Pharmacotherapy for the Treatment of Acute Bipolar II Depression: Current Evidence

Holly A. Swartz, MD, and Michael E. Thase, MD

Objective: Bipolar II disorder is a common, recurrent, and disabling psychiatric illness, and yet little is known about how best to treat it. The pressing clinical need for evidence-based approaches to the treatment of bipolar II disorder, coupled with recent publication of pertinent studies, calls for an updated review of this literature. This review focuses on a critical examination of the evidence supporting the efficacy of treatments for acute depressive episodes in bipolar II disorder.

Data Sources: A MEDLINE (via Ovid) search of journals, covering the period from January 1950 to January 2009, was performed to identify relevant studies. Keywords used were *bipolar II disorder*, *bipolar disorder*, *bipolar depression*, and *pharmacotherapy*. Studies were further limited to those that were in adult samples, published in peer-reviewed journals, and written in English.

Study Selection: We examined all randomized trials evaluating the use of pharmacotherapy in the treatment of acute bipolar II depression. Studies with mixed samples of bipolar I and II or bipolar II and unipolar depression were examined as well. Twenty-one randomized trials were identified and reviewed.

Data Extraction: Therapeutic agents were rated according to the quality of evidence supporting their efficacy as treatments for bipolar II depression.

Data Synthesis: Ninety percent of relevant trials were published after 2005. Quetiapine was judged as having compelling evidence supporting its efficacy. Lithium, antidepressants, and pramipexole were judged as having preliminary support for efficacy. Lamotrigine was considered to have mixed support.

Conclusions: Although progress has been made, further research on bipolar II depression is warranted.

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Corresponding author: *Holly A. Swartz, MD, Western Psychiatric Institute and Clinic, 3811 O'Hara St, Pittsburgh, PA 15213 (swartzha@upmc.edu).*

Bipolar II disorder is a common,[1] recurrent,[2] and disabling[3] psychiatric illness. First described in the 1970s by Dunner and colleagues[4] and part of the official *Diagnostic and Statistical Manual of Mental Disorders* nomenclature since 1994, bipolar II disorder is defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[5] as a lifetime history of at least 1 episode of major depression plus at least 1 episode of hypomania. Initial reports suggested that bipolar II disorder might be viewed as a more benign form of bipolar I disorder because, by definition, individuals suffering from the disorder never experience full-blown mania. Accumulating evidence, however, has clarified that, because bipolar II disorder is characterized by multiple and often more protracted depressive episodes,[6] it is at least as disabling as bipolar I disorder.[3] Indeed, relative to individuals suffering from bipolar I disorder, individuals with bipolar II disorder experience a more chronic course of illness, with more lifetime days spent depressed[2] and a lower probability of returning to premorbid levels of functioning between episodes[7] than for those with bipolar I disorder. The lifetime incidence of bipolar II varies widely on the basis of the method of classification, with estimates ranging from as low as 1.1%[1] to as high as 11%.[8] Thus, its prevalence is—at minimum—comparable to that of bipolar I, and, if the highest estimated prevalence is accepted, it approaches that of major depressive disorder.

Bipolar I and II diagnoses appear stable over time.[9,10] For example, in 1 study, fewer than 5% of patients with bipolar II disorder developed a manic episode over 2 years of prospective follow-up, suggesting that most individuals with bipolar II do not "convert" to bipolar I.[11] Indeed, an important argument for the fact that these are distinct illnesses lies in the fact that both bipolar I and II diagnoses appear to be stable over time, rather than the latter a *forme fruste* of the former.[9,10] Converging data strongly support the position that bipolar I and II disorders are separate illnesses with distinct courses, demographic features, and phenotypic manifestations.[1,3,7,12] Preliminary data from genetic[13,14] and neuroimaging[15] studies also support this view.

Whether or not bipolar II disorder is viewed as a distinct condition, there are good reasons to suspect that it may warrant a distinct treatment approach. For example, hypomania significantly complicates the presentation of depressive episodes,[16] and these recurrent, "mixed" depressive episodes dominate the course of illness,[17] driving the significant morbidity associated with bipolar II.[6] As a common disorder, information regarding its treatment should be readily available. Although international consensus groups have recently made efforts to distinguish between the 2 bipolar phenotypes with respect to interpreting the extant evidence base,[18–20] earlier treatment guidelines for bipolar disorder provided few specific recommendations for the management of bipolar II disorder,[21–23] forcing clinicians to "borrow" strategies that have only been systematically evaluated in individuals with bipolar I disorder. While it is no doubt informative to consider trials evaluating agents in individuals with either unipolar or bipolar I disorder, these data may ultimately prove to be misleading for the proper management of bipolar II disorder. Careful consideration of trials conducted in individuals who specifically meet criteria for bipolar II disorder

Table 1. Definitions of Categories of Evidence Used to Classify Treatments for Acute Bipolar II Depression

Designation	Definition
Type A	Rigorously tested in double-blind, randomized, placebo-controlled trials with specified outcome measures and adequate sample size
Type B	Demonstrates preliminary evidence of efficacy in open-label or small randomized trials but about which definitive statements of efficacy cannot be made because of limitations in the trial design or evidence base

is critically important to guiding the informed management of patients who suffer from an illness characterized by a distinct course, phenomenology, and, most likely, biology. The pressing clinical need for evidence-based approaches to the treatment of bipolar II disorder, coupled with recent publication of pertinent studies, calls for an updated review of this literature. As the majority of individuals with bipolar II disorders who present for treatment will do so in an acute depressive episode, the current review focuses on a critical review of the evidence for treating acute depressive episodes in bipolar II disorder.

METHOD

We examined all randomized trials evaluating the use of pharmacotherapy in the treatment of acute bipolar II depression. A MEDLINE (via Ovid) search of journals, covering the period from January 1950 to January 2009, supplemented by bibliographic cross-referencing, was performed to identify the relevant studies. The keywords used were *bipolar II disorder*, *bipolar disorder*, *bipolar depression*, and *pharmacotherapy*. Articles directly pertaining to the pharmacotherapy of bipolar II disorder were identified. Studies with mixed samples of bipolar I and II or bipolar II and unipolar were examined as well. Given the paucity of data on this topic, even studies that admixed subjects with bipolar I and II disorder without considering bipolar II results separately are reported. Studies discussed in this review were further limited to those that were in adult samples, published in peer-reviewed journals, and written in English. Results are organized by therapeutic agents. For each study, we discuss study design (sample size, allocation, study duration, etc), describe outcome measures, and summarize key findings.

To provide the reader with a means of evaluating each treatment, we rate each agent according to the strength of the data presented. Appropriate outcome criteria were deemed (1) change in acute depressive symptoms and (2) induction of treatment-emergent hypomania. It is beyond the scope of this article to evaluate the impact of agents as long-term maintenance treatments. We stratify therapies according to the weight of the empirical evidence that stands behind each therapy in support of its clinical efficacy in bipolar II depression. As summarized in Table 1, well-tested therapies with demonstrated efficacy are identified in the text as "type A." These include only those therapies that have been rigorously tested in double-blind, randomized, placebo-controlled trials with specified outcome measures and adequate sample size. Less well-tested therapies (designated "type B") include therapies that show preliminary evidence of efficacy in open-label or small randomized trials but about which definitive statements of efficacy cannot be made because of limitations in the empirical evidence (eg, small, underpowered trials; lack of adequate control condition; poorly specified outcomes).

RESULTS

Findings from the above literature search yielded 21 randomized trials, which are summarized in Table 2 (1 report includes 5 individual randomized trials[24]). The smallest trial included only 8 subjects with bipolar II disorder[25]; the largest included 321 subjects pooled from 2 nearly identical studies.[26] Ten of the trials were adjunctive trials—that is, the agents were tested in combination with mood stabilizers. The other 11 trials were monotherapy studies. Study duration ranged from 6 weeks to 9 months, although the majority of the studies were short-term trials (6–12 weeks). The earliest date of publication was 2000, and over 90% (19/21) were published in 2006 or later.

Quetiapine

Quetiapine therapy of bipolar II depression was examined as a secondary aim of the eponymous BOLDER studies (BipOLar DEpRession).[41,42] This pair of nearly identical industry-sponsored, 8-week, multicenter, randomized, double-blind, placebo-controlled studies evaluated the efficacy of 2 fixed doses of quetiapine—300 mg/d or 600 mg/d—as monotherapy for bipolar depression, with about two-thirds of participants meeting criteria for bipolar I and one-third meeting criteria for bipolar II disorder. In BOLDER I, both doses of quetiapine were effective in the overall study group, and quetiapine therapy was not associated with an increased risk of treatment-emergent affective switches. However, the mean drug versus placebo difference within the bipolar II cohort (n = 182) was not statistically significant.[41] In BOLDER II, both doses of quetiapine were again found to be efficacious, and an exploratory analysis of the subset of subjects meeting criteria for bipolar II (n = 152) found significant separation from placebo as early as week 1 in the 300 mg/d group, with an overall effect size of 0.5 in the 300 mg/d group and 0.64 in the 600 mg/d group.[42]

When considered together, BOLDER I and II comprise the largest number of subjects with bipolar II in an acute treatment study to date. Suppes et al[26] presented post hoc analyses combining data on the subjects with bipolar II (N = 321) from both BOLDER trials and found that improvement in mean Montgomery-Asberg Depression Rating Scale (MADRS) scores from baseline through week 8 was significantly greater with quetiapine 300 mg/d (n = 107) and 600 mg/d (n = 106) relative to placebo (n = 108). Mean reductions in MADRS scores over 8 weeks were 17.1, 17.9, and 13.3 for quetiapine 300 mg/d, 600 mg/d, and placebo, respectively. Effect sizes were moderate (0.45 and 0.54 with 300 mg/d and 600 mg/d, respectively). Remission rates (defined as MADRS

Table 2. Summary of Randomized Trials for Treatment of Acute Bipolar II Depression

Authors	Design	Sample	Treatment	Duration	Monotherapy or Adjunctive	Key Results	Quality of Evidence
Suppes et al[26]	Post hoc analyses of 2 double-blind randomized controlled trials (RCTs)	321 Bipolar II	Quetiapine 300 mg/d vs quetiapine 600 mg/d vs placebo	8 wk	Monotherapy	Effect sizes were moderate (0.45 and 0.54 with 300 mg/d and 600 mg/d, respectively). Remission rates were 39.3%, 37.7%, and 20.4% for quetiapine 300 mg/d, 600 mg/d, and placebo, respectively	Type A: data derived from well-designed industry-sponsored RCTs, but these were post hoc analyses
Frye et al[30]	Double-blind, crossover RCT	14 Bipolar II, 11 bipolar I, 6 unipolar, with refractory mood episodes	Lamotrigine vs gabapentin vs placebo	Each agent was administered for 6 wk for a total trial length of 18 wk	Monotherapy	Response rate for lamotrigine (52%) was superior to gabapentin (26%) and placebo (23%). No separate analyses were conducted for the bipolar II subgroup	Type B
Nierenberg et al[37]	Randomized with equipoise stratification	21 Bipolar II, 25 bipolar I, 1 bipolar not otherwise specified (NOS), with treatment-resistant depression	Lamotrigine vs inositol vs risperidone	16 wk	Adjunctive	No differences among groups on the primary outcome measure. Post hoc secondary analyses suggested that lamotrigine may be superior to risperidone, with inositol showing an intermediate effect. No separate analyses were conducted for the bipolar II subgroup	Type B
van der Loos et al[38]	Randomized	40 Bipolar II, 84 bipolar I	Lithium plus lamotrigine vs lithium plus placebo	8 wk	Adjunctive	Significantly more patients responded to adjunctive lamotrigine (51.6%) than placebo (31.7%). No separate analyses were conducted for the bipolar II subgroup	Type B: bipolar subgroup analyses were not reported separately
Calabrese et al[24]	Summary of 5 double-blind RCTs	305 Bipolar II, 833 bipolar I	Lamotrigine vs placebo	7–10 wk	Monotherapy	Lamotrigine did not differ significantly from placebo on primary outcomes, including in the bipolar II trial. Overall effect sizes on the 17-item HDRS ranged from 0.04 to 0.34	Type A: meta-analysis of RCTs, but data do not support efficacy of lamotrigine
Suppes et al[35]	Open-label, randomized	98 Bipolar II	Lamotrigine vs lithium	16 wk	Monotherapy	Both groups showed significant improvement on HDRS scores over time, with no differences in outcomes between groups. Dropout rates were 42%. 76% of the lamotrigine group and 59% of the lithium group met criteria for remission without switch into hypomania	Type B: open-label trial
Amsterdam et al[27]	Open-label, randomized	83 Bipolar II	Lithium vs venlafaxine	12 wk	Monotherapy	Venlafaxine was superior to lithium, even among the subset of patients with a history of rapid cycling, on measures of depressive symptoms as well as proportions responding and remitting. Rates of treatment-emergent affective symptoms were low and comparable between groups	Type B
Ghaemi et al[29]	Double-blind RCT	9 Bipolar II/NOS, 9 bipolar I	Divalproex vs placebo	6 wk	Monotherapy	Divalproex was superior to placebo on measures of depressive symptoms. The authors did not report separate outcomes for the bipolar II/NOS cohort	Type B
Sachs et al[31]	Double-blind RCT with equipoise stratification	114 Bipolar II, 240 bipolar I	Antidepressant (bupropion or paroxetine) vs placebo	26 wk	Adjunctive	No difference in response rates between groups receiving antidepressants and placebo. Rates of treatment-emergent affective switches did not differ between groups	Type A: data do not support efficacy of adjunctive antidepressant

(continued)

Table 2 (continued). Summary of Randomized Trials for Treatment of Acute Bipolar II Depression

Authors	Design	Sample	Treatment	Duration	Monotherapy or Adjunctive	Key Results	Quality of Evidence
Schaffer et al[25]	Double-blind, randomized	8 Bipolar II, 12 bipolar I	Citalopram vs lamotrigine	12 wk	Adjunctive	Both groups showed clinically significant improvement on MADRS scores with no statistically significant differences between groups. No separate analyses were conducted for the bipolar II subgroup	Type B
Young et al[32]	Double-blind, randomized	16 Bipolar II, 11 bipolar I	Paroxetine or a second mood stabilizer (lithium or divalproex)	6 wk	Adjunctive	Both groups improved over time, but there were no significant differences between groups. There were higher dropout rates in the mood stabilizer group. Results for the bipolar II subgroup were not reported separately	Type B
Leverich et al[28]	Randomized	42 Bipolar II, 115 bipolar I, 2 bipolar NOS	Sertraline vs bupropion vs venlafaxine	10 wk	Adjunctive	Overall response rates ranged from 43%–55% and did not differ among agents. Results for the bipolar II subgroup were not reported separately	Type B
Parker et al[33]	Randomized, double-blind, placebo-controlled crossover study	10 Bipolar II	Escitalopram vs placebo	9 mo	Monotherapy	Escitalopram was associated with significant reductions in depression severity, percentage of days depressed or high, and impairment relative to placebo, and there was no worsening of course	Type B
Zarate et al[34]	Double-blind RCT	21 Bipolar II	Pramipexole vs placebo	6 wk	Adjunctive	Pramipexole was associated with greater reductions in depression scores and no greater rates of switching	Type B
Frye et al[36]	Double-blind RCT	21 Bipolar II, 64 bipolar I	Modafinil vs placebo	6 wk	Adjunctive	There were statistically significant differences in response rates between placebo and modafinil in the entire sample and in the bipolar I cohort, but there were no differences in response rates within the bipolar II subgroup	Type B: bipolar II subgroup was small, and there were no differences in response rates reported in this subgroup
Keck et al[39]	Double-blind RCT	33 Bipolar II, 86 bipolar I, 1 bipolar NOS	Ethyl-eicosapentaenoate (EPA) vs placebo	4 mo	Adjunctive	No differences in outcome measures across treatment groups in the entire sample. Outcomes for the bipolar II subgroup were not reported separately	Type B
Frangou et al[40]	Double-blind RCT	10 Bipolar II, 65 bipolar I	EPA 1 g/d or 2 g/d vs placebo	12 wk	Adjunctive	There were statistically significantly greater differences in symptomatic improvement between placebo and EPA (both doses) in the entire sample. Outcomes for the bipolar II subgroup were not reported separately	Type B

Abbreviations: HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale.

scores ≤ 8 and Young Mania Rating Scale [YMRS] scores ≤ 8 at week 8) were 39.3%, 37.7%, and 20.4% for quetiapine 300 mg/d, 600 mg/d, and placebo, respectively, which translates into the relatively meaningful number needed to treat (NNT) of < 6. The rate of treatment-emergent affective switches was lower on active drug than placebo. Secondary analyses of the individual BOLDER studies indicated that quetiapine therapy was as effective for those with a history of 4 or more affective episodes in the preceding year as it was for the patients with less frequent episodes of illness.

Based on the available evidence, quetiapine is considered a "type A" agent with pooled data from 2 large randomized controlled trials (RCTs) supporting its efficacy. Primary limitations to concluding efficacy for quetiapine include (1) absence of long-term follow-up, (2) supporting data were derived in a post hoc fashion from pooled data rather than from a single data set with an a priori hypothesis, and (3) lack of replication by a second, independent (ie, non–industry-sponsored) group.

Lamotrigine

Lamotrigine has enjoyed an exceptionally controversial status with respect to the management of bipolar II depression. Its initial "favored status" was probably sparked by a study comparing the addition of lamotrigine or placebo to mood stabilizers as a maintenance treatment for individuals with either bipolar I or II disorder, rapid-cycling.[43] This study found a 6-week difference in median survival time to a new mood episode favoring lamotrigine. Indeed, 52 subjects met criteria for bipolar II in that trial, and differences favoring lamotrigine were consistently greater for patients with bipolar II than patients with bipolar I.

Small studies of lamotrigine monotherapy contributed to its growing reputation as a treatment for bipolar disorder. For instance, Frye and colleagues[30] conducted a small (N = 31) double-blind, crossover RCT of lamotrigine and gabapentin in subjects with refractory mood disorders. Their sample included 14 individuals meeting criteria for bipolar II disorder, currently depressed. Subjects were randomly assigned to a sequence of pill placebo, lamotrigine (up to 500 mg/d), and gabapentin (up to 4,800 mg/d) monotherapy, each given over a 6-week period. Thus, the trial consisted of three 6-week phases. On the primary outcome measure of response (defined by a Clinical Global Impressions scale for bipolar disorder [CGI-BP] rating of "much improved" or "very much improved"), they found lamotrigine was superior to gabapentin and placebo in the overall sample, but there were no separate analyses conducted for the bipolar II subgroup.

Ultimately, a large positive trial of lamotrigine monotherapy for the acute treatment of bipolar I depression[44] coupled with maintenance trials supporting lamotrigine's efficacy as a prophylactic treatment for bipolar I disorder[45] led to lamotrigine's favored status as a treatment for bipolar depression in several treatment guidelines for bipolar disorder.[21,46] However, these guidelines failed to consider several studies that, until recently, had remained unpublished—including the only large, randomized, placebo-controlled trial conducted to date that focused exclusively on individuals with bipolar II depression. Calabrese and colleagues[24] recently summarized acute bipolar depression outcomes for 5 double-blind, placebo-controlled, clinical trials of lamotrigine, including data from 4 previously unpublished studies. These studies ranged from 7 to 10 weeks in duration and included 305 subjects who met criteria for acute bipolar II depression. One of the 5 studies included only subjects meeting criteria for bipolar II disorder (n = 221). In 4 of the 5 studies, lamotrigine was titrated to 200 mg/d by week 5 or 6. In 1 study, lamotrigine was flexibly dosed from 100 mg/d to 400 mg/d. One study included a third comparator arm of low-dose (50 mg/d) lamotrigine. The primary outcome measure was the 17-item Hamilton Depression Rating Scale (HDRS) in 2 studies and the MADRS in 3 studies. Secondary endpoints included an expanded version of the HDRS (31 items), CGI (severity and improvement subscales), and the mood item of the HDRS. In no study did lamotrigine differ significantly from placebo on the primary endpoint, and, in most cases, it did not differ on secondary efficacy endpoints. Overall effect sizes on the 17-item HDRS ranged from 0.04 to 0.34. The authors argue that a high placebo response rate may have contributed at least in part to failure to detect differences between placebo and lamotrigine.

Geddes and colleagues[47] subsequently conducted a meta-analysis and "meta-regression" utilizing individual participant data from the 5 trials reviewed in the Calabrese et al[24] 2008 report. The authors found a modest advantage of lamotrigine over placebo in both the bipolar I and II groups. Interestingly, they found a treatment by severity interaction such that lamotrigine was superior to placebo in individuals with HDRS scores > 24 at baseline. They note, however, that the overall NNT of 11 "is at the margins of being clinically worthwhile," although NNT = 7 in the more severely depressed sample. They found no differences between the bipolar I and II subgroups.

These "mixed reviews" for lamotrigine as a monotherapy for bipolar II disorder are further confounded by a recent report by Suppes and colleagues,[35] in which they randomly assigned subjects meeting criteria for bipolar II depression to either lithium (n = 54) or lamotrigine (n = 44) and followed them for 16 weeks. They found significant improvements in 17-item HDRS and YMRS scores in both groups over time with no significant between-group differences. The Suppes et al[35] trial was notable, however, for relatively high dropout rates (42%) across conditions.

Lamotrigine has shown some promise as an adjunctive treatment for bipolar depression. Nierenberg and colleagues[37] evaluated lamotrigine, inositol, and risperidone as adjunctive treatments for patients with treatment-resistant bipolar depression. They enrolled patients meeting diagnostic criteria for bipolar I (n = 25), bipolar II (n = 21), or bipolar not otherwise specified (NOS; n = 1) who were in a current major depressive episode that was nonresponsive to a combination of adequate doses of established mood stabilizers plus at least 1 antidepressant. In this study, patients

were randomly assigned to open-label, adjunctive treatment with lamotrigine, inositol, or risperidone for up to 16 weeks. Primary endpoint was "recovery" defined as presences of no more than 2 symptoms meeting *DSM-IV* threshold criteria for a mood episode for 8 weeks. Equipoise randomization was used, which allowed patients and their clinicians to eliminate unacceptable treatment options.[48] Although this approach was chosen to maximize patient acceptability, the authors suggested that it resulted in a fragmented sample size and limited power for comparisons, contributing to a finding of lack of differences among groups on the primary outcome measure. Recovery rate with lamotrigine was 23.8%, whereas the recovery rates with inositol and risperidone were 17.4% and 4.6%, respectively. Secondary analyses of the entire group (bipolar I and II) on measures of improvement in depressive symptoms, overall severity, and functioning at end of study suggested that lamotrigine was superior to risperidone as an augmenting strategy for treatment-resistant bipolar depression, with inositol showing an intermediate effect.[37] Van der Loos and colleagues[38] randomly assigned 124 depressed individuals meeting criteria for either bipolar I or II disorder who were receiving lithium to 8 weeks of add-on treatment with either lamotrigine or placebo. Thirty-two percent of the sample (n = 40) met criteria for bipolar II disorder. On the primary outcome measure (change in MADRS score from baseline to week 8), lamotrigine was significantly more efficacious than placebo (−15.4 vs −11.0, $P = .024$) in the total sample. Response rates in the lamotrigine group (51.6%) were significantly higher than in the placebo group (31.7%; $P = .03$). The investigators state that the sample size was too small to evaluate treatment-by-subgroup interactions with respect to bipolar I versus bipolar II subtypes.

Despite the high rating of lamotrigine in many practice guidelines, available evidence suggests that lamotrigine monotherapy lacks definitive efficacy in bipolar II depression, specifically because the single large RCT completed in bipolar II depression failed to support its efficacy. Although several smaller studies do provide modest support for its utility, these trials are not as methodologically strong as the failed trial. Involving adjunctive use of lamotrigine, the Nierenberg et al[37] trial lacked a placebo-control comparator,[37] as did the recent Suppes et al trial.[35] At this point in time, it appears that the story with lamotrigine is complex, suggesting that it may be more effective with some subgroups and in some contexts. For instance, perhaps it may be more helpful as an adjunctive treatment rather than as monotherapy. Thus, although we rate lamotrigine as a type A medication, given the quality of the evidence that has been used to explore its utility, much of that evidence points to its lack of efficacy. Thus, lamotrigine (both as monotherapy and adjunctive treatment) is best considered a second-line option for acute bipolar II depression.

Lithium

Although lithium has been the cornerstone of therapy for bipolar disorder for almost 40 years, it has not been systematically studied as an acute phase therapy of bipolar II depression, and we were unable to locate any published data from placebo-controlled trials. Several studies have evaluated lithium as a prophylactic treatment for bipolar II disorder, with mostly positive findings,[49–52] but relatively few data are available evaluating its efficacy as an acute treatment. Recently, Amsterdam and colleagues[27] compared open-label lithium (n = 40) to venlafaxine (n = 43) as monotherapies for bipolar II depression. The choice of venlafaxine monotherapy was an interesting comparator, as it has been associated with relatively higher rates of treatment-induced hypomania, mania, and switching (as compared to selective serotonin reuptake inhibitors [SSRIs] such as sertraline and paroxetine), despite concomitant treatment with mood stabilizers.[28,53,54] Subjects received up to 375 mg/d of venlafaxine (mean maximum of 186 mg/d), and lithium was titrated to steady state serum levels of 0.5–1.5 mmol/L. Subjects were followed for 12 weeks, and the primary outcome measure was an expanded (28 item) version of the HDRS. Secondary outcome measures included the YMRS scores and proportion responding and remitting. Amsterdam and colleagues[27] found a large efficacy advantage for venlafaxine on the primary outcome measure (HDRS) as well as the proportions responding (75% with venlafaxine and 27% with lithium for rapid cyclers; 55% with venlafaxine and 16% with lithium for non–rapid cyclers) and remitting (75% with venlafaxine and 7% with lithium for rapid cyclers; 32% and 8% for non–rapid cyclers). Rates of treatment-emergent affective symptoms were low: 7 subjects in the total sample experienced an increase in YMRS scores at 2 or more study visits, and only 1 subject experienced a YMRS score ≥ 12 at any study visit. There were no differences between groups in rates of treatment-emergent elevations in YMRS scores, even among those with histories of rapid cycling. As described above, the recent open trial of Suppes and colleagues[35] comparing lithium and lamotrigine is supportive of lithium but not definitive. Notably, 59% of subjects achieved remission with lithium alone, but dropout rates were high (42%).

On the basis of the available evidence, lithium has preliminary support for efficacy as treatment for bipolar II depression, primarily on the basis of the single positive trial by Suppes and colleagues[35] and therefore should be classified as a type B agent. However, both randomized trials conducted to date were open-label studies without placebo comparators, limiting conclusions that can be drawn.

Valproate

There are remarkably few data on valproate for the treatment of bipolar II disorder. A single, small trial was conducted in a mixed sample of individuals meeting criteria for bipolar I (n = 9) and bipolar II/NOS (n = 9), in which patients with acute depression were randomly assigned to either divalproex monotherapy or placebo for 6 weeks. Divalproex titrated to a serum level of 70–90 ng/dL. The primary outcome measures were the MADRS and Mania Rating Scale (MRS). There were significantly greater reductions in MADRS scores in the group assigned to divalproex compared to placebo over time, and no significant increase

in MRS scores. The authors did not report separate outcomes for the bipolar II/NOS cohort.[29]

On the basis of the limited available evidence, efficacy of valproate in the treatment of bipolar II depression is not established.

Antidepressants

Antidepressants are controversial agents in the armamentarium for bipolar. On the one hand, there are concerns about both limited efficacy and risk of inducing hypomanic or manic switches, yet on the other hand, these agents are widely used in clinical practice.[55] It is also true that the risk/benefit ratio may be different in bipolar I and II disorder. For instance, Altshuler and colleagues[54] published a report showing that, among individuals with bipolar disorder treated with an antidepressant (in conjunction with a mood stabilizer), rates of switching were lower among those with bipolar II disorder than those with the bipolar I phenotype. In this trial, a switch was defined as a score ≥ 3 (mildly ill) on the CGI mania subscale or ≥ 13 on the YMRS. This was not observed in the larger, placebo-controlled study conducted as part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) project.[31] Of note, a treatment-emergent affective switch in STEP-BD was stringently defined as meeting *DSM-IV* criteria for hypomania (or mania) or requiring intervention by a treating clinician for clinically significant treatment-emergent mood elevation. Relevant studies are reviewed below.

The STEP-BD trial included 114 subjects meeting criteria for bipolar II. Participants entered this study in a major depressive episode and received concurrent therapy with mood stabilizers. Patients were randomly assigned to receive adjunctive antidepressant (n = 54; either bupropion or paroxetine) or placebo (n = 60). Median dose of paroxetine was 30 mg/d (range, 20–40 mg/d). Median dose of bupropion was 300 mg/d (range, 150–338 mg/d). Response was defined as a 50% improvement from baseline SUM-D score (a version of the current mood modules of the Structured Clinical Interview for *DSM-IV*, modified to include continuous symptom subscales for depression) without meeting *DSM-IV* criteria for hypomania or mania. There was no evidence of antidepressant efficacy relative to placebo. Although the antidepressants were not effective, they were also no more likely than placebo to be associated with treatment-emergent affective switches.[31]

Several smaller studies have been conducted evaluating antidepressants as augmentation strategies for bipolar II depression. Schaffer and colleagues[25] randomly assigned 20 subjects with depression meeting criteria for either bipolar I or II disorder (8 subjects met criteria for bipolar II) who were currently receiving a mood-stabilizing medication to either citalopram or lamotrigine. Citalopram was dosed from 20 to 50 mg/d, and lamotrigine was dosed to a maximum of 200 mg/d (100 mg/d for patients on divalproex). Over the 12-week study period, both groups showed clinically significant improvement on MADRS scores, and there were no statistically significant differences between groups.[25] Young and colleagues[32] randomly assigned 27 subjects with depression meeting criteria for either bipolar I or II disorder (16 subjects met criteria for bipolar II) who were currently receiving a mood-stabilizing medication to 6 weeks of either paroxetine or a second mood stabilizer (lithium or divalproex). Mean dose of paroxetine was 36 mg/d. Mean serum level of lithium was 0.9 mmol/L. Mean serum level of divalproex was 510 mmol/L. The primary outcome measure was HDRS. Analyses showed a main effect for time, but no effect for group or group × time interaction, indicating that both groups got better over time, but no significant differences between groups. The authors note that there were higher dropout rates in the group assigned to a second mood stabilizer, suggesting that paroxetine may be a more practical approach. Results for the bipolar II subgroup were not reported separately.[32]

Leverich and colleagues,[28] as part of a larger Stanley Bipolar Network study including subjects meeting criteria for bipolar I and II disorder, randomly assigned subjects with depression meeting criteria for bipolar II disorder to adjunctive sertraline (n = 14), bupropion (n = 13), or venlafaxine (n = 15). The acute phase of the study lasted 10 weeks, and the primary outcome measure was continuous daily mood as measured by the Life Chart Method. Efficacy data were not reported separately for the bipolar II cohort, but overall response rates ranged from 43%–55% and did not differ among pharmacotherapeutic agents.

Use of antidepressants as monotherapy in bipolar I disorder is contraindicated because of the high risk of inducing mania and mood cycling.[56] Indeed, most formal treatment guidelines advise against using antidepressants as monotherapy in patients with bipolar disorder—without regard to bipolar subtype—because of the magnitude of these risks,[21–23] especially among those receiving tricyclic antidepressants.[57] Nevertheless, there are some interesting preliminary data suggesting that antidepressants may be safely used as monotherapy, at least in a subset of individuals with bipolar II disorder.

Initial support for antidepressant monotherapy in bipolar II depression came from open-label trials by Amsterdam and colleagues[58] showing 54% remission rates in a sample (n = 80) treated with fluoxetine. Of note, this group of investigators observed a very low (3.8%) new onset of hypomanic symptoms during fluoxetine therapy. The same group conducted a small, 6-week, double-blind, randomized trial comparing daily versus bid dosing of venlafaxine (up to 225 mg) in 15 women meeting criteria for acute bipolar II depression. The primary outcome measure was ≥ 50% reduction in the 21-item version of the HDRS. Overall response rate was 63% in the sample, with 0% switch rate.[59] Most recently, as described above, they found venlafaxine to be more effective and no more likely than lithium to induce treatment-emergent affective switches in a randomized open-label study.[27] Parker and colleagues[33] conducted a 9-month, randomized, double-blind, placebo-controlled, crossover study in a small (n = 10) sample of medication-naive subjects meeting criteria for bipolar II disorder. They concluded that administration of escitalopram was associated with significant reductions in

depression severity, percentage of days depressed or high, and impairment relative to placebo and that there was no worsening of course. This led Parker[60] to assert that SSRIs may constitute "mood stabilizers" for bipolar II disorder, although the evidence base for such an assertion is currently rather limited.

Antidepressants are considered "type B" agents for bipolar II depression. As augmenting agents, the data are mixed, and there are relatively large differences observed across studies with respect to the risk of treatment-emergent affective switches. Whereas several studies suggest efficacy, the largest trial conducted to date (STEP-BD) found no evidence of efficacy. As monotherapy, several open studies and 2 randomized trials suggest that this may be a promising approach. The first randomized trial was very small (n = 10), which demonstrates feasibility, but does not confirm efficacy. The second randomized trial of Amsterdam and colleagues[58] used open-label pharmacotherapy, which limits conclusions that can be drawn. Thus, although the data remain limited at present, the use of antidepressants as monotherapy may be considered an option for the management of bipolar II depression if alternative approaches have failed.

Pramipexole

Zarate and colleagues[34] evaluated the dopamine agonist, pramipexole, as treatment for bipolar II depression. In a double-blind RCT, subjects meeting criteria for acute bipolar II depression despite therapeutic levels of either lithium or valproate were randomly assigned to augmentation therapy with either pramipexole (n = 10) or placebo (n = 11) for 6 weeks. The primary outcome measure was the MADRS. Average dose of pramipexole was 1.7 ± 0.90 mg/d. Pramipexole showed advantages over placebo on rates of response (60% vs 9%), rates of remission (40% vs 9%), and percent change in MADRS scores (47.1 ± 27.2 vs 12.4 ± 25.0). One subject in the pramipexole group and 2 subjects in the placebo group reached YMRS scores ≥ 12 for 1 week.

Pramipexole is a "type B" agent for bipolar II depression. Because it has only been tested in 1 small trial, the evidence supporting its efficacy must be considered very preliminary. Nevertheless, this initial trial was promising.

Modafinil

Modafinil is a novel "alerting" medication, US Food and Drug Administration (FDA)–approved to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hyponea syndrome, and shift work sleep disorder. It is also used to treat idiopathic hypersomnolence. Although classified by the FDA as a psychostimulant, modafinil appears to have little abuse potential and has a generally favorable tolerability profile. Frye and colleagues[36] randomly assigned subjects with bipolar depression (n = 85) who did not obtain adequate benefit from treatment with a mood stabilizer (with or without concomitant antidepressant therapy) to 6 weeks of adjunctive treatment with either modafinil or placebo. A subset of the sample met criteria for bipolar II disorder (n = 21). Modafinil was titrated to 200 mg/d (mean dose = 177 mg/d). Primary outcome measures were the Inventory of Depressive Symptoms (IDS) and CGI (severity subscale). In the entire sample (both bipolar I and II), there were significant improvements on the primary endpoints in the modafinil group relative to the placebo group, with medium effect sizes (0.47 and 0.63 on the IDS and CGI, respectively). However, the authors reported that the endpoint IDS scores, controlling for baseline score, were significantly lower in patients with a diagnosis of bipolar I compared to bipolar II ($F_{1,84} = 6.58$, $P = .012$). They also reported that while there were significant differences between placebo and modafinil response rates in the bipolar I cohort (defined as 50% reduction in IDS scores), there were no differences in response rates within the bipolar II group (1 of 7 in the modafinil group vs 1 of 14 in the placebo group).[36]

Modafinil has been tested in 1 trial that included a small number of patients with bipolar II. Although the evidence from this trial was favorable overall, the bipolar II subgroup apparently did not obtain as much benefit as the patients with bipolar I disorder—although this could be explained by the small number of subjects randomly assigned per study arm and the inability to distinguish between outcomes with such small sample sizes. Additional data are required to establish efficacy.

Omega-3 Fatty Acids

Keck and colleagues[39] conducted a 4-month, placebo-controlled randomized trial evaluating the efficacy of an omega-3 fatty acid, ethyl-eicosapentaenoate (EPA). The EPA was administered in conjunction with mood-stabilizing medication at a dose of 6 g/d. Investigators randomly assigned 120 subjects with bipolar disorder, including 33 individuals with bipolar II disorder who were acutely depressed (n = 14) or rapid cycling (n = 19). Primary outcome measures included the IDS and YMRS. There were no differences in outcome measures across treatment groups in the entire sample. Outcomes for the bipolar II subgroup were not reported separately.[39] Frangou and colleagues[40] evaluated adjunctive EPA at much lower doses (1 g/d and 2 g/d) than the Keck et al[39] trial. They randomly assigned 75 subjects with bipolar disorder, including individuals with bipolar II disorder (n = 10), who had at least mild depressive symptoms (17-item HDRS score ≥ 10) to receive 12 weeks of double-blind treatment with either EPA 1 g/d, EPA 2 g/d, or placebo. Primary outcome measures included the 17-item HDRS, the CGI, and the YMRS. Improvement in depression scores (17-item HDRS and CGI) were significantly greater in individuals receiving either dose of EPA compared to placebo, and there were no increases in mania scores. Of note, individuals in this trial received ongoing medication management and had their medications adjusted as needed during the course of the trial. Outcomes for the bipolar II subgroup were not reported separately.[40]

Data from these 2 EPA trials in bipolar depression are conflicting, with 1 study showing lack of efficacy and the

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Table 3. Summary of Quality of Evidence for Pharmacotherapy for Bipolar II Depression and Implications for Clinical Practice

Medication	Rating of Quality of Evidence	Implications for Treatment of Bipolar II Depression
Quetiapine	Type A: pooled data from 2 large studies support its efficacy	Consider as a first-line option
Lamotrigine	Type A: very small effect size when used as monotherapy in 5 individual randomized controlled trials (RCTs); modest advantage over placebo when examined in "meta-regression"; suggestion of advantage over placebo when used as augmentation strategy	Consider as a second-line option both as monotherapy and as an augmentation strategy
Lithium	Type B: single positive open-label trial and historical clinical experience	Consider as a second-line option
Antidepressants/selective serotonin reuptake inhibitors (SSRIs)	Type B: preliminary results of open-label studies of antidepressants as monotherapy are promising; controlled trials of antidepressants as augmentation strategy show no advantage over placebo	Consider SSRI monotherapy as a second-line option; antidepressants as a group may have limited utility as an augmentation strategy, although further testing of individual agents is indicated
Pramipexole	Type B: 1 small RCT suggests utility as augmentation strategy	Consider pramipexole as a second-line augmentation strategy
Valproate	Not established	Inadequate data
Modafinil	Adjunctive treatment was associated with improvement in a mixed bipolar I/II cohort, but no clear signal for bipolar II subjects emerged	Inadequate data
Omega-3 fatty acids	A small number of individuals with bipolar II were included in 2 large RCTs but were not examined separately	Inadequate data; available information is conflicting about its benefit as an add-on treatment in mixed bipolar I/II samples

other showing benefit. However, because the bipolar II subgroups were small in both trials and results were not reported separately, definitive statements about efficacy in bipolar II are not indicated.

DISCUSSION

The extant literature yields 2 rigorously tested compounds for bipolar II depression: quetiapine and lamotrigine. Quetiapine was subjected to rigorous testing under double-blind, placebo-controlled conditions and, with adequate power for separate analyses of patients with bipolar II in pooled analyses, was shown to separate from placebo on the primary outcome measure of depressive symptoms. Limitations of the available quetiapine data include the fact that the evidence comes from only industry-sponsored trials (ie, there are as of yet no independent replications of these findings). However, the research is methodologically sound, and the results strongly support the efficacy of quetiapine as treatment for bipolar II depression with demonstration of a moderate effect size compared to placebo. The only other agent that has been tested under comparably rigorous conditions is lamotrigine. Although there are mixed signals from meta-analyses that included subjects with both bipolar I and II, the single lamotrigine trial that focused on bipolar II depression was a double-blind, placebo-controlled, industry-sponsored registration trial, and the active drug failed to separate from placebo. Thus, the evidence does not justify ranking lamotrigine monotherapy as a first-line agent for bipolar II depression. Analyses from a "mega-regression" suggest that lamotrigine monotherapy may play a role in the treatment of patients with more severe depression, and smaller trials suggest it may have efficacy when used as an adjunctive agent, but additional data will need to be collected before definitive statements can be made. Thus, of the 2 identified type A agents, practicing clinicians should consider quetiapine as a first-line option for the management of bipolar II depression. Lamotrigine—both as monotherapy and as an adjunctive treatment—should be considered a second-line option.

Lithium, antidepressants, and pramipexole were deemed "type B" agents—that is, the available data suggest efficacy but are inconclusive. Within this group, the data supporting the utility of antidepressants for the management of bipolar II depression are perhaps most interesting. The results of the recent study of Amsterdam and colleagues,[27] which are derived from a randomized but open-label trial, suggest that the risk of switch in bipolar II disorder are low and rates of response reasonably high. By contrast, the results of the somewhat larger STEP-BD trial,[31] differ from those of Amsterdam et al,[27] at least in terms of efficacy, in that the subset of patients with bipolar II who received antidepressants as add-on therapy (as opposed to monotherapy) were no more likely to respond than those who were randomly assigned to placebo for add-on therapy. Going forward, it will be important to clarify the differential effects of antidepressants as monotherapy versus adjunctive therapy in this population. Pramipexole and lithium appear promising, but larger trials are needed to establish clear efficacy. At this point, the available data support the use of all 3 of these agents—lithium, antidepressant (SSRI) monotherapy, and pramipexole (adjunctive)—as second-line options for the management of bipolar II depression. It should be noted that within this category, the data for pramipexole are more limited than the data for lithium and antidepressants.

Inadequate evidence is available to evaluate the utility of modafinil, valproate, and omega-3 fatty acids in the management of bipolar II depression. The small modafinil trial did not suggest a signal for efficacy in the subjects with bipolar II. The data for the mixed bipolar I and II cohorts for the 2 published omega-3 trials are conflicting, with 1 study failing to show an advantage for EPA over placebo. However, neither omega-3 trial examined the bipolar II cohorts separately, therefore no specific conclusions can be drawn about this population. At this point, extant data do not provide

substantive guidance to clinicians, and therefore these agents should be used with caution.

Many questions remain unanswered about the acute phase management of bipolar II depression. This disorder has long been understudied, and, as a result, little information has been available for evidence-based care. As indicated by this review, however, there appears to be hope on the horizon: 90% of the randomized trials that were included in this article were published in the preceding 3 years. As summarized in Table 3, extant data begin to provide direction for clinicians who are managing patients with bipolar II depression. Quetiapine has emerged as a first-line treatment option, and lithium, SSRIs, lamotrigine, and pramipexole can all be used as second-line alternatives. Additional research, however, is required to provide adequate information for practicing clinicians. Future studies should consider incorporating longer periods of follow-up in acute study designs because it will be important to evaluate whether agents that are associated with acute reductions in symptoms also confer decreased risk for longer-term mood instability. It would also be helpful to develop strategies to better understand and categorize heterogeneity within the bipolar II phenotype in order to explore differential responses to pharmacotherapy within bipolar II subgroups. Data from these types of studies would further help to guide informed clinical decision making for individuals who suffer from bipolar II disorder and the physicians who care for them.

Drug names: bupropion (Aplenzin, Wellbutrin, and others), citalopram (Celexa and others), divalproex (Depakote and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), gabapentin (Neurontin and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), modafinil (Provigil), paroxetine (Paxil, Pexeva, and others), pramipexole (Mirapex and others), quetiapine (Seroquel), sertraline (Zoloft and others), risperidone (Risperdal and others), valproate sodium (Depacon and others), venlafaxine (Effexor and others).

Author affiliations: Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh (Dr Swartz); and Department of Psychiatry, Mood and Anxiety Disorders Treatment and Research Program, University of Pennsylvania School of Medicine, Philadelphia (Dr Thase), Pennsylvania.

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