Published in final edited form as:
CNS Spectr. 2013 August ; 18(4): 199–208. doi:10.1017/S1092852913000102.

A Systematic Review of the Evidence for the Treatment of Acute Depression in Bipolar I Disorder

Michael A. Cerullo and
Clinical Assistant Professor of Psychiatry and Behavioral Neuroscience, University of Cincinnati

Stephen M. Strakowski
Senior Associate Dean for Research, UCCOM Vice-President for Research, UC Health The Dr. Stanley & Mickey Kaplan Professor & Chairman of Psychiatry and Behavioral Neuroscience

Abstract

In this article we examined evidence for the acute treatment of depression in bipolar I disorder, focusing on double-blind, placebo-controlled studies with a definite primary outcome measure and published in peer review journals. Quetiapine and olanzapine/fluoxetine are currently approved by the FDA for the treatment of bipolar depression and a number of additional agents (including other atypical antipsychotics, mood stabilizers, antidepressants, and novel compounds) have been studied with varying degrees of efficacy. The medication with the most evidence for efficacy in bipolar depression is quetiapine with five studies showing positive efficacy compared to placebo. In contrast five studies of lamotrigine were negative although meta-analyses of the pooled have found some treatment effects. Two studies of olanzapine and olanzapine/fluoxetine and three small studies of divalproex showed significant efficacy in treating bipolar depression. Two studies of aripiprazole found no differences compared to placebo. Early research on lithium in bipolar depression had significant methodological flaws and only one study of lithium met our primary search criteria. To better understand the role of anti-depressants we also examined studies of antidepressants as adjunctive treatment of bipolar depression in participants taking mood stabilizers or atypical antipsychotics. These studies reported mixed results for a variety of antidepressants but the majority found no differences compared to placebo. Other studies of adjunctive treatment were also discussed. There has been one positive adjunctive study each of lamotrigine, omega-3 fatty acids, modafinil, and Armodafinil while there was one negative trial each of omega-3 fatty acids, ziprasidone, and levetiracetam.

Introduction

Bipolar disorder is a serious psychiatric illness resulting in depression and mania that affects approximately 1.5% of the population and represents a significant source of individual morbidity and societal cost.[1] Patients with bipolar disorder spend considerably more time in

Address correspondence to: Michael Cerullo, Dept. of Psychiatry and Behavioral Neuroscience, University of Cincinnati COM, 260 Stetson Street, Suite 3200, Cincinnati, OH 45219-0516. Telephone: 513-558-6658; Fax: 513-558-0187; Michael.Cerullo@uc.edu.

Disclosure information:
Michael Cerullo does not have any disclosures.
Stephen Strakowski has the following disclosures:
University of Nebraska, Consultant, Consulting Fees
Eli Lilly, Research Support, Research Support
Janssen/J&J, Research Support, Research Support
AstraZeneca, Research Support, Research Support
Sumatomo, Research Support, Research Support
Pfizer, Research Support, Research Support

depressive rather than manic episodes and suffer more morbidity during depression.[2] Until quite recently most treatment studies of bipolar disorder focused on the treatment of mania or less often on maintenance treatment.[3–5] Yet the treatment of bipolar depression is one of the most difficult psychopharmacological challenges psychiatrists face. Fortunately, over the last decade and a half there has been renewed interest in the treatment of the depressive phase of bipolar disorder and a number of well designed randomized double blind placebo controlled trials in several different classes of medications have been published.[4,6] Additionally, in the last few years the number of studies has increased enough to allow the first round of meta-analyses.[4,6–10] Nevertheless the total number of well controlled studies of bipolar depression is relatively small, especially in comparison to the severity of the problem.[4,6] Only two medications are FDA approved for the treatment of bipolar depression; olanzapine-fluoxetine combination and quetiapine.[11]

The focus of this review paper is the acute treatment of depressive episodes in bipolar I disorder. The literature on the treatment of bipolar type II is very sparse and will not be discussed in this article.[12] Studies were included in this review if they were the primary treatment for bipolar depression, were randomized and double-blind, had a placebo arm, included a clearly defined outcome measure, and were published in a peer reviewed journal. The literature search for appropriate studies used the search engines PubMed and Scopus. Searches were performed using the key words “bipolar,” “depression,” “treatment,” and “double-blind.” Additional manual searches were made using references of the studies identified as well as reviewing previous meta-analyses and review articles. Another initial criterion was that the study included only participants with bipolar type I disorder. However, many studies included a mix of bipolar type I and II participants, and nearly one third of the studies that meet the other search criteria would have had to be rejected. Therefore we removed this exclusion criterion, but whenever possible report the number of bipolar II participants included in each arm of the study. The initial inclusion criteria could not address one of the major controversies in the treatment of bipolar depression, the use of antidepressants. Most of the studies of antidepressants are as adjunctive treatments.[13] Therefore we included a secondary set of criteria: studies of adjunctive treatment of bipolar depression were included if they were randomized and double-blind, had a placebo arm, and included a clearly defined outcome measure. Given limited data on the efficacy of primary or adjunctive treatments (i.e. there are no gold standard effective treatments), direct comparisons without placebo were not included and there are only a handful of such studies in any case.[14,15]

The discussion that follows organizes treatments by medication class. The evidence for the efficacy of each medication is then discussed. In addition to efficacy it is also necessary to examine the tolerability of the medications in the specific studies of bipolar depression. Therefore we also briefly discuss tolerability if the medication was shown to be effective.

Atypical Antipsychotics

Quetiapine

Efficacy—Quetiapine is one of only two drugs approved by the FDA for the treatment of bipolar depression. Five studies of quetiapine met our primary search criteria (see Table 1).[16–20] The five studies involved a total of 2539 participants on quetiapine or placebo and all five studies found that quetiapine significantly reduced the symptoms of depression as measured by the Montgomery-Asberg depression rating scale (MADRS). In three of the studies the dose of quetiapine was separated into two arms, 300 mg and 600 mg.[16,17,20] There were no significant differences in treatment efficacy between the two doses, suggesting that relatively lower doses of quetiapine are effective and perhaps better tolerated for treating depression. One limitation of most of these studies when drawing conclusions

about bipolar I was the inclusion of bipolar II participants. One half to one third of the participants in the Young et al.[20] and Thase et al.[17] studies had a diagnoses of bipolar II and it was not possible to determine the percentage of participants with bipolar II in Calabrese et al.[16] and McElroy et al.[18] (See Table 1.).

Vieta et al.[6] performed a meta-analysis of the data from the five studies discussed above.[16–20] They looked at pooled responses to both 300 and 600 mg doses. Both dosing groups showed significant decreases in MADRS scores and significant rates of response and remission compared to the placebo group. There was very little difference in these measures between the 300 and 600 mg dose groups, further supporting the notion that lower doses of quetiapine are appropriate for bipolar depression.

Tolerability—Common side effects of quetiapine included sedation, somnolence, dry mouth, and dizziness being the most common side effects reported. [16–20] While all the studies showed higher discontinuation rates in the quetiapine group this was not statistically significant when the data were combined by Vieta et al.[6] in their meta-analyses. Other than these nuisance side effects, the major concerns were potential weight gain and metabolic syndrome. All five studies found increased weight gain in the quetiapine group compared to the placebo group that was further found to be dose related in studies using multiple doses. [16–20] The weight gain data from all five studies was combined in a meta-analysis by De Fruyte et al.[8] and showed a weighted mean increase of 1.1 kg in the 300 mg dose and 1.35 kg in the 600 mg dose. All studies also found significant increases in fasting serum glucose that was dose related in studies using multiple doses. Two of three studies that reported triglyceride levels found increases in the quetiapine group.[18–20]

Olanzapine and Olanzapine-Fluoxetine

Efficacy—Two studies of olanzapine or olanzapine-fluoxetine met our primary search criteria (see Table 1). Olanzapine-fluoxetine was the first medication approved for the treatment of bipolar depression in 2003.[21] Tohen et al.[22] and Tohen et al.[21] examined olanzapine alone at doses ranging from 5 to 20 mg in 1261 participants. Both studies showed a significant improvement in MADRS scores compared to the placebo group. Tohen et al.[21] examined olanzapine-fluoxetine and found that it showed significant improvement in MADRS compared to placebo and olanzapine alone.

Tolerability—Somnolence, increased appetite, headache, dry mouth, sedation and diarrhea were common side effects in the olanzapine and olanzapine-fluoxetine groups. [21–22] Tohen et al. [22] and Tohen et al. [21] found significantly greater weight gain (>7% of body weight) in the olanzapine and olanzapine-fluoxetine groups compared to placebo. Both studies also found increases in fasting glucose and cholesterol in the olanzapine and olanzapine-fluoxetine groups compared to placebo. There were no differences in these measures between the olanzapine and olanzapine-fluoxetine groups.[21] One concern about using anti-depressants is treatment-emergent mania, but Tohen et al. [21] found no differences in emergent mania between the Olanzapine-Fluoxetine and placebo groups.

Aripiprazole

Efficacy—Two studies of aripiprazole met our primary inclusion criteria and both studies were published in Thase et al. (see Table 1).[23] These studies had 374 and 375 participants, respectively. Neither study found any significant effect of aripiprazole on the primary outcome measure (decrease of MADRS scores) at 8 weeks. Aripiprazole was titrated over 6 weeks to 15 to 30 mg based on doses used to successfully treat mania. Because the aripiprazole group separated from placebo group at the 5 week time point in both studies the authors suggested that the final dosing may have been too high. Participants in the

aripiprazole groups had higher levels of akathsia, EPS, insomnia, nausea, and dry mouth compared to the placebo groups. There were no differences in weight gain, fasting glucose, or lipid profile in the aripiprazole group.

Ziprasidone

Efficacy—Two studies of ziprasidone met our primary inclusion criteria and both studies were published in Lombardo et al. (see Table 1).[24] The first studied examined 165 participants on low dose (40 to 80 mg) ziprasidone and 171 participants on high dose ziprasidone (120 to 160 mg) and the second studied examined 185 participants on doses of 40 to 160 mg. Neither study found a significant effect of ziprasidone on the primary outcome measure (decrease of MADRS scores).

The only other published study examining ziprasidone in bipolar depression was as an adjunct in patients who were already taking lamotrigine, lithium, or divalproex (see Table 2).[25] In this study Sachs et al. [25] examined ziprasidone in doses of up to 160 mg in 147 participants. The treatment group failed to separate from the placebo group in the primary and secondary outcomes.

Mood Stabilizers

Lamotrigine

Efficacy—The five studies of lamotrigine that met our primary inclusion criteria were all published in the same paper by Calabrese et al.[26] (see Table 1), although one of the studies in that paper was initially published by itself.[27] The total number of participants in all five studies was 1072, making lamotrigine the second most studied treatment for bipolar depression behind quetiapine. In all five studies the primary outcome measure, change in either the Hamilton rating scale for depression (HAM-D) or MADRS, did not differ significantly from placebo. Shortly after the original studies were published a meta-analysis was performed combining data from the 5 studies.[7] The pooled data showed that lamotrigine participants did have increased rates of response compared to those on placebo, but the effect was relatively small. Geddes et al.[7] then stratified the patients by symptoms severity using HAM-D scores. They found that lamotrigine had a large positive treatment effect in participants with severe depression (HAM-D $\geq$24), but no effect in participants with moderate depression (HAM-D<24). However this finding may be explained by lower rates of placebo response in severe depression rather than as increased effectiveness of lamotrigine in more severe depression. A second meta-analysis of this data by Vieta et al.[6] also found a significant reduction in depressive symptoms in the lamotrigine group.

One additional study met our secondary inclusion criteria (see Table 2).[28] Van der Loos et al.[28] studied lamotrigine as an adjunctive treatment with lithium in 124 participants and found it significantly decreased depressive symptoms compared to adjunctive placebo. Finally, although it did not meet our initial search criteria because of the lack of a placebo group, a double-blind direct comparison of olanzapine-fluoxetine and lamotrigine is worth mentioning.[29] Participants in the olanzapine-fluoxetine group showed greater improvement in the CGI scale, the primary outcome measure, compared to the lamotrigine group.

Tolerability—Overall lamotrigine was well tolerated in all 5 studies.[26] Headache, nausea, non-serious rash, dry mouth, dizziness, and diarrhea were the most common side effects reported. There were no reports of any serious rash in the studies. Lamotrigine did not increase the incidence of manic episodes compared with placebo.

Divalproex

Efficacy—Three smaller studies of divalproex have been published that met our primary inclusion criteria (see Table 1).[30–32] The three studies included a total of 97 participants on divalproex or placebo. All three studies showed significant improvement in their primary outcome measure (decrease in HAM-D or MADRS) compared to placebo. Two of these studies were limited by their inclusion of participants with bipolar II: Muzina et al.[32] included an unspecified number of bipolar II participants in each group and in Ghaemi et al.[31] participants with bipolar II made up half of each group. Bond et al.[10] published a meta-analysis including data from the Davis et al.[30] and Ghaemi et al.[31] studies along with data from 2 unpublished placebo-controlled trials of divalproex with a total a total of 97 participants in the 4 studies. They found that the rates of response and remission were significantly greater in the divalproex group.

Tolerability—Overall divalproex was well tolerated in these studies with little difference in participant dropout compared to placebo. The most common side effects of divalproex seen were sedation, changes in appetite, myalgias/weakness, dizziness, fatigue, and dry mouth.[30–32]

Lithium

In the late 1960's when lithium was being introduced as a treatment for mania in the US there was also an interest in its effectiveness in treating depression. This resulted in almost a dozen publications in the following decade. Yet all of these studies had significant limitations and none met our primary or secondary search criteria. Baron et al.[33], Goodwin et al.[34], and Noyes et al.[35] included placebo arms but were limited by the inclusion of only 6, 13, and 6 participants with bipolar disorder, respectively. The largest of these early research studies were those by Stokes et al.[36] and Goodwin et al.[37] with larger sample sizes of 38 and 40 participants with bipolar I, respectively. Goodwin et al.[37] found lithium to be effective in reducing depressive symptoms while Stokes et al.[36] found no change from placebo. Yet the interpretation both studies was severely limited by the rapid alteration between placebo and lithium; one week in the Stokes et al.[36] study and an average of one and a half weeks in the Goodwin et al.[37] study. Therefore there was only one study of lithium as monotherapy that met our primary search criteria. The Young et al.[20] study of quetiapine mentioned previously included a lithium comparison arm (see Table 1). Lithium did not differ in reducing the symptoms of depression compared to placebo. There have been several placebo controlled studies of adjunctive medications added to lithium that met our secondary search criteria (mostly of antidepressants, see table 2),[24,25,38–41] two of which were discussed above and four are discussed below.

Levetiracetam

Efficacy—Levetiracetam is a newer anti-epileptic medication that was studied in bipolar depression in one small study which met our secondary search criteria. Saricicek et al.[42] studied levetiracetam as an adjunctive treatment in participants who were taking mood stabilizers, antidepressants, or antipsychotics (see Table2). The treatment group failed to separate from the placebo group in the primary outcome, change in HAM-D scores.

Antidepressants

Antidepressants

Given the controversy surrounding the use of antidepressants in bipolar disorder, it is surprising how little controlled research addresses the question. Only one study of antidepressant monotherapy met our initial search criteria.[18] McElroy et al.[18], in the study of

quetiapine mentioned previously, used paroxetine as a comparison treatment arm. Paroxetine did not differ compared to placebo in reducing the symptoms of depression. The major limitation to this study was the low dose (20 mg) of paroxetine used.

There have been four studies using antidepressants as adjuncts to mood stabilizers or antipsychotics in the acute treatment of bipolar depression that met our secondary search criteria. One study already discussed was the use of fluoxetine with olanzapine.[21] Sachs et al.[40] studied paroxetine and buproprion SR as adjunctive treatments in 366 participants taking a mood stabilizer or atypical antipsychotic. Neither medication differed from placebo in reducing symptoms of depression. Nemeroff et al.[39] studied paroxetine and imipramine as adjunctive treatment in 112 participants taking lithium plus either carbamazepine or divalproex. Once again neither medication differed from placebo. However, a post-hoc analysis of the data revealed that paroxetine was effective when the lithium level was subtherapeutic (<0.8), suggesting a possible role as an adjunct if patients are unable tolerate higher lithium doses. These two studies used adequate dosing for all four antidepressants and therefore ruled out inadequate dosing as an explanation for their lack of efficacy. Lastly, Cohn et al.[38] examined imipramine and fluoxetine in 89 participants. Concomitant medications were not clearly stated and a significant percentage of the participants were also on lithium; hence the study met our secondary inclusion criteria. Both medications significantly reduced depressive symptoms as measured by the HAM-D compared to placebo, and fluoxetine also significantly reduced symptoms compared to imipramine.

Two important meta-analyses of antidepressant efficacy in bipolar depression have used data from the above studies along with direct comparison studies without a placebo arm.[13,14] The initial meta-analyses found that antidepressants were moderately effective in bipolar depression.[14] However, this meta-analysis was criticized for including olanzapine monotherapy as a placebo and using a disproportionate inclusion of subjects from one study.[43] A latter meta-analysis by Sidor and MacQueen[13] that included data from more recent studies found no significant treatment effect of anti-depressants. Finally, the newer antidepressants, desvenlafaxine and duloxetine, were not included in the above trials or meta-analyses so their efficacy and potential for inducing mania are unknown.

Tolerability

One concern with using antidepressants in bipolar disorder is the risk of inducing mania, also known as switching. However, the 5 studies of antidepressants mentioned previously all found small rates of switching.[18,21,38–40] Sidor et al.[13] performed a meta-analysis on clinical trials of antidepressants in bipolar disorder and also found no evidence that antidepressants induce mania. Broader reviews outside of these controlled studies have also looked at the question and found mixed results. Goldberg et al.[44] and Tondo et al.[45] found relatively high rates of switching. Patients who had tried multiple antidepressants, had a family history of bipolar disorder, and were on tricyclic antidepressants had the highest risk of switching. Licht et al.[46] found that mood stabilizers protected against the induction of mania.

Other Treatments

Modafinil/Armodafinil

Two studies examining the stimulants modafinil and armodafinil met our secondary search criteria (see Table 2).[41,47] Frye et al.[47] found that modafinil significantly reduced depressive symptoms in 41 participants with bipolar I or II disorder compared to the placebo group. Calabrese et al.[41] examined armodafinil in 128 participants with bipolar I disorder and also found a significant reduction in depressive symptoms compared to placebo. In these studies modafinil was added to a mood stabilizer while over half of the participants were also on an antidepressant.

Tolerability

Neither modafinil nor armodafinil was associated with increased incidence of mania. Nearly 70% of participants in the modafinil and armodafinil group were able to complete the study. Headache, nausea, and insomnia were the most common side effects reported in the treatment groups.

Omega-3 fatty acids

Two small studies of omega-3 fatty acids as adjunctive treatment for bipolar depression met out secondary search criteria (see Table 2).[48,49] The findings in these studies were mixed with Stoll et al.[48] finding some benefit in depression while Keck et al.[49] found no benefit in the treatment group. The studies used relatively high doses of omega-3 fatty acids; 9.6g per day in Stoll et al.[48] and 6 g in Keck et al.[49]

Tolerability

Side effects were mild in both studies with gastrointestinal symptoms being most common and no differences were found in bleeding time in the Keck et al.[49] study (Bleeding times were not reported in the Stoll et al.[48] study).

Conclusion

The medication with the most evidence for efficacy in bipolar depression is quetiapine. Quetiapine has been studied in the greatest number of participants in five studies which all showed significantly greater efficacy compared to placebo in reducing symptoms of depression.[16–20] Quetiapine had only mild nuisance side effects but did have significant side effects of weight gain and increased fasting serum glucose levels. In contrast, lamotrigine also had five studies in bipolar depression, but all five were negative.[26] Pooled data from all five lamotrigine studies did show significant efficacy, especially among participants with more severe depression.[6,7] Outside of quetiapine and lamotrigine the number of studies of primary treatment of bipolar depression and number of participants in those studies diminishes greatly. Two studies of olanzapine and olanzapine-fluoxetine and three small studies of divalproex showed significant efficacy in treating bipolar depression.[21,22,30–32] Two studies each of aripiprazole and ziprasidone found no differences compared to placebo.[23–25] Early research on lithium in bipolar depression had significant methodological flaws and only one study of lithium met our primary search criteria. That study included lithium as direct comparison of quetiapine (along with placebo) and did not find any effect.[20] Antidepressants also had very limited data as primary treatments of bipolar depression with only one study of paroxetine, again in a comparison arm with quetiapine, showing no efficacy.[18]

Given the limited data it is difficult to directly compare the 5 medications that showed positive primary treatment effects in depression: quetiapine, lamotrigine, olanzapine, olanzapine/fluoxetine, and divalproex. Three recent meta-analyses have included data from the majority of treatment studies discussed in this review.[4,6,8] Not surprisingly, the studies with the fewest number of subjects often had the greatest relative risk reduction. Given that these small studies showed the greatest variance among subjects this observation cannot be taken as evidence that they are more effective. Instead, we are left with a qualitative assessment that quetiapine has the most evidence of efficacy in bipolar depression followed by olanzapine. Head-to-head trials, which include a placebo arm, are needed to appropriately test differences among interventions.

In terms of adjunctive treatments for bipolar depression, the main class of medications studied was antidepressants. These studies reported mixed results for a variety of

antidepressants but the majority found no differences compared to placebo. The most recent and inclusive meta-analysis of adjunctive antidepressant treatment found they have no efficacy.[13] Outside of antidepressants there was one positive adjunctive study of lamotrigine, omega-3 fatty acids, modafinil, and Armodafinil while there was one negative trial of omega-3 fatty acids, ziprasidone, and levetiracetam.[25,28,41,42,47–49]

The studies discussed in this review were all short term and do not address questions about maintenance treatment of bipolar disorder. While long term maintenance treatment of bipolar disorder is a large topic which falls outside the scope of this review, two studies which bridge the gap between acute and maintenance treatment are worth mentioning. Altshuler et al.[50] examined 3 different adjunctive antidepressants in bipolar depression. They then followed 83 responders for one year while continuing the double blind treatment assignments and found that 53% of the participants maintained remission. Ghaemi et al.[51] followed 70 responders from the Systematic Treatment Enhancement Program for Bipolar Depression (STEP-BP) on mood stabilizers and adjunctive antidepressants. Subjects were openly randomized to either continue or discontinue their antidepressants for 1 to 3 years. There were no differences in remission rates in the two groups suggesting no benefit to long term antidepressant continuation.

Treating depression in patients with bipolar I disorder remains a clinical challenge. Unlike a decade and a half ago there is now more quality research to guide decisions. Yet only a few medications have received adequate study as primary treatments. Larger well controlled studies are needed of traditional mood stabilizers: lithium, divalproex, and carbamazepine. In addition, the role if any, of antidepressants remains controversial and more research is needed here as well. Finally, for all treatments, many patients do not respond to monotherapy for bipolar depression, so novel approaches are sorely needed for this serious public health problem.

Acknowledgments

This study was supported by NIMH grants K23MH081214 (Cerullo) and P50MH077138 and R01MH071931 (Strakowski).

References

1. Narrow W, Rae D, Robins L, et al. Revised Prevalence Estimates of Mental Disorders in the United States: Using a Clinical Significance Criterion to Reconcile 2 Surveys' Estimates. Arch Gen Psych. 2002; 59:115–123.
2. Judd L, Akiskal H. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. J Affect Disord. 2003; 73:123–131. [PubMed: 12507745]
3. Zornberg G, Pope H. Treatment of depression in bipolar disorder: New directions for research. J Clin Psychopharmacol. 1993; 13(6):397–408. [PubMed: 8120153]
4. Van Lieshout RJ, MacQueen GM. Efficacy and acceptability of mood stabilizers in the treatment of acute bipolar depression: Systematic review. Br J Psychiatry. 2010; 196:266–273. [PubMed: 20357301]
5. Nivoli AM, Colom F, Murru A, et al. New treatment guidelines for acute bipolar depression: A systematic review. J Affect Disord. 2011; 129:14–26. [PubMed: 20538341]
6. Vieta E, Locklear J, Gunther O, et al. Treatment options for bipolar depression: A systematic review of randomized, controlled trials. J Clin Psychopharmacol. 2010; 30(5):579–590. [PubMed: 20814319]
7. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: Independent meta-analysis and meta-regression of individual patient data from five randomized trials. Br J Psychiatry. 2009; 194:4–9. [PubMed: 19118318]

8. De Fruyt F, Deschepper E, Audenaert K, et al. Second Generation antipsychotics in the treatment of bipolar depression: A systematic review and meta-analysis. J Psychopharmacol. 2011; 26(5):603–617. [PubMed: 21940761]
9. Smith LA, Cornelius VR, Azorin JM, et al. Valproate for the treatment of acute bipolar depression: Systematic review and meta-analysis. J Affect Disord. 2010; 122:1–9. [PubMed: 19926140]
10. Bond DJ, Lam RW, Yatham LN. Divalproex sodium versus placebo in the treatment of acute bipolar depression: A systematic review and meta-analysis. J Affect Disord. 2010; 124:228–234. [PubMed: 20044142]
11. Fountoulakis KN, Grunze H, Panagiotidis P, Kaprinis G. Treatment of bipolar depression: An update. J Affect Disord. 2008; 109:21–34. [PubMed: 18037498]
12. Dodd BM. Bipolar II disorder: A review. Bipolar Disorders. 2005; 7:11–21. [PubMed: 15654928]
13. Sidor MM, MacQueen GM. Antidepressants for the acute treatment of bipolar depression: A systematic review and meta-analysis. J Clin Psychiatry. 2011; 72(2):156–167. [PubMed: 21034686]
14. Gijsman H, Geddes J, Rendell J, Nolen W, Goodwin G. Antidepressants for bipolar depression: A systematic review of randomized, controlled trials. Am J Psychiatry. 2004; 161(9):1537–1547. [PubMed: 15337640]
15. Spanemberg L, Massuda R, Lovato L, et al. Pharmacological treatment of bipolar depression: Qualitative systematic review of double-blind randomized clinical trials. Psychiar Q. 2012; 83:161–175.
16. Calabrese JR, Keck PE, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry. 2005; 162(7):1351–1360. [PubMed: 15994719]
17. Thase ME, Macfadden W, Weisler RH, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression. J Clinl Psychopharmacol. 2006; 26(6):600–609.
18. McElroy S, Weisler R, Chang W, et al. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). J Clin Psychiatry. 2010; 71(2):163–174. [PubMed: 20122366]
19. Suppes T, Datto C, Minkwitz M, et al. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. J Affect Disord. 2010; 121:106–115. [PubMed: 19903574]
20. Young AH, FRCPsych, McElroy SL, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). J Clin Psychiatry. 2010; 71(2):150–162. [PubMed: 20122369]
21. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry. 2003; 60:1079–1088. [PubMed: 14609883]
22. Tohen M, McDonnell DP, Case M, et al. Randomized, double-blind, placebo-controlled study of olanzapine in patients with bipolar I depression. Br J Psychiatry. 2012 (Epub ahead of print).
23. Thase ME, Jonas A, Khan A, et al. Aripiprazole monotherapy in non-psychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. J Clin Psychopharmacol. 2008; 28(1):13–20. [PubMed: 18204335]
24. Lombardo L, Sachs G, Kolluri S, Kremer C, Yang R. Two 6-week, randomized, double-blind, placebo-controlled studies of ziprasidone in outpatients with bipolar I depression. J Clin Psychopharmacol. 2012; 32(4):470–478. [PubMed: 22722504]
25. Sachs GS, Ice KS, Chappell PB. Efficacy and safety of adjunctive oral ziprasidone for acute treatment of depression in patients with bipolar I disorder: A randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2011; 72(10):1413–1422. [PubMed: 21672493]
26. Calabrese JR, Huffman RF, White RL, et al. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. Bipolar Disorders. 2008; 10:323–333. [PubMed: 18271912]
27. Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I disorder. J Clin Psychiatry. 1999; 60(2):79–88. [PubMed: 10084633]

28. van der Loos ML, Mulder PG, Hartong EG, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: A multicenter, double-blind, placebocontrolled trial. J Clin Psychiatry. 2009; 70(2):223–231. [PubMed: 19200421]
29. Brown EB, McElroy SL, Keck PE, et al. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. J Clin Psychiatry. 206; 67:1025–1033. [PubMed: 16889444]
30. Davis LL, Bartolucci A, Petty F. Divalproex in the treatment of bipolar depression: A placebo-controlled study. J Affect Disord. 2005; 85:259–266. [PubMed: 15780695]
31. Ghaemi SN, Gilmer WS, Goldberg JF, et al. Divalproex in the treatment of acute bipolar depression: A preliminary double-blind, randomized, placebo-controlled pilot study. J Clin Psychiatry. 2007; 68(12):1840–1844. [PubMed: 18162014]
32. Muzina DJ, Gao K, Kemp DE. Acute efficacy of divalproex sodium versus placebo in mood stabilizer-naive bipolar I or II depression: A double-blind, randomized, placebo-controlled trial. J Clin Psychiatry. 2011; 72(6):813–819. [PubMed: 20816041]
33. Baron MB, Gershon ES, Rudy V, et al. Lithium carbonate response in depression. Arch Gen Psychiat. 1975; 32:1107–1111. [PubMed: 1101845]
34. Goodwin FK, Murphy DL, Bunney WE. Lithium-carbonate treatment in depression and mania. Arch Gen Psychiat. 1969; 21:486–496. [PubMed: 4896983]
35. Noyes R, Dempsey GM, Blum A, Cavanaugh GL. Lithium treatment of depression. Compr Psychiatry. 1974; 15(3):187–193. [PubMed: 4826041]
36. Stokes PE, Stoll PM, Shamoian CA, Patton MJ. Efficacy of lithium as acute treatment of manic-depressive illness. Lancet. 1971; 1:1319–1325. [PubMed: 4103395]
37. Goodwin FK, Murphy DL, Dunner DL, Bunney WE. Lithium response in unipolar versus bipolar depression. Am J Psychiatry. 1972; 129(1):76–79.
38. Cohn JB, Collins G, Ashbrook E, Wernicke JF. A comparison of fluoxetine imipramine and placebo in patients with bipolar depressive disorder. Int Clin Psychopharmacol. 1989; 4:313–322. [PubMed: 2607128]
39. Nemeroff CB, Evans DL, Gyulai L, et al. Double-blind, placebo controlled comparison of Imipramine and paroxetine in the treatment of bipolar depression. Am J Psychiatry. 2001; 158(6): 906–912. [PubMed: 11384898]
40. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J oMed. 2007; 356(17):1711–1722.
41. Calabrese JR, Ketter TA, Youakim JM, et al. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder: A randomized, multicenter, double-blind, placebo-controlled, proof-of-concept study. J Clin Psychiatry. 2010; 71(10):1363–1370. [PubMed: 20673554]
42. Saricicek A, Maloney K, Muralidharan A, et al. Levetiracetam in the management of bipolar depression: A randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2011; 72(6): 744–750. [PubMed: 21034692]
43. Ghaemi, Goodwin. Antidepressants for bipolar depression. Am J Psychiatry. 2005; 162(8):1545–1546. [PubMed: 16055786]
44. Goldberg JF, Truman CJ. Antidepressant-induced mania: An overview of current controversies. Bipolar Disorders. 2003; 5:407–420. [PubMed: 14636364]
45. Tondo L, Vazquez G, Baldessarini RJ. Mania associated with antidepressant treatment: comprehensive meta-analytic review. Acta Psychiatr Scand. 2010; 121:404–414. [PubMed: 19958306]
46. Licht RW, Gijsman H, Nolen WA, Angst J. Are antidepressants safe in the treatment of bipolar depression? A critical evaluation of their potential risk to induce switch into mania or cycle acceleration. Acta Psychiatr Scand. 2008; 118:337–346. [PubMed: 18754834]
47. Frye MA, Grunze H, Suppes T, et al. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. Am J Psychiatry. 2007; 164:1242–1249. [PubMed: 17671288]
48. Stoll AL, Severus WE, Freeman MP, et al. Omega 3 fatty acids in bipolar disorder. Arch Gen Psychiatry. 1999; 56:407–412. [PubMed: 10232294]

49. Keck PE, Mintz J, McElroy SL, et al. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. Biol Psychiatry. 2006; 60:1020–1022. [PubMed: 16814257]

50. Altshuler LL, Post RM, Hellemann G, et al. Impact of antidepressant continuation after acute positive or partial treatment response for bipolar depression: A blinded randomized study. J Clin Psychiatry. 2009; 70(4):450–457. [PubMed: 19358785]

51. Ghaemi SN, Ostacher MM, El-Mallakh RS, et al. Antidepressant discontinuation in bipolar depression: A systematic treatment enhancement program for bipolar disorder (STEP-BP) randomized clinical trial of long-term effectiveness and safety. J Clin Psychiatry. 2010; 71(4):372–380. [PubMed: 20409444]

Table 1

Studies of primary medications for the treatment of bipolar depression.

Study	Treatment	Dose	Study Duration	Number Treatment	Number Placebo	Primary Outcome	Treatment superior to placebo	Remission rate treatment	Remission rate placebo
Calabrese et al. 2005	Quetiapine	300 mg	8 weeks	181 (BPII*)	181 (BPII*)	Change in MADRS	Yes	53%	28%
Calabrese et al. 2005	Quetiapine	600 mg	8 weeks	180 (BPII*)	181 (BPII*)	Change in MADRS	Yes	53%	28%
Thase et al. 2006	Quetiapine	300 mg	8 weeks	155 (51 BP II)	161	Change in MADRS	Yes	52%	37%
Thase et al. 2006	Quetiapine	600 mg	8 weeks	151 (50 BP II)	161	Change in MADRS	Yes	52%	37%
McElroy et al. 2010	Quetiapine	300 mg	8 weeks	245 (BPII*)	121 (BPII*)	Change in MADRS	Yes	65%	55%
McElroy et al. 2010	Quetiapine	600 mg	8 weeks	247 (BPII*)	121 (BPII*)	Change in MADRS	Yes	69%	55%
Young et al. 2010	Quetiapine	300 mg	8 weeks	255 (95 BP II)	129 (51 BP II)	Change in MADRS	Yes	70%	55%
Young et al. 2010	Quetiapine	600 mg	8 weeks	263 (101 BP II)	129 (51 BP II)	Change in MADRS	Yes	70%	55%
Suppes et al. 2010	Quetiapine XR	300 mg	8 weeks	133 (26 BP II)	137 (27 BP II)	Change in MADRS	Yes	54%	39%
Tohen et al. 2003	Olanzapine	5–20 mg	8 weeks	370	377	Change in MADRS	Yes	33%	25%
Tohen et al. 2003	Olanzapine/Fluoxetine	6–12 mg/25–50 mg	8 weeks	86	377	Change in MADRS	Yes	49%	25%
Tohen et al. 2012	Olanzapine	5–20 mg	6 weeks	343	171	Change in MADRS	Yes	39%	29%
Thase et al. 2008	Aripiprazole	5–30 mg	8 weeks	186	188	Change in MADRS	No	30%	28%
Thase et al. 2008	Aripiprazole	5–30 mg	8 weeks	187	188	Change in MADRS	No	26%	29%
Lombadro et al. 2012	Ziprasidone	40–80 mg	6 weeks	165	168	Change in MADRS	No	NA	NA
Lombadro et al. 2012	Ziprasidone	120–160 mg	6 weeks	171	168	Change in MADRS	No	NA	NA
Lombadro et al. 2012	Ziprasidone	120–160 mg	6 weeks	185	196	Change in MADRS	No	NA	NA
Calabrese et al. 2008	Lamotrigine	50 mg	7 weeks	66	66	Change in HAM-D	No	NA	NA
Calabrese et al. 2008	Lamotrigine	200 mg	8 weeks	63	66	Change in HAM-D	No	NA	NA
Calabrese et al. 2008	Lamotrigine	100–400 mg	10 weeks	103 (42 BP II)	103 (42 BP II)	Change in HAM-D	No	NA	NA
Calabrese et al. 2008	Lamotrigine	200 mg	8 weeks	133	124	Change in MADRS	No	NA	NA
Calabrese et al. 2008	Lamotrigine	200 mg	8 weeks	200	128	Change in HAM-D	No	NA	NA
Davis et al. 2005	Divalproex	Mean 80 mcg/ml	8 weeks	13	12	Change in HAM-D	Yes	46%	25%
Ghaemi et al. 2007	Divalproex	70–90 mcg/ml	6 weeks	9 (5 BP II)	9 (4 BPII)	Change in MADRS	Yes	NA	NA
Muzina et al. 2010	Divalproex	>50 mcg/ml	6 weeks	26 (BPII*)	28 (BPII*)	Change in MADRS	Yes	23%	11%

Study	Treatment	Dose	Study Duration	Number Treatment	Number Placebo	Primary Outcome	Treatment superior to placebo	Remission rate treatment	Remission rate placebo
Young et al. 2010	Lithium	600–1800 mg	8 weeks	136 (49 BP II)	129 (51 BP II)	Change in MADRS	No	63%	55%
McElroy et al. 2010	Paroxetine	20 mg	8 weeks	122 (BPII *)	121 (BPII *)	Change in MADRS	No	57%	55%

* The number of participants with bipolar II in each group is unavailable.

MADRS - Montgomery-Åsberg depression rating scale

HAM-D - Hamilton rating scale for depression

Table 2

Studies of adjunctive medications for the treatment of bipolar depression.

Study	Treatment	Dose	Study Duration	Concomitant meds	Number Treatment	Number Placebo	Primary Outcome	Treatment superior to placebo
van der Loos et al. 2009	Lamotrigine	200 mg	8 weeks	Lithium	64	60	Change in MADRS	Yes
Sachs et al. 2011	Ziprasidone	40–160 mg	6 weeks	Lamotrigine, lithium, or divalproex	147	147	Change in MADRS	No
Saricicek et al. 2011	Levetiracetam	500–3000 mg	6 weeks	Mood stabilizers or antidepressants or antipsychotics	17 (5 BP II)	15 (4 BP II)	Change in HAM-D	No
Cohn et al. 1989	Imipramine	75–300 mg	6 weeks	Lithium, other meds not specified	30 (DSM III criteria for BP)	29	Change in HAM-D	Yes
Cohn et al. 1989	Fluoxetine	20–80 mg	6 weeks	25% patients on lithium	30 (DSM III criteria for BP)	29	Change in HAM-D	Yes
Nemeroff et al. 2001	Paroxetine	20–50 mg	10 weeks	Lithium + carbamazepine or divalproex	33	43	Change in HAM-D and CGI	No
Nemeroff et al. 2001	Imipramine	150–300 mg	10 weeks	Lithium + carbamazepine or divalproex	36	43	Change in HAM-D and CGI	No
Sachs et al. 2007	Paroxetine	10–40 mg	6–26 weeks	Mood stabilizer or atypical antipsychotic	93 (BPII *)	187	Euthymia for 8 consecutive weeks	No
Sachs et al. 2007	Buproprion SR	150–375 mg	6–26 weeks	Mood stabilizer or atypical antipsychotic	86 (BPII *)	187	Euthymia for 8 consecutive weeks	No
Frye et al. 2007	Modafinil	100–200 mg	6 weeks	Mood stabilizer ± an antidepressant	41(7 with BP II)	46	Change in IDS	Yes
Calabrese et al.	Armodafinil	150 mg	8 weeks	Lithium, olanzapine, or divalproex.	128	129	Change in IDS	Yes
Goldberg et al.	Pramipexole	1–2.5 mg	6 weeks	Mood stabilizers	12	10	Change in HAM-D	Yes
Stoll et al.	Omega-3 fatty acids	9.6 g	16 weeks	Treatment as usual	14 (BPII *)	16	Study discontinuation	Yes
Keck et al.	Omega-3 fatty acids	6 g	16 weeks	Mood stabilizers	29 (6 with BP II)	29	Study discontinuation	No

* The number of participants with bipolar II in each group is unavailable.

MADRS - Montgomery-Åsberg depression rating scale

HAM-D - Hamilton rating scale for depression