Evidence-Based Long-Term Treatment of Bipolar II Disorder

Trisha Suppes, M.D., Ph.D., and Ellen B. Dennehy, Ph.D.

Bipolar II disorder is a distinct, lifelong mental illness that affects at least 1.5 million people in the United States, is associated with a high incidence of comorbidity, and ends with completed suicide in 10% to 15% of diagnosed individuals. Bipolar II disorder is characterized by at least 1 major depressive episode with 1 or more hypomanic episodes, as opposed to manic or mixed episodes. While it is expected that there may be similarities in approaches to managing patients with bipolar I and bipolar II disorders, data suggest differential patient responses to pharmacologic treatments, supporting the need for research specifically in patients with bipolar II disorder. Despite the prevalence and severity of the disorder, a well-developed scientific database informing long-term treatment choices for bipolar II disorder as an illness differing from bipolar I disorder and major depressive disorder is virtually absent. A review of the limited and sometimes contradictory information stresses that more research is needed into prophylactic and maintenance treatment of bipolar II disorder.

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Conservative estimates place the prevalence of bipolar II disorder at 0.5%, or 1.5 million individuals, in the United States.[1] In Europe, where broader criteria require fewer days of hypomania for diagnosis of bipolar II disorder, prevalence estimates for all bipolar spectrum illnesses including bipolar I range from 3% to 6%.[2] Researchers have highlighted the problems of underdiagnosis and misdiagnosis (frequently as unipolar depression) of bipolar II disorder due to the preponderance of depressive symptoms and the relative subtlety of hypomania.[3] Hypomanic episodes are commonly underreported by patients in the clinical setting, perhaps due to lack of insight into their symptoms. Further, the duration (at least 4 days) of a hypomanic episode required by the DSM-IV for a diagnosis of bipolar II disorder exceeds the actual duration of most hypomanic episodes.[3] Ghaemi et al.[4] reported that 40% of a group of patients with bipolar disorder had been previously misdiagnosed with major depression. Given these data, it is possible that bipolar II disorder may occur in 1% or more of the population.

From the Department of Psychiatry, Bipolar Disorder Clinic and Research Program, University of Texas Southwestern Medical Center, Dallas.

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Corresponding author and reprints: Trisha Suppes, M.D., Ph.D., Department of Psychiatry, Bipolar Disorder Clinic and Research Program, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9070 (e-mail: trisha.suppes@utsouthwestern.edu).

Prior to 1994 and the publication of the DSM-IV, bipolar II disorder was not considered a discrete disorder. Instead, this form of illness occupied a residual category termed *atypical bipolar disorder*.[5] More recently, the weight of studies[6–9] has confirmed the existence of bipolar II disorder as distinct from both bipolar I disorder and major depressive disorder. This distinction is made on the strength of family history and inheritance patterns, differential course of illness, and differential response to medications in pharmacologic studies. Further, the National Institute of Mental Health Collaborative Depression study has demonstrated the stability of bipolar I and bipolar II diagnoses over a 10-year follow-up period.[10,11] A diagnosis of bipolar II disorder requires the presence or history of at least 1 depressive episode and the presence or history of at least 1 hypomanic episode, as opposed to a manic or mixed episode (Table 1).[12]

COURSE OF ILLNESS, SUICIDALITY, AND COMORBIDITY

Some evidence shows that patients with bipolar II disorder have more frequent mood episodes, especially depressive episodes, than patients with bipolar I disorder.[13] In a study by Tondo et al.,[14] a sample of 317 patients, of whom 129 had bipolar II disorder, were followed in naturalistic treatment for a mean of 8.38 years before and 6.35 years during lithium maintenance treatment. Patients with bipolar II disorder had significantly higher episode frequency (cycling), averaging 2.30 episodes per year versus 1.65 episodes per year among patients with bipolar I disorder. Additionally, patients with bipolar II disorder had

Table 1. DSM-IV Diagnostic Criteria for Bipolar II Disorder[a]

A.	Presence or history of at least 1 major depressive episode
B.	Presence or history of at least 1 hypomanic episode
C.	No presence or history of manic or mixed episodes
D.	A and B not better accounted for by another disorder
E.	Symptoms cause marked distress or functional impairment

[a]Adapted from the DSM-IV.[12]

2.4 times more episodes of depression per year and spent 1.7-fold more time experiencing depressive episodes than did patients with bipolar I disorder. This suggests that patients with bipolar II disorder may exhibit rapid cycling more often than patients with bipolar I disorder. However, other studies[15,16] have found the degree of psychosocial disability to be similar and equally severe in both bipolar I and bipolar II disorders.

The DSM-IV describes the risk of suicide as equally high across the bipolar spectrum, with completed suicide occurring in 10% to 15% of individuals. Vieta et al.[17] found equal degrees of suicidality between persons with bipolar I disorder and those with bipolar II disorder. However, a meta-analysis by Rihmer and Pestality,[18] which determined that suicide risk is higher among individuals with bipolar disorder than among those with unipolar depression, found that the risk of suicide is higher for individuals with bipolar II than for those with bipolar I disorder. There are also case series on completed suicides that found a greater number of suicides in patients with bipolar II, as opposed to bipolar I, disorder.[15]

Increased suicide risk has been associated with higher rates of comorbidity. Other psychiatric disorders, especially substance abuse or dependence and anxiety, are frequently comorbid with bipolar II disorder.[17] A recent epidemiological review showed that bipolar spectrum disorders were twice as likely to be accompanied by another Axis I lifetime disorder than to exist alone.[19] Comorbidity has been associated with earlier age at onset, accelerated cycling, and increased episode severity over time.[19] These clinical features have themselves been associated with more severe illness and poorer prognosis in bipolar disorder.[20]

LONG-TERM TREATMENT OF BIPOLAR II DISORDER

Treatment of bipolar II disorder poses a number of challenges, including the risk of initial misdiagnosis, frequently as major depressive disorder. Currently, treatment guidelines for bipolar disorder, including the American Psychiatric Association guidelines,[21] European Consensus Conference,[22] and the Texas Implementation of Medication Algorithms (in earlier phases known as the Texas Medication Algorithm Project),[20,23] do not include recommendations specific to the treatment of bipolar II disorder. However, bipolar II disorder is a distinct illness, and the frequency and prominence of its depressive aspects may warrant the use of long-term treatments differing from those used to manage bipolar I disorder. Existing research fails to address fundamental questions regarding treatment for bipolar II, such as whether or not patients with bipolar II require ongoing use of mood-stabilizing medications. Additionally, the specification of rapid cycling in bipolar II disorder may represent a clinical subtype requiring specific and differential pharmacologic treatment. At present, there is insufficient research to guide clinicians in their choice of pharmacotherapy for patients with bipolar II disorder. Only a few well-developed studies exist to inform the long-term treatment of these individuals.

Lithium

Lithium has long been the standard, although it is no longer considered the only[24] maintenance treatment for bipolar disorder. Studies suggest that there may be a different prophylactic response to lithium in patients with bipolar II disorder compared with those with bipolar I (Table 2).

In an open, uncontrolled, prospective clinical evaluation of 129 patients with bipolar II disorder receiving lithium maintenance therapy, Tondo et al.[14] found a significant decrease in both cycling and time spent ill. Patients were seen 4 to 12 times per year and were followed for a mean of 6.35 years. During lithium maintenance treatment, short-term use of adjunctive medication was 1.8 times more likely for patients with bipolar I disorder than for patients with bipolar II disorder. Survival analyses indicated that mean time to recurrence of symptoms for patients with bipolar I disorder was 17 months compared with 100 months for patients with bipolar II disorder. The authors concluded that patients with bipolar II disorder experienced greater overall therapeutic benefit from lithium maintenance treatment than did those with bipolar I disorder.

A number of double-blind controlled studies support the prophylactic efficacy of lithium specifically in bipolar II disorder. Dunner et al.[25] assessed the prophylactic efficacy of lithium versus placebo for prevention of mood symptoms in a 33-month double-blind trial with 26 subjects with bipolar disorder. Subjects in the lithium group were significantly less likely to experience a depressive episode than subjects in the placebo group. Subjects receiving lithium also experienced fewer episodes of hypomania than did subjects receiving placebo, but this finding was not statistically significant.

Fieve et al.[26] included 18 patients with bipolar II disorder in a double-blind study of the prophylactic efficacy of lithium versus placebo. All patients were asymptomatic at study entry and were seen every 4 weeks for 4 years. The study design used an intent-to-treat analysis, which allowed for the treatment of emerging symptoms. Among the patients with bipolar II disorder, those receiving lithium experienced almost 50% fewer depressive episodes than did those receiving placebo. Mean duration of depressive episodes was 57 days for patients in the lithium group and

Table 2. Lithium Studies in the Long-Term Treatment of Bipolar II Disorder

Study	N	Duration, Design	Study Drugs	Results
Tondo et al[14]	129	Mean 6.35 y	Lithium vs placebo	Lithium effect for bipolar II disorder > bipolar I
Dunner et al[25]	26	33 mo	Lithium vs placebo	Lithium effect > placebo for depression; nonsignificant effects for mania
Fieve et al[26]	18	4 y	Lithium vs placebo	Lithium effect > placebo for prevention of depression
Kane et al[27]	22	2 y	Lithium, imipramine, Lithium + imipramine	Lithium effect nonsignificant for bipolar II disorder
Greil and Kleindienst[29]	57	2.5 y	Lithium vs carbamazepine	No difference

194 days for patients in the placebo group. While these results are not as robust as those observed in the bipolar I sample, they suggest that lithium may be an effective prophylaxis for depressive symptoms in patients with bipolar II disorder.

Lithium has also been tested in combination with and in comparison with other pharmacotherapeutic agents. Kane et al.[27] studied patients with recurrent major depressive disorder (N = 27) and bipolar II disorder (N = 22) in remission. Patients were randomly assigned to receive lithium, the antidepressant imipramine, lithium plus imipramine, or placebo in a double-blind manner. Among the patients with bipolar II disorder, maintenance treatment with lithium alone was most effective, with these patients staying in treatment a mean of 19.0 months before relapse, self-initiated withdrawal, or termination of the study. Patients assigned to imipramine plus lithium stayed in treatment a mean of 16.0 months, whereas patients receiving imipramine or placebo stayed a mean of 5.6 months and a mean of 5.0 months, respectively. Lithium was found to prevent relapse of any type in both illnesses, but no such effect was found for imipramine in either illness. The role of antidepressants in treating bipolar disorder is controversial in general. Whether the most appropriate treatment options for patients with bipolar II disorder include antidepressant monotherapy is unclear. It is possible that an antidepressant used in the absence of a mood stabilizer may destabilize a patient with bipolar disorder, inducing mania, hypomania, or cycle acceleration.[28]

Anticonvulsants

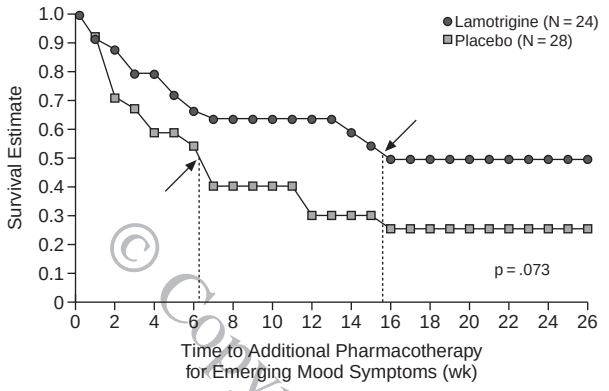
Anticonvulsants have been compared with lithium and placebo in some prophylactic studies, but these studies are few and indicate the need for further research. A group of 57 subjects, diagnosed with bipolar II disorder or bipolar disorder not otherwise specified, participated in a randomized clinical trial comparing the prophylactic efficacy of lithium versus the anticonvulsant carbamazepine.[29] Subjects were randomly assigned to either agent and followed for up to 2.5 years. Results indicated that there were no significant differences between the 2 drugs in prophylactic efficacy for this population.

To date, no randomized or controlled studies of the anticonvulsant divalproex in the long-term treatment of bipolar II disorder have been completed. However, divalproex has been assessed in the maintenance treatment of bipolar I disorder[30] and may prove to be one of the top choices for the management of rapid-cycling bipolar II disorder. A recent open case series[31] assessed the efficacy of once-daily divalproex for 19 patients with bipolar II disorder and depressive symptoms. Twelve of the sample were classified as responders, demonstrating at least a 50% decrease in Hamilton Rating Scale for Depression (HAM-D) scores. It should be noted that baseline HAM-D scores were significantly lower in responders (mean score = 18.6) than in nonresponders (mean score = 27.0). Medication-naive patients (N = 11) demonstrated greater improvement with once-daily divalproex than patients (N = 8) who had never been treated with mood stabilizers.

It has been suggested that rapid-cycling bipolar disorder accounts for a substantial proportion of bipolar disorder that is resistant to lithium treatment. Calabrese and Delucchi[32] assessed the efficacy of divalproex for the treatment of rapid-cycling bipolar disorder over 7.8 months in a prospective, open trial. The sample of 55 individuals diagnosed with bipolar disorder by DSM-III-R criteria included 30 subjects with bipolar II disorder and a history of rapid cycling. In the acute setting, more patients with rapid-cycling bipolar II disorder responded (N = 28) to divalproex than did patients with rapid-cycling bipolar I disorder (N = 21). Twenty-three responders in the bipolar II group (versus 14 responders in the bipolar I group) exhibited a marked response. While encouraging, the response to divalproex was not equally strong across the course of illness. Divalproex appeared to have minimal-to-moderate antidepressant efficacy. These studies, however, were limited by an open and uncontrolled design. While they suggest a potential role for divalproex in the long-term treatment of bipolar II disorder, current data more substantially support the efficacy of lithium and lamotrigine as maintenance agents.

Lamotrigine is an anticonvulsant drug of the phenyltriazine class that has been shown to be effective in the treatment of partial complex seizures. Lamotrigine has a documented antidepressant effect in patients with bipolar I disorder,[28] and a growing body of research indicates that it may have a role in the treatment of patients with the prominent depressive symptoms common in bipolar II disorder. Lamotrigine was compared with placebo in a long-term study of patients with rapid-cycling bipolar disorder (Figure 1). In the initial phase, patients were entered in any mood state, and open lamotrigine was titrated

Figure 1. Lamotrigine vs. Placebo in Rapid-Cycling Bipolar II Patients[a,b]



[a]Adapted with permission from Calabrese et al.[33]
[b]Arrows indicate median time.

gradually. After 4 to 8 weeks of exposure to lamotrigine, other medications were tapered. If patients tolerated the taper and met predefined criteria for "wellness," they were randomly assigned to double-blind lamotrigine treatment or placebo and followed for 26 weeks, regardless of emergent mood symptoms or addition of other medications. Of the initial 324 subjects, 180 participated in the second phase. The primary efficacy measure was time to addition of medication for a mood episode or symptoms, and by this measure there were no significant differences between treatment groups. However, for a subgroup of 52 patients with bipolar II disorder, median time to additional pharmacotherapy was significantly greater for those receiving lamotrigine than for those receiving placebo (17 weeks vs. 7 weeks).

The role of antidepressant medication in the treatment of bipolar disorder is controversial in general. What the appropriate treatment is for patients with bipolar II disorder and whether it should include antidepressant monotherapy or continuation treatment is not well understood. Several acute trials have suggested that monotherapy with fluoxetine,[34,35] tranylcypromine,[36] or venlafaxine[37] is efficacious in the treatment of depression in patients with bipolar II disorder. However, these limited acute trials suggest an increased rate of reported "agitation" as well as clear switch in a percentage of these patients, and concerns linger regarding the potential of an antidepressant to destabilize a patient with bipolar II disorder in the absence of a mood stabilizer.

Haykal and Akiskal[38] completed a long-term study of antidepressants in patients with bipolar II disorder. This small case series (N = 6) of bupropion added to lithium and/or levothyroxine for patients with rapid-cycling bipolar II disorder suggests that use of bupropion may prolong remission of depression without increasing rate of switch in this population.

CONCLUSION

Although conservative prevalence estimates place the number of individuals with bipolar II disorder at 1.5 million in the United States alone, bipolar II disorder is underrecognized as a distinct mental illness requiring its own body of research data. Bipolar II disorder carries with it a high rate of comorbidity and a grave risk of suicide, but long-term treatment is complicated by misdiagnosis, lack of established treatment guidelines, and, above all, a paucity of pharmacologic data. More research is needed on pharmacotherapeutic options including antidepressants, divalproex, and anticonvulsants such as lamotrigine in the long-term treatment of bipolar II disorder, as well as on particular features of bipolar II disorder such as depressive symptomatology and rapid cycling.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), divalproex (Depakote), fluoxetine (Prozac and others), lamotrigine (Lamictal), levothyroxine (Synthroid, Levoxyl, and others) tranylcypromine (Parnate), venlafaxine (Effexor).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, bupropion, carbamazepine, divalproex, fluoxetine, imipramine, lamotrigine, levothyroxine, tranylcypromine, and venlafaxine are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

REFERENCES

1. Regier DA, Farmer ME, Rae DS, et al. One-month prevalence of mental disorders in the United States and sociodemographic characteristics: the Epidemiologic Catchment Area study. Acta Psychiatr Scand 1993;88: 35–47
2. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 1998;50:143–151
3. Bowden CL. Strategies to reduce misdiagnosis of bipolar depression. Psychiatr Serv 2001;52:51–55
4. Ghaemi SN, Sachs GS, Chiou AM, et al. Is bipolar disorder still underdiagnosed? are antidepressants overutilized? J Affect Disord 1999;52:135–144
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition. Washington, DC: American Psychiatric Association; 1980
6. Dunner DL. A review of the diagnostic status of "bipolar II" for the DSM-IV work group on mood disorders. Depression 1993;1:2–10
7. Endicott J, Nee J, Andreasen N, et al. Bipolar II: combine or keep separate? J Affect Disord 1985;8:17–28
8. Fieve RR, Go R, Dunner DL, et al. Search for biological/genetic markers in a long-term epidemiological and morbid risk study of affective disorders. J Psychiatr Res 1984;18:425–445
9. Gershon ES, Hamovit J, Guroff J, et al. A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. Arch Gen Psychiatry 1982;39:1157–1167
10. Coryell W, Endicott J, Maser J, et al. Long-term stability of polarity distinctions in the affective disorders. Am J Psychiatry 1995;152:385–390
11. Akiskal HS, Maser JD, Zeller PJ, et al. Switching from "unipolar" to bipolar II: an 11-year prospective study of clinical and temperamental predictors in 559 patients. Arch Gen Psychiatry 1995;52:114–123
12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
13. Vieta E, Gasto E, Otero A, et al. Differential features between bipolar I and bipolar II disorder. Compr Psychiatry 1997;38:98–101
14. Tondo L, Baldessarini RJ, Hennen J, et al. Lithium maintenance treatment of depression and mania in bipolar I and bipolar II disorders. Am J Psychiatry 1998;155:638–645

15. MacQueen GM, Young LT. Bipolar II disorder: symptoms, course, and response to treatment. Psychiatr Serv 2001;52:358–361
16. Coryell W, Keller M, Endicott J, et al. Bipolar II illness: course and outcome over a 5-year period. Psychol Med 1989;19:129–141
17. Vieta E, Colom F, Martinez-Aran A, et al. Bipolar II disorder and comorbidity. Compr Psychiatry 2000;41:339–343
18. Rihmer Z, Pestality P. Bipolar II disorder and suicidal behavior. Psychiatr Clin North Am 1999;22:667–673
19. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am J Psychiatry 2001;158:420–426
20. Suppes T, Swann AC, Dennehy EB, et al. Texas Medication Algorithm Project: development and feasibility testing of a treatment algorithm for patients with bipolar disorder. J Clin Psychiatry 2001;62:439–447
21. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder. Am J Psychiatry 1994;151:1–36
22. Goodwin GM, Bourgeois ML, Conti L, et al. Treatment of bipolar depressive mood disorders: algorithms for pharmacotherapy. Int J Psychiatr Clin Pract 1997;1:S9–S12
23. Suppes T, Dennehy EB, Swann AC, et al. Report of the Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder 2000. J Clin Psychiatry 2002;63:288–299
24. Bowden CL. Key treatment studies of lithium in manic-depressive illness: efficacy and side effects. J Clin Psychiatry 1998;59(suppl 6):13–19
25. Dunner DL, Stallone F, Fieve RR, et al. Lithium carbonate and affective disorders: a double-blind study of prophylaxis of depression in bipolar illness. Arch Gen Psychiatry 1976;33:117–120. Correction 1982;39: 1344–1345.
26. Fieve RR, Kumbaraci R, Dunner DL. Lithium and prophylaxis of depression in bipolar I, bipolar II, and unipolar patients. Am J Psychiatry 1976; 133:925–929
27. Kane JM, Quitkin FM, Rifkin A, et al. Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness. Arch Gen Psychiatry 1982;39:1065–1069
28. Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. J Clin Psychiatry 1999;60:79–88
29. Greil W, Kleindienst N. Lithium versus carbamazepine in the maintenance treatment of bipolar II disorder and bipolar disorder not otherwise specified. Int Clin Psychopharmacol 1999;14:283–285
30. Bowden CL, Calabrese JR, McElroy SL, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Arch Gen Psychiatry 2000;57:481–489
31. Winsberg ME, DeGolia SG, Strong CM, et al. Divalproex therapy in medication naive and mood stabilizer naive bipolar II depression. J Affect Disord 2001;67:207–212
32. Calabrese JR, Delucchi GA. Spectrum of efficacy of valproate in 55 patients with rapid-cycling bipolar disorder. Am J Psychiatry 1990;147: 431–434
33. Calabrese JR, Suppes T, Bowden CL, et al. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. J Clin Psychiatry 2000;61:841–850
34. Amsterdam JD, Garcia-Espana F, Fawcett J, et al. Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. J Clin Psychopharmacol 1998;18:435–440
35. Simpson SG, DePaulo JR. Fluoxetine treatment of bipolar II depression. J Clin Psychopharmacol 1991;11:52–54
36. Himmelhoch JM, Thase ME, Mallinger AG, et al. Tranylcypromine versus imipramine in anergic bipolar depression. Am J Psychiatry 1991;148: 910–916
37. Amsterdam J. Efficacy and safety of venlafaxine in the treatment of bipolar II major depressive episode. J Clin Psychopharmacol 1998;18:414–417
38. Haykal RF, Akiskal HS. Bupropion as a promising approach to rapid cycling bipolar II patients. J Clin Psychiatry 1990;51:450–455