combination of a mood stabilizer and an atypical antipsychotic would be appropriate if the patient with hypomania does not respond to monotherapy with an initial antimanic agent.

Treatment of Acute Bipolar Depression

Because depressive symptoms occur far more frequently than hypomanic symptoms, the greatest challenge in the management of bipolar II disorder is treating acute bipolar symptoms and preventing relapse of depressive symptoms without destabilizing the patient's mood and inducing a switch into hypomania or mania. There is controversy about whether patients with bipolar II are at lower risk of antidepressant-induced switch than those with bipolar I disorder.[26,27] In the absence of double-blind, placebo-controlled data on antidepressants in bipolar II disorder, this question of safety remains unanswered. There is likewise a dearth of studies on the efficacy of antidepressant monotherapy in bipolar II depression. However, Himmelhoch and colleagues,[28] in a randomized double-blind trial, reported that tranylcypromine was more effective than imipramine in treating anergic bipolar I and bipolar II depression. In that study, 21% of tranylcypromine patients switched to hypomania/mania in comparison to 25% of imipramine patients during the 6-week acute phase. Amsterdam and colleagues[29] reported that fluoxetine was as effective in bipolar II patients as in matched and unmatched unipolar depressed patients in a 12-week open-label phase of a double-blind relapse-prevention study. Manic switch occurred in 3.8% of bipolar II pa-

tients, 0.3% of unmatched unipolar patients, and none of the matched unipolar patients. In another recent double-blind relapse-prevention study[30] of bipolar II disorder, open-label fluoxetine for 8 weeks was reported to be effective, with 38% of bipolar II depressed patients meeting criteria for response. Hypomanic switch occurred in 7.3% of patients in this study. Venlafaxine monotherapy was found to be as effective in bipolar II patients as it was in unipolar depressed patients in 2 studies,[31,32] with no significant switching to hypomania. However, in a randomized controlled study[33] of venlafaxine versus paroxetine add-on to mood stabilizers in bipolar I and bipolar II depressed patients, although the efficacy was similar, switch to hypomania/mania occurred in 13% of adjunctive venlafaxine patients but only 3% of adjunctive paroxetine patients.

A placebo-controlled crossover study[34] that included 17 bipolar I and 16 bipolar II depressed patients reported a 64% response rate to lithium. An open-label trial[35] concluded that 63% of bipolar II depressed patients examined responded to divalproex but also noted that psychotropic medication–naive patients were more than twice as likely to respond to divalproex than those who were only mood stabilizer-naive. Lamotrigine was found effective in treatment-refractory bipolar I and bipolar II depressed patients in an open-label study, but results were not reported separately for the subgroups.[36]

In a double-blind trial,[37] pramipexole add-on to lithium or valproate led to improvement in 60% of bipolar II depressed patients (versus 9% of those who received placebo add-on). Quetiapine monotherapy was effective in bipolar I and bipolar II depressed patients in a double-blind placebo-controlled trial,[38] but subgroup analysis revealed that the differences between quetiapine and placebo were not statistically significant for the patients with bipolar II.

Given the scarcity of controlled evidence, how should clinicians manage patients with acute bipolar II depression? Is monotherapy with an antidepressant appropriate, or should patients be treated with lithium, valproate, or lamotrigine monotherapy? Given the continuing controversy about inducing a switch to mania or hypomania with antidepressants and an absence of strong placebo-controlled data, the safest option may be to treat bipolar II depressed patients with mood-stabilizer monotherapy or an antidepressant in combination with lithium or valproate. Since lamotrigine appears to have efficacy in prophylaxis of bipolar depression, monotherapy with lamotrigine may be appropriate for some patients. In non–rapid-cycling patients with rarely occurring hypomanias, judicious use of antidepressant monotherapy may be considered. Antidepressant monotherapy is not recommended in patients with rapid-cycling bipolar II disorder.

Maintenance Treatment of Bipolar II Disorder

Lithium has long been used as a mood stabilizer and is a first-line recommendation in treatment algorithms. Early double-blind trials that included patients with bipolar II disorder showed that lithium reduced the frequency of depressive episodes.[39,40] In data[41,42] drawn from populations with bipolar I and II disorders, lithium monotherapy was shown to reduce hospitalizations by 98%, to reduce time spent ill by 80%, and to reduce mood episodes by 68% in bipolar II patients. Further, lithium therapy remained effective for up to 30 years.[42] In an open randomized study,[43] there was a nonsignificant trend toward greater efficacy for carbamazepine than for lithium in patients with bipolar II disorder and bipolar disorder not otherwise specified.

The efficacy of lamotrigine monotherapy in acute bipolar II depression remains unclear, but in a study by Calabrese and colleagues[44] involving patients with rapid-cycling bipolar I and II disorders, analysis of survival time in study (i.e., time to discontinuation for any reason) showed superiority of lamotrigine over placebo, particularly in bipolar II patients. Among patients with rapid-cycling bipolar II disorder, lamotrigine appeared to have prophylactic efficacy for both hypomanic and depressive episodes. More bipolar II patients in the lamotrigine group (46%) than in the placebo group (18%) remained stable over 6 months. However, according to the primary outcome measure of time to additional pharmacotherapy for emerging symptoms, there was a trend—but no statistically significant difference—favoring lamotrigine over placebo among rapid-cycling bipolar II patients. In the double-blind relapse-prevention study,[29] fluoxetine had similar efficacy in bipolar II and in matched as well as unmatched unipolar depressed patients over 26, 50, and 62 weeks. At the close of a 6-month open-label study[25] of risperidone in the treatment of bipolar II hypomania, 60% of patients were reported asymptomatic while 78% were reported significantly improved.

Overall, lithium and lamotrigine appear to have the best documented efficacy in prophylaxis of bipolar II disorder and should be used as first-line agents. If a patient has breakthrough episodes while taking these agents, other options could be considered.

Psychosocial Treatments

Adjunctive nonpharmacologic (psychosocial) therapies for bipolar disorders are discussed in detail in this supplement.[45] Given the preponderance of depressive symptoms and the unresolved question of antidepressant risk, interventions like psychoeducation may be particularly useful for patients with bipolar II disorder. Psychosocial treatments may prove especially helpful in equipping a patient to cope effectively with residual or recurring symptoms of depression, and intensive clinical management can itself be a form of psychosocial support.

Drug names: aripiprazole (Abilify), carbamazepine (Epitol, Tegretol, and others), divalproex (Depakote), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), paroxe-

tine (Paxil and others), pramipexole (Mirapex), quetiapine (Seroquel), risperidone (Risperdal), tranylcypromine (Parnate), venlafaxine (Effexor), ziprasidone (Geodon).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, aripiprazole is not approved by the U.S. Food and Drug Administration for the treatment of hypomania or mania; carbamazepine is not approved for the treatment of bipolar disorder; divalproex is not approved for the treatment of acute depression or the prophylaxis of bipolar disorder; fluoxetine, imipramine, lamotrigine, lithium, paroxetine, pramipexole, quetiapine, tranylcypromine, and venlafaxine are not approved for the treatment of bipolar II depression; and olanzapine, risperidone, and ziprasidone are not approved for the treatment of hypomania.

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