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

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Abstract

Objective—Bipolar II (BP 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 BP II disorder, coupled with recent publication of pertinent studies, call 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 BP II disorder.

Methods—We examined all randomized trials evaluating the use of pharmacotherapy in the treatment of acute BP II depression. 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.” Articles pertaining to pharmacotherapy of BP II disorder were identified. Studies with mixed samples of BP I and II or BP II and unipolar were examined as well. Studies were further limited to adult samples, publication in peer-reviewed journals, and in English. Twenty-one randomized trials were identified and reviewed. Therapeutic agents were rated according to the quality of evidence supporting their efficacy as treatments for BP II depression.

Results—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 BP II depression is warranted.

INTRODUCTION

Bipolar II (BP 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 DSM nomenclature since 1994[5], DSM-IV defines BP II disorder as a lifetime history of at least one episode of major depression plus at least one episode of hypomania[5]. Initial reports suggested that BP II disorder might be viewed as a more benign form of BP I disorder

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because, by definition, individuals suffering from the disorder never experience full-blown mania. Accumulating evidence however, has clarified that, because BP II disorder is characterized by multiple and often more protracted depressive episodes[6], it is at least as disabling as BP I disorder[3]. Indeed, relative to individuals suffering from BP I disorder, individuals with BP 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 BPI disorder. The lifetime incidence of BP II varies widely based on 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 BP I and, if the highest estimated prevalence is accepted, it approaches that of major depressive disorder.

BP I and II diagnoses appear stable over time[9, 10]. For example, in one study fewer than 5% of patients with BP II disorder developed a manic episode over two years of prospective follow-up, suggesting that most individuals with BP II do not "convert" to BP I[11]. Indeed, an important argument for the fact that these are distinct illnesses lies in the fact that both BP 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 BP 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 BP 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 BP 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 two BP 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 BP II disorder[21–23], forcing clinicians to "borrow" strategies that have only been systematically evaluated in individuals with BP I disorder. While it is no doubt informative to consider trials evaluating agents in individuals with either unipolar or BP I disorder, these data may ultimately prove to be misleading for the proper management of BP II disorder. Careful consideration of trials conducted in individuals who *specifically meet criteria for BP II disorder* are 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 BP II disorder, coupled with recent publication of pertinent studies, call for an updated review of this literature. As the majority of individuals with BP 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 BP II disorder.

METHODS

We examined all randomized trials evaluating the use of pharmacotherapy in the treatment of acute BP 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 BP II disorder were identified. Studies with mixed samples of BP I and II or BP II and unipolar were examined as well. Given the paucity of data on this topic, even studies that admixed subjects with BP I and II disorder without considering BP II results separately are reported. Studies discussed in this review were further limited to adult samples, publication in peer-reviewed journals and 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 a) change in acute depressive symptoms and b) induction of treatment-emergent hypomania. It is beyond the scope of this manuscript 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 BP 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 about which definitive statements of efficacy cannot be made because of limitations in the empirical evidence (i.e., small, under-powered trials, lack of adequate control condition, poorly specified outcomes, etc.).

RESULTS

Findings from the above literature search yield 21 randomized trials which are summarized in Table 2 [One report includes 5 individual randomized trials[24]]. The smallest trial included only 8 subjects with BP II disorder[25]; the largest included 321 subjects pooled from two nearly identical studies[26]. Ten of the trials were adjunctive trials—that is, the agents were tested in combination with mood stabilizers. The other eleven 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 BP II depression was examined as a secondary aim of the eponymous BOLDER studies (**B**ip**OL**ar **DE**p**R**ession). This pair of nearly identical industry-sponsored, 8-week, multi-center, randomized, double-blind, placebo-controlled studies evaluated the

efficacy of two fixed doses of quetiapine - 300 or 600 mg/day - as monotherapy for bipolar depression, with about two thirds of participants meeting criteria for BPI and one third meeting criteria for BP II disorder[27, 28]. 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 vs placebo difference within the BP II cohort (N=182) was not statistically significant[27]. 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 BP 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 600 mg/d group[28].

When considered together, BOLDER I and II comprise the largest number of BP II subjects in an acute treatment study to date. Suppes et al. presented *post hoc* analyses combining data on the BP II subjects (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)[26]. 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 ≤ 8 and Young Mania Rating Scale (YMRS) ≤ 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 two large RCTs supporting its efficacy. Primary limitations to concluding efficacy for quetiapine include a) absence of long-term follow-up, b) 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 c) lack of replication by a second, independent (i.e., non-industry-sponsored) group.

Lamotrigine

Lamotrigine has enjoyed an exceptionally controversial status with respect to the management of BP 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 BP I or II disorder, rapid-cycling[29]. This study found a 6-week difference in median survival time to a new mood episode favoring lamotrigine Indeed, fifty-two subjects met criteria for BP II in that trial, and differences favoring lamotrigine were consistently greater for BP II than BP I patients.

Small studies of lamotrigine monotherapy contributed to its growing reputation as a treatment for BP disorder. For instance, Frye and colleagues 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 BP II disorder, currently depressed. Subjects were randomly assigned to a sequence of pill placebo, lamotrigine (up to 500mg) and gabapentin (up to 4800 mg) 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 Impression scale for bipolar disorder (CGI-BP) 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 BP II subgroup[30].

Ultimately, a large positive trial of lamotrigine monotherapy for the acute treatment of BP I depression[31] coupled with maintenance trials supporting lamotrigine's efficacy as a prophylactic treatment for BP I disorder[32] led to lamotrigine's favored status as a treatment for bipolar depression in several treatment guidelines for BP disorder[21, 33]. 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 BP II depression. Calabrese and colleagues recently summarized acute bipolar depression outcomes for five double-blind, placebo-controlled, clinical trials of lamotrigine, including data from four previously unpublished studies[24]. These studies ranged from 7–10 weeks in duration and included 305 subjects who met criteria for acute BP II depression. One of the five studies included only subjects meeting criteria for BP II disorder (N=221). In four of the five studies, lamotrigine was titrated to 200 mg by week 5 or 6. In one study, lamotrigine was flexibly dosed from 100–400 mg. One study included a third comparator arm of low dose (50 mg) lamotrigine. The primary outcome measure was the 17-item Hamilton Depression Rating Scale (Ham-D) in two studies, and the MADRS in three studies. Secondary endpoints included an expanded version of the Ham-D (31 items), CGI (severity and improvement subscales) and the mood item of the Ham-D. In no study did lamotrigine differ significantly from placebo on the primary endpoint, and in most cases did not differ on secondary efficacy endpoints. Overall effect sizes on the 17-item Ham-D ranged from 0.04–0.34. The authors argue that a high placebo response rate may have contributed to at least in part to failure to detect differences between placebo and lamotrigine.

Geddes and colleagues[34] subsequently conducted a meta-analysis and "meta-regression" utilizing individual participant data from the five trials reviewed in the Calabrese 2008 report. The authors found a modest advantage of lamotrigine over placebo in both the BP I and II groups. Interestingly, they found a treatment by severity interaction such that lamotrigine was superior to placebo in individuals with Ham-D scores >24 at baseline. They note, however, that the overall number needed to treat (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 BP I and II subgroups.

These "mixed reviews" for lamotrigine as a monotherapy for BP II disorder are further confounded by a recent report by Suppes and colleagues[35] in which they randomly assigned subjects meeting criteria for BP II depression to either lithium (n=54) or lamotrigine (n=44) and followed them for 16 weeks. They found significant improvements in HRSD17 and YMRS scores in both groups over time with no significant between group differences. The

Suppes et al. trial was notable, however, for relatively high dropout rates (42%) across conditions.

Lamotrigine has shown some promise as an adjunctive treatment for BP depression. Nierenberg and colleagues evaluated lamotrigine, inositol, and risperidone as adjunctive treatments for patients with treatment resistant bipolar depression. They enrolled patients meeting diagnostic criteria for BP I (n=25), BP II (n=21), or BP 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 one 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[36]. 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 (BP 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 randomly assigned 124 depressed individuals meeting criteria for either BP 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 BP 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 versus −11.0, p=0.024) in the total sample. Response rates in the lamotrigine group (51.6%) were significantly higher than in the placebo group (31.7%) (p=0.03). The investigators state that the sample size was too small to evaluate treatment-by-subgroup interactions with respect to BP I versus BP II subtypes[38].

Despite the high rating of lamotrigine in many practice guidelines, available evidence suggests that lamotrigine monotherapy lacks definitive efficacy in BP 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: the Nierenberg et al. trial, involving adjunctive use of lamotrigine, 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 of lack of efficacy. Thus, lamotrigine (both as monotherapy and adjunctive treatment) is best considered a second-line option for acute BP 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 BP II disorder, with mostly positive findings[39–42], but relatively little date is available evaluating its efficacy as an acute treatment. Recently, Amsterdam and colleagues[43] compared open-label lithium (N=40) to venlafaxine (N=43) as monotherapies for BP 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 SSRIs such as sertraline and paroxetine) despite concomitant treatment with mood stabilizers[44–46]. Subjects received up to 375 mg of venlafaxine (mean maximum of 186 mg) 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 Ham-D. Secondary outcome measures included the YMRS scores and proportion responding and remitting. Amsterdam and colleagues found a large efficacy advantages for venlafaxine on the primary outcome measure (Ham-D) 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 two or more study visits, and only one 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 comparing lithium and lamotrigine is supportive of lithium but not definitive[35]. Notably, 59% of subjects achieved remission with lithium alone, but drop-out rates were high (42%).

Based on the available evidence, lithium has preliminary support for efficacy as treatment for BP II depression, based primarily on the single positive trial by Suppes and colleagues 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 BP II disorder. A single, small trial was conducted in a mixed sample of individuals meeting criteria for BP I (n=9) and BP II/NOS (n=9) in which acutely depressed patients 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 BP II/NOS cohort[47].

Based on the limited available evidence, efficacy of valproate in the treatment of BP II depression is not established.

Antidepressants

Antidepressants are controversial agents in the armamentarium for BP. On the one hand, there are concerns about both limited efficacy and risk of inducing (hypo)manic switches, yet on the other hand, these agents are widely used in clinical practice [48]. It is also true that the risk/benefit ratio may be different in BP I and II disorder. For instance, Altshuler and colleagues published a report showing that among individuals with BP disorder treated with an antidepressant (in conjunction with a mood stabilizer), rates of switching were lower among those with BP II disorder than those with the BP 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 [45]. 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 [49]. 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 BP 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 (range 20–40 mg). Median dose of bupropion was 300 mg (range 150–338 mg). 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[49].

Several smaller studies have been conducted evaluating antidepressants as augmentation strategies for BP II depression. Schaffer and colleagues randomly assigned 20 depressed subjects meeting criteria for either BP I or II disorder (8 subjects met criteria for BP II) who were currently receiving a mood stabilizing medication to either citalopram or lamotrigine. Citalopram was dosed from 20–50 mg/d and lamotrigine was dosed to 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 randomly assigned 27 depressed subjects meeting criteria for either BP I or II disorder (16 subjects met criteria for BP 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. Primary outcome measure was Ham-D. Analyses showed a main effect for time, but no effect for group or group X 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 BP II subgroup were not reported separately[50].

Leverich and colleagues, as part of a larger Stanley Bipolar Network study including subjects meeting criteria for BP I and II disorder, randomized depressed subjects meeting criteria for BP 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 BP II cohort, but overall response rates ranged from 43–55% and did not differ among pharmacotherapeutic agents[46].

Use of antidepressants as monotherapy in BP I disorder is contraindicated because of the high risk of inducing mania and mood cycling[51]. Indeed, most formal treatment guidelines advise against using antidepressants as monotherapy in bipolar patients—without regard to bipolar subtype—because of the magnitude of these risks[22, 23, 52], especially among those receiving tricyclic antidepressants[53]. Nevertheless, there are some interesting preliminary data suggesting that antidepressants may be safely used as monotherapy, at least in a subset of individuals with BP II disorder.

Initial support for antidepressant monotherapy in BP II depression came from open-label trials by Amsterdam and colleagues 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 hypomanic symptoms during fluoxetine therapy[54]. 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 females meeting criteria for acute BP II depression. Primary outcome measure was ≥50% reduction in the 21-item version of the Ham-D. Overall response rate was 63% in the sample, with 0% switch rate[55]. 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[43]. Parker and colleagues conducted a 9-month, randomized, double-blind, placebo-controlled, cross-over study in small (N=10) sample of medication naïve subjects meeting criteria for BP 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[56]. This led Parker to assert that SSRIs may constitute “mood stabilizers” for BP II disorder[57], although the evidence base for such an assertion is currently rather limited.

Antidepressants are considered “Type B” agents for BP 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 monontherapy, several open studies and two 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 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 BP II depression if alternative approaches have failed.

Pramipexole

Zarate and colleagues evaluated the dopamine agonist, pramipexole, as treatment for BP II depression. In a double-blind, RCT, subjects meeting criteria for acute BP 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% v. 9%), remission (40% v. 9%), and % change in MADRS scores (47.1 ± 27.2 v 12.4 ± 25.0). One subject in the pramipexole group and 2 subjects in the placebo group reached YMRS scores ≥ 12 for 1 week[58].

Pramipexole is a “Type B” agent for BP II depression. Because it has only been tested in one 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, 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 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 BP II disorder (n=21). Modafinil was titrated to 200 mg (mean dose, 177 mg/d). Primary outcome measures were the Inventory of Depressive Symptoms (IDS) and CGI (severity subscale). In the entire sample (both BP 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 BP I compared to BP II ($F=6.58$, $df=1,84$, $p=0.012$). They also reported that while there were significant differences between placebo and modafinil response rates in the BP I cohort (defined as 50% reduction in IDS scores), there were no differences in response rates within the BP II group (1 out of 7 in the modafinil group v. 1 out of 14 in the placebo group)[59].

Modafinil has been tested in one trial that included a small number of patients with BPII. Although the evidence from this trial was favorable overall, the BP II subgroup apparently did not obtain as much benefit as the patients with BPI disorder—although this could be explained by the small number of subjects randomized per study arm and the inability to

distinguish between outcomes with such small sample sizes. Additional data is required to establish efficacy.

Omega-3 Fatty Acids

Keck and colleagues conducted a 4-month, placebo-controlled randomized trial evaluating the efficacy of an omega-3 fatty acid, ethyl-eicosapentanoate (EPA). EPA was administered in conjunction with mood stabilizing medication at a dose of 6 g/d. Investigators randomized 116 subjects with BP disorder, including 33 individuals with BP 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 BP II subgroup were not reported separately [60]. Frangou and colleagues evaluated adjunctive EPA at much lower doses (1 g/d and 2 g/d) than the Keck et al. trial. They randomly assigned 75 subjects with BP disorder, including individuals with BP II disorder (n=10), who had at least mild depressive symptoms (HSRD-17 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 HRSD-17, the CGI, and YMRS. Improvement in depression scores (HRSD-17 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 on-going medication management and had their medications adjusted as needed during the course of the trial. Outcomes for the BP II subgroup were not reported separately[61].

Data from these two EPA trials in bipolar depression are conflicting, with one study showing lack of efficacy and the other showing benefit. However, because the BP II subgroups were small in both trials and results were not reported separately, definitive statements about efficacy in BP II are not indicated.

DISCUSSION

The extant literature yields two rigorously tested compounds for BP 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 bipolar II patients 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 (i.e., 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 BP 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 both BP I and II subjects, the single lamotrigine trial that focused on BP 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 BP II depression. Analyses from a “mega regression” suggest that lamotrigine monotherapy may play a role in the treatment of more severely depressed patients, and

smaller trials suggest it may have efficacy when used an adjunctive agent, but additional data will need to be collected before definitive statements can be made. Thus, of the two 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 the management of BP II depression are perhaps most interesting. The results of the recent study of Amsterdam and colleagues[43], which are derived from a randomized but open label trial, suggest that the risk of switch in BP II disorder are low and rates of response reasonably high. By contrast, the results of the somewhat larger STEP-BD trial[49], differ from those of Amsterdam et al., at least in terms of efficacy, in that the subset of bipolar II patients who received antidepressants as add-on therapy (as a 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 three 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 BP II subjects. The data for the mixed BP I and II cohorts for the two published omega-3 trials are conflicting, with one study failing to show an advantage for EPA over placebo. However, neither omega-3 trial examined the BP 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 BP II depression. This disorder has long been under-studied, 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 manuscript 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 BP II

phenotype in order to explore differential responses to pharmacotherapy within BP II subgroups. Data from these types of studies would further help to guide informed clinical decision making for individuals who suffer from BP II disorder and the physicians who care for them.

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Table 1

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

Designation	Definition
Type A	Rigorously tested in 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

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 RCTs	321 BP II	Quetiapine 300 mg/d versus quetiapine versus 600 mg/d versus placebo	8 weeks	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.	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 BP II, 11 BP I, 6 unipolar, with refractory mood episodes	Lamotrigine versus gabapentin versus placebo	Each agent was administered for 6 weeks, for a total trial length of 18 weeks	Monotherapy	Response rate for lamotrigine (52%) was superior to gabapentin (26%) and placebo (23%). No separate analyses were conducted for the BP II subgroup.	Type B
Nierenberg et al.[37]	Randomized with equipoise stratification	21 BP II, 25 BP I, 1 BP NOS with treatment resistant depression	Lamotrigine, versus inositol versus risperidone	16 weeks	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 BP II subgroup.	Type B
van der Loos et al.[38]	Randomized	40 BP II, 84 BP I	Lithium plus lamotrigine versus lithium plus placebo	8 weeks	Adjunctive	Significantly more patients responded to adjunctive lamotrigine (51.6%) than placebo (31.7%). No separate analyses were conducted for the BP II subgroup.	Type B: BP subgroup were not reported separately
Calabrese et al.[24]	Summary of 5 double-blind, RCTs.	305 BP II, 833 BP I	Lamotrigine versus placebo	7–10 weeks	Monotherapy	Lamotrigine did not differ significantly from placebo on primary outcomes, including in the BP II trial. Overall effect sizes on the 17-item	Type A: Meta analysis of RCTs, but data do not support efficacy of lamotrigine

Authors	Design	Sample	Treatment	Duration	Monotherapy or Adjunctive	Key Results	Quality of Evidence
						Ham-D ranged from 0.04–0.34 Ham-D ranged from 0.04–0.34	
Suppes et al.[35]	Open-label, randomized	98 BP II	Lamotrigine versus lithium	16 weeks	Monotherapy	Both groups showed significant improvement on Ham-D scores over time with no differences in outcomes between groups. Drop-out 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.[43]	Open-label, randomized	83 BP II	Lithium versus venlafaxine	12 weeks	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.[47]	Double blind RCT	9 BP II/ NOS, 9 BP I	Divalproex versus placebo	6 weeks	Monotherapy	Divalproex was superior to placebo on measures of depressive symptoms. The authors did not report separate outcomes for the BP II/NOS cohort	Type B
Sachs et al.[49]	Double blind, RCT with equipoise stratification	114 BP II, 240 BP I	Antidepressant (bupropion or paroxetine) v. placebo	26 weeks	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
Schaffer et al.[25]	Double-blind, randomized	8 BP II, 12 BP I	Citalopram v. lamotrigine	12 weeks	Adjunctive	Both groups showed clinically significant improvement on MADRS scores with	Type B

Authors	Design	Sample	Treatment	Duration	Monotherapy or Adjunctive	Key Results	Quality of Evidence
						no statistically significant differences between groups. No separate ana	
						no statistically significant differences between groups. No separate ana	
						no statistically significant differences between groups. No separate ana	
						no statistically significant differences between groups. No separate ana	
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						no statistically significant differences between groups. No separate ana	
Young et al.[50]	Double-blind, randomized	16 BP II, 11 BP I	Paroxetine or a second mood stabilizer (lithium or divalproex)	6 weeks	Adjunctive	Both groups improved over time, but there were no significant differences between groups. Higher dropout rates in the mood stabilizer group. Results for the BP II subgroup were not reported separately	Type B
Leverich et al.[46]	Randomized	42 BP II, 115 BP I, 2 BP NOS	Sertraline versus bupropion versus venlafaxine	10 weeks	Adjunctive	Overall response rates ranged from 43–55% and did not differ among agents. Results for the BP II subgroup were not reported separately	Type B
Parker et al.[56]	randomized, double-blind, placebo-controlled, cross-over study	10 BP II	Escitalopram versus placebo	9-months	Monotherapy	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.	Type B
Zarate et al.[58]	Double-blind, RCT	21 BP II	Pramipexole versus placebo	6 weeks	Adjunctive	Pramipexole was associate with greater reductions in depression scores and no greater rates of switching.	Type B
Frye et al.[59]	Double-blind, RCT	21 BP II, 64 BP I	Modafinil versus placebo	6 weeks	Adjunctive	There were statistically significant differences in response rates between placebo and modafinil in the entire sample and in the BP I cohort, but there were no differences in response rates within the BP II subgroup	Type B: BP II subgroup was small, and there were no differences in response rates reported in this subgroup

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Authors	Design	Sample	Treatment	Duration	Monotherapy or Adjunctive	Key Results	Quality of Evidence
Keck et al.[60]	Double-blind, RCT	33 BP II, 86 BP I, 1 BP NOS	Ethyl-eicosapentano ate (EPA) versus placebo	4 months	Adjunctive	No differences in outcome measures across treatment groups in the entire sample. Outcomes for the BP II subgroup were not reported separately	Type B
Frangou et al.[61]	Double-blind RCT	10 BP II, 65 BP I	Ethyl-eicosapentano ate (EPA) 1 g/d or 2 g/d versus placebo	12 weeks	Adjunctive	There were statistically significant greater differences in symptomatic improvement between placebo and EPA (both doses) in the entire sample. Outcomes for the BP II subgroup were not reported separately.	Type B

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 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 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 (SSRI)	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: One small RCT suggest 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 BP I/II cohort, but no clear signal for BP II subjects emerged	Inadequate data
Omega-3 Fatty Acids	A small number of individuals with BP II were included in two large RCTs but were not examined separately.	Inadequate data; available information is conflicting about its benefit as an add-on treatment in mixed BP I/II samples.