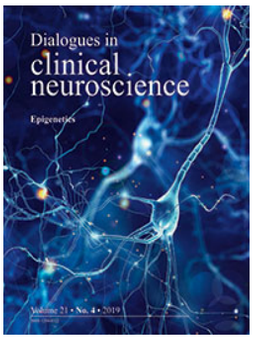

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Dialogues in Clinical Neuroscience

ISSN: (Print) (Online) Journal homepage: informahealthcare.com/journals/tdcn20

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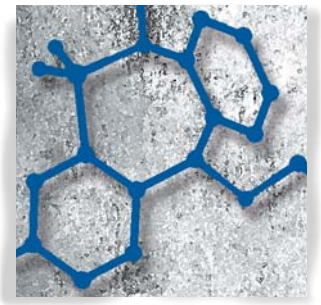
To cite this article: David E. Kemp, David J. Muzina, Roger S. McIntyre & Joseph R. Calabrese (2008) Bipolar depression: trial-based insights to guide patient care, Dialogues in Clinical Neuroscience, 10:2, 181-192, DOI: 10.31887/DCNS.2008.10.2/dekemp

To link to this article: https://doi.org/10.31887/DCNS.2008.10.2/dekemp

Bipolar depression: trial-based insights to guide patient care

David E. Kemp, MD; David J. Muzina, MD; Roger S. McIntyre, MD; Joseph R. Calabrese, MD



For the majority of patients with bipolar disorder, major depressive episodes represent the most debilitating and difficult-to-treat illness dimension. Patients spend significantly more time depressed than manic or hypomanic, and attempt suicide more frequently during this illness phase, yet the availability of treatments remains limited. The discovery of more effective therapeutics for managing depressive episodes is arguably the greatest unmet need in bipolar disorder. This article provides an evidence-based summary of pharmacological treatments for the acute and longitudinal management of bipolar depression. Clinical trial results are reviewed for a diverse array of compounds, inclusive of traditional mood stabilizers (eg, lithium and divalproex), atypical antipsychotics, unimodal antidepressants, and modafinil. Where applicable, differences in efficacy across compounds are examined through discussion of number needed to treat and effect size determinations. A pragmatic clinical approach is presented for management of the depressed phase of bipolar disorder.

Dialogues Clin Neurosci. 2008;10:181-192.

Background

Although mania and hypomania are the essential and more florid features of bipolar disorder, debilitating depressive symptoms and episodes dominate the longitudinal course, and are less responsive to treatment. Moreover, the initial presentation of bipolar disorder is often depression, which delays the establishment of the correct diagnosis and initiation of appropriate guideline concordant care. During the past decade, there has been a growing appreciation of the harmful dysfunction associated with depression as part of bipolar disorder. For example, patients diagnosed with and/or screening positive for bipolar disorder evince greater deficits in work, social, and family functioning when experiencing depressive versus manic symptoms.[1] Similarly, in a systematic 20-year prospective study, Judd and colleagues[2] identified minor depression or dysthymia to be more disabling than hypomania, as well as a trend for major depression to be more impairing than mania. Across the bipolar (BP) I and II subtypes, a parallel gradient between the level of psychosocial impairment and severity of depressive symptoms has been documented. The risk of suicide, which averages 0.4% per year among patients with bipo-

Keywords: *bipolar disorder; bipolar depression; anticonvulsant; unimodal antidepressant; atypical antipsychotic; number needed to treat; maintenance trial*

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Selected abbreviations and acronyms

5-HT	*serotonin*
BOLDER	*Bipolar Depression Studies (quetiapine)*
BP	*bipolar disorder*
CGI	*Clinical Global Impressions*
MADRS	*Montgomery-Asberg Depression Rating Scale*
OFC	*olanzapine-fluoxetine combination*
STEP-BD	*Systematic Treatment Enhancement Program for Bipolar Disorder*

lar disorder, also appears greater during phases of depression and dysphoric-agitated mixed states than during mania.[3]

Severely disrupting the life course of afflicted individuals, bipolar disorder is associated with high rates of unemployment,[4] medical comorbidity,[5] decreased work productivity,[6] and a reduced quality of life.[7] Even when symptoms are subsyndromal in nature, impairments in role functioning are frequently apparent.[8]

Collectively, the high morbidity and mortality associated with bipolar depression warrants considerable attention. Despite intensified efforts to characterize the antimanic effects of atypical antipsychotics, relatively few studies had tested these agents in bipolar depression. For example, of the seven available atypical agents in the US, five have been studied in pivotal randomized, placebo-controlled acute mania registration trals prior to the initiation of the first placebo-controlled trial of an atypical antipsychotic (ie, quetiapine) in bipolar depression.

Longitudinal observations which aim to characterize the symptomatic structure of bipolar disorder have highlighted its pleomorphic and changeable symptomatic expression. Bipolar disorder is more accurately categorized as a dimensional (versus modal) phenomenon, with substantial intraindividual shifts in polarity and symptom expression from threshold to subsyndromal severity. Patients with BP-I self-report depressive symptoms three times more frequently than manic symptoms.[9] An even greater depressive burden is reported by patients with BP-II, who experience some degree of depressive symptoms during more than half of all weeks during longitudinal follow-up.[10] Individuals with BP-II disorder spend nearly 40 times more days depressed than hypomanic and more days cycling or in a mixed state. However, it is possible that retrospective recall bias influenced this data, since patients are more likely to recall episodes of depression than episodes of hypomania.[11] When assessing mood state prospectively, through the use of daily life-charting methodology, the ratio of depression to mania/hypomania was found to be similar in subjects with BP-I or II.[12] Nevertheless, the burden of depression in bipolar disorder is consistent with recent findings from the NIH-sponsored Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).[13] In this STEP-BD report evaluating the effectiveness of guideline-based care, mood episode recurrence among 858 patients followed a median of 56.2 weeks after recovery and was experienced by 48.5% of the cohort, with depressive episodes comprising the majority of recurrences (70%). Observations of lower acute recovery rates and longer time to remission from an index depressive episode further underscore the clinical challenge in managing bipolar depression.

During the past decade, a growing number of randomized controlled trials have added to the empirical basis for selecting and sequencing treatments for bipolar depression. The overarching objective of this article is to provide practitioners with an evidence-based summary of the pharmacological treatments for bipolar depression.

We conducted a PubMed search of all English-language articles published between January 1966 and July 2007. The search was limited to randomized, double-blind, placebo-controlled trials for the treatment of acute bipolar depression. The search was augmented with a manual review of article reference lists and conference proceedings. Articles prioritized for review were based on adequacy of sample size (ie, an enrolled sample size ≥40 subjects), the use of standardized experimental procedures, validated assessment measures, and author consensus regarding overall manuscript quality.

Unimodal antidepressants in the management of bipolar depression

There is genuine complexity in the role of conventional unimodal antidepressants in the acute and/or maintenance treatment of bipolar depression. Despite the absence of large, adequately powered, randomized controlled trials in bipolar disorder, antidepressants are frequently prescribed as monotherapy and adjunctively to other conventional mood-stabilizing therapies. The hazard for treatment of urgent affective switching and cycle acceleration are well characterized, particularly in the context of antidepressant monotherapy. A recent meta-analysis of heterogeneous trials involving conventional antidepressants in bipolar disorder suggested that the

therapeutic index of these treatments is not unfavorable.[14] These results, however, are at odds with recent findings from the STEP-BD program which evaluated the efficacy, safety, and tolerability of adjunctive antidepressants in bipolar disorder.[15] In this trial, patients with BP-I or II were randomly assigned to treatment with bupropion, paroxetine, or placebo added to an FDA-approved antimanic agent. The trial employed an equipoise-stratified randomization design; thus, psychiatrists could choose from three strata (placebo vs bupropion, placebo vs paroxetine, or placebo vs either antidepressant) to allow research participation, even if the patient held a clear preference for one antidepressant versus another. A total of 366 patients enrolled in the study and were randomized to receive either a mood stabilizer plus placebo (N=187) or a mood stabilizer plus an antidepressant (N=179).

As opposed to simple measurements of response, durable recovery was uniquely chosen as the primary outcome measure, defined as a state of euthymia for 8 consecutive weeks. Secondary outcomes included traditional rates of response based on a ≥50% improvement on the Structured Clinical Interview for DSM-IV continuous symptom subscale for depression. In the end, rates of durable recovery were similar between the antidepressant (23.5%) and placebo (27.3%) groups (P=0.4). Response rates also did not differ between groups, and BP-I subjects were as likely to respond (25.4%) as were BP-II subjects (20.4%). Adjunctive antidepressant administration was not found to confer a greater benefit than mood-stabilizer monotherapy in the treatment of bipolar depression. Additionally, antidepressants were not associated with an increase in cycling between the depressive and manic poles. In summary, the study found neither an advantage nor disadvantage associated with use of the antidepressants bupropion or paroxetine.

Conventional mood stabilizers and atypical antipsychotics

Lithium

Although lithium is the oldest agent studied for the acute treatment of bipolar depression, it remains a viable and underutilized option with established efficacy in various trial designs and clinical experience. Zornberg and Pope,[16] in a comprehensive review of controlled investigations of lithium, identified eight studies that demonstrated lithium to be more effective than placebo in the treatment of acute bipolar depression. Nevertheless, most of the constituent studies in their analysis were older investigations (ie, published prior to 1978), or limited by several methodological shortcomings. For instance, our search strategy was unable to identify any moderately sized studies of lithium for the acute treatment of bipolar depression. Furthermore, early trials employed crossover as opposed to parallel designs introducing the possibility for carryover effects. The abrupt discontinuation of lithium may also have biased efficacy assessments, as acute withdrawal of lithium leads to, and hastens, a high probability of relapse.[17] Since most pivotal randomized control trials with pharmacological agents are designed primarily for registration purposes, the lack of commercial interest in this compound provides partial explanation for its understudy in bipolar depression.

A more recent study by Nemeroff and colleagues[18] evaluated and compared the efficacy of adjunctive paroxetine or imipramine to lithium in the treatment of BP-I depression as part of a randomized, double-blind, placebo-controlled trial. Among the total sample (n=117), placebo was as effective as paroxetine or imipramine on continuous measures of depression. However, among patients stratified on the basis of low lithium levels (≤0.8 mEq/L), both paroxetine and imipramine were superior to placebo. These data provide indirect, yet controlled evidence for lithium's plasma level-dependent (ie, 0.8 mEq/L or higher) efficacy. A further asset attributed to lithium is its ability to lower mortality due to completed and attempted suicide in populations of individuals with bipolar disorder.[19] Lithium-treated patients may be less likely to attempt suicide, require hospitalization for suicidal behavior, or complete suicide than bipolar patients treated with either valproate or carbamazepine.[20] Despite the advantages attributed to lithium, this cation is associated with many unacceptable side effects, a low rate of adherence, the need for plasma level monitoring, thyroid and renal surveillance, and serious safety concerns in overdose.

Lamotrigine

The anticonvulsant lamotrigine was the first compound studied for the acute treatment of BP-I depression in a large-scale, randomized, double-blind, parallel-group, placebo-controlled design.[21] In this initial 7-week efficacy trial, 195 subjects were randomized to lamotrigine 50

mg/day, lamotrigine 200 mg/day, or placebo. By week 3, whereas all subjects were receiving lamotrigine 50 mg/day, a significant difference was observed between both of the active treatment arms and placebo. However, at trial conclusion, only the lamotrigine 200 mg/day dose was superior to placebo at reducing depressive symptoms as measured by the Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impressions-Improvement (CGI-I), and Clinical Global Impressions-Severity (CGI-S) scales. Rates of response (≥50% decrease in MADRS total score) were greater with lamotrigine than placebo, regardless of whether a dose of 50 or 200 mg/day was administered.

After completion of this 7-week trial, four additional placebo-controlled monotherapy studies of lamotrigine were conducted in patients experiencing an acute episode of bipolar depression.[22] Two trials enrolled subjects with BP-I, one study enrolled subjects with BP-II, and another enrolled subjects with either BP-I or II. In each of these 4 studies, neither the mean-change-from-baseline scores on the MADRS or Hamilton Depression Rating Scale (HAM-D; 17-item scale), nor the percentage of treatment responders on the MADRS or HAM-D, differed significantly between lamotrigine and placebo. In each of the studies, the placebo response rates were generally quite high, ranging from 39% to 49%. Conceivably, the only signal for antidepressant efficacy appeared in the trial of BP-II subjects, where the percentage of CGI-I responders was higher in the lamotrigine group (61% vs 45%, $P<0.05$). This finding is consistent with a previous maintenance trial of lamotrigine in rapid-cycling bipolar disorder, where subjects with BP-II demonstrated a significantly greater study survival than placebo-treated subjects.[23] In all five multicenter monotherapy depression studies of lamotrigine completed to date, the drug was well tolerated, with headache, nausea, and rash representing the most common side effects. No reports of serious rash occurred in any of the acute bipolar depression trials.

Thus far, the five clinical trials pertaining to lamotrigine as discussed in this review have focused entirely on its use as a monotherapy for bipolar depression. Recently, however, investigators from the Netherlands and Spain have expanded the assessment of lamotrigine to explore its efficacy as an add-on treatment to lithium for the management of BP-I or II.[24] Subjects who remained depressed despite adequate treatment with lithium (plasma levels 0.6 to 1.2 mmol/L) were subsequently randomized to lamotrigine or placebo for 8 weeks of double-blind therapy. Among the 124 subjects (68% BP-I and 32% BP-II), a significant change on the MADRS total score from baseline to end point was evinced in the lamotrigine group (-15.38 points vs -11.03 points; $P=0.024$). In this study, the MADRS proved a more sensitive indicator of antidepressant response than CGI-BP scores, with 51.6% of subjects achieving ≥50% reduction in MADRS total score as compared with 31.7% in the placebo group ($P=0.03$). Statistical separation with lamotrigine was noticeable as early as week 4.

These findings add to a growing literature that supports the use of lamotrigine in acute bipolar depression, but suggests the agent may play an important role as an adjunct to conventional mood stabilizers. In a second phase of this study,[24] nonresponders to combination treatment (lithium plus lamotrigine or lithium plus placebo) were subsequently administered paroxetine in an open-label fashion for an additional 8 weeks. At the end-point assessment, no significant difference in MADRS score reduction was observed between treatment arms. As all of the initial nonresponders received paroxetine without the use of a placebo control, it is unknown whether paroxetine truly provided antidepressant benefit, or whether a subgroup of subjects merely required a longer duration of treatment with lamotrigine to attain a similar magnitude of improvement. Overall, triple therapy with lithium, lamotrigine, and paroxetine did not appear to result in greater symptom reduction than the combination of lithium and paroxetine.

Carbamazepine and divalproex

Even though carbamazepine is widely utilized in the treatment of bipolar disorder, we were unable to identify any randomized, parallel, placebo-controlled trials evaluating this agent in acute bipolar depression. The interpretation of results from earlier trials of carbamazepine were complicated by several methodological issues including crossover designs and evaluation of mixed cohorts containing unipolar and bipolar subjects.[25,26]

Initial interest in the use of divalproex monotherapy for bipolar depression was provided by an open study that suggested benefit in medication-naïve subjects with BP-II.[27] Subsequently, Sachs and colleagues conducted the first multicenter trial comparing divalproex with placebo in 43 subjects with bipolar depression (types I, II, or not otherwise specified).[28] In this 8-week study, no significant difference was observed between treatment arms in

mean change from baseline on the HAM-D. Two smaller controlled trials in bipolar depression have been conducted that demonstrate superiority of monotherapy divalproex over placebo.[29,30] In total, the controlled trial evidence evaluating divalproex in bipolar depression rests on the outcomes of 87 patients spread across three separate trials. This limited population size beckons for larger studies to confirm or refute findings that suggest divalproex may wield independent antidepressant efficacy in bipolar disorder.

Olanzapine and the olanzapine-fluoxetine combination

In 2003, an olanzapine-fluoxetine combination (OFC) was the first compound approved by the US FDA for the treatment of bipolar depression. This decision directed attention to the atypical antipsychotic drugs as appealing considerations for treating both the manic and depressed phases of bipolar disorder. The evidence for OFC's efficacy on categorical and continuous measures of depression was derived from two pooled, 8-week, placebo-controlled trials comparing olanzapine monotherapy and OFC against placebo in BP-I depression.[31] On the primary outcome measure of change from baseline to endpoint severity in MADRS score, as well as key secondary measures including rates of response and remission, olanzapine- and OFC-treated subjects achieved significantly greater improvement than placebo-treated subjects. An analysis of individual MADRS items showed OFC to improve sadness, reported sadness, lassitude, the inability to feel, and pessimistic thoughts; whereas olanzapine monotherapy improved more vegetative symptoms of depression—reduced sleep, reduced appetite, and inner tension. Neither compound was found to reduce suicidal thinking. The clinical appeal of OFC is tempered by metabolic concerns of weight gain and hyperglycemia that are more highly associated with olanzapine than with other atypical antipsychotics.[32]

Quetiapine

Quetiapine is the only monotherapeutic agent approved by the US FDA for acute bipolar depression. Quetiapine's approval for bipolar depression in 2006 was based on results of two identically-designed pivotal trials conducted in the US. A unique design feature of the quetiapine development program in bipolar depression was the inclusion of individuals with BP-II disorder. In the first of these companion trials, collectively termed the BOLDER (BipOLar DEpRession) studies, 360 patients with BP-I and 182 patients with BP-II were randomized to receive 8 weeks of treatment with either quetiapine 600 mg/day, 300 mg/day, or placebo.[33] A significant reduction in baseline-to-end point MADRS total score was evidenced in both of the quetiapine arms over placebo. Similarly, rates of response and remission were also higher in quetiapine-treated subjects. A subgroup analysis, however, did not find subjects with BP-II to demonstrate a significant improvement on the primary outcome measure at the 8-week end point. Unlike olanzapine monotherapy, an analysis of individual MADRS items showed quetiapine to not only reduce the core symptoms of depression, but to also lower suicidal thoughts to a greater extent than placebo.

A confirmatory study, BOLDER II, replicated the initial findings in BOLDER I, providing additional support for a specific antidepressant effect with quetiapine.[34] Although the magnitude of the overall treatment effect was smaller than observed in BOLDER I, both the quetiapine 600 mg/day and 300 mg/day doses were superior to placebo at reducing depressive symptoms. This effect was maintained regardless of the bipolar subtype (type I or II) or the presence of rapid-cycling, a course specifier traditionally associated with poor treatment response. There was no indication that larger doses of quetiapine provided additional antidepressant benefit, suggesting that a total daily dose of 300 mg be the recommended target.

In an attempt to explain quetiapine's antidepressant activity, Goldstein and colleagues[35] have recently reported that norquetiapine, the dealkylated active metabolite of quetiapine, possesses very high affinity for serotonin $(5\text{-HT})_{2A}$ receptors (Ki=3nM). Since (positron emission tomography (PET) studies indicate that selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and electroconvulsive therapy also downregulate the 5-HT_{2A} receptor, this point of mechanistic commonality may provide explanation for quetiapine's relatively robust and broad spectrum effect in mood disorders. In addition, Goldstein also reported that norquetiapine binds with high affinity to the 5-HT_{2C} receptor (Ki=18.5 nM), acts as a potent inhibitor of the noradrenergic transporter, and exerts partial agonist activity at the 5-HT_{1A} receptor. Partial agonist effects at 5-HT_{1A} receptors may implicate frontal cortex dopamine release as an alternative explanation for the efficacy of quetiapine in depression.

Aripiprazole

As a class, the atypical antipsychotics have demonstrated clear superiority over placebo in the treatment of acute mania. Emerging evidence, however, urges restraint in assuming that all atypicals share similar efficacy for the treatment of acute depressive episodes in bipolar disorder. This point is illustrated by recent data involving the dopamine partial agonist aripiprazole. Predicated upon uncontrolled reports suggesting aripiprazole might improve depressive symptoms in treatment-resistant unipolar major depressive disorder[36] and bipolar disorder,[37,38] two identical multicenter, double-blind trials were conducted to compare aripiprazole with placebo in BP-I subjects experiencing a nonpsychotic major depressive episode.[39] Subjects were entered into an 8-week trial and initiated on aripiprazole 10 mg daily (5 mg twice daily), then flexibly dosed to 5 to 30 mg/day. In both studies, a pattern of early statistical significance emerged, but during later study weeks this separation dissipated. By the trial end point, no significant difference was found in either of the two trials on the primary efficacy measure of mean change from baseline-to-end point score on the MADRS. Similarly, no differences were observed on any of the secondary efficacy measures. When pooling study results, a large proportion of subjects receiving aripiprazole developed akathisia (24.4%) as compared with placebo-treated subjects (3.8%). It is unknown whether attempts to prevent or mitigate akathisia by initiating aripiprazole at doses lower than 10 mg/day or by aggressive and early use of β-blockers have the potential to enhance tolerability and improve measured efficacy.
A summary of the trials discussed above can be seen in *Table I*.

Gauging clinical efficacy

One means of comparing treatment effects among different agents is through the use of effect size determinations (improvement over placebo divided by pooled standard deviation). With olanzapine monotherapy, the effect size was small (0.32) but became moderate (0.68) with the addition of fluoxetine in bipolar I depression.[31] The advantage of OFC over olanzapine alone was of the same magnitude as the difference favoring olanzapine alone over placebo.[40] In BOLDER I, the effect size of quetiapine was large (~0.9) for both the 600 and 300 mg/day groups,[33] but in the replication trial decreased to a moderate size.[34]

Apart from effect size determinations, an alternate means of translating research findings into clinically relevant terms is through calculation of the number needed to treat (NNT =1/responders on active compound minus responders on placebo). The NNT represents the number of patients who would require treatment with the drug under investigation in order for one additional patient to achieve the desired outcome. Hence, the NNT is a pragmatic means of comparing the magnitude of categorical response across various drug treatments. Cookson and colleagues[41] calculated the NNT for rates of response and remission in the 8-week BOLDER I trial. At study conclusion, the NNT values to achieve response (≥50% reduction in MADRS score) for both the quetiapine 600 and 300 mg/day dose were 5 (95% CI, 4-9). This indicates that 5 patients would require treatment with quetiapine in order for 1 additional patient to achieve a response as compared with placebo. Data from other large bipolar depression trials reveal the NNT values to be 12 for olanzapine (95% CI, 7-62), 4 for OFC (95% CI, 3-8), and 4 for lamotrigine 200 mg/d (95% CI, 3-10). However, as the four negative trials with lamotrigine had not yet been released at the time of this analysis, the true NNT for lamotrigine is likely to be much higher. It should also be noted that the NNT may vary according to the baseline clinical and demographic profile of the enrolled subjects. Thus, cross-study comparisons should be interpreted with caution.

Treatment-refractory bipolar depression

Our review identified only one randomized trial that evaluated pharmacological agents for the relief of treatment-resistant bipolar depression.[42] This study assessed the adjunctive benefit of adding open inositol, lamotrigine, or risperidone to conventional mood stabilizers. Criteria for treatment-resistant depression, defined as being nonresponsive to a mood stabilizer plus one or two antidepressant trials during a major depressive episode, was met by each of the 66 subjects. After up to 16 weeks of treatment, no difference in the rate of recovery (8 weeks of ≤ 2 DSM-IV threshold criteria for a major depressive, manic, or hypomanic episode) was observed for subjects taking lamotrigine (24%), inositol (17%), or risperidone (5%).

Maintenance treatment of bipolar depression

Upon achieving an acute antidepressant response in bipolar disorder, the conventional wisdom is to maintain

the drug regimen which resulted in initial symptom reduction. An exception to this tenet involves the use of conventional antidepressants, where some authors have argued for antidepressant discontinuation after approx-

Agent(s) and author		Study duration/ diagnostic subtype	Number completed/ enrolled (%)	Responders[a] / remitters (%)	Reduction in MADRS or IDS-C (*P*)
Atypical antipsychotic monotherapy					
Aripiprazole	Thase et al, 2008[39]	8 weeks BP-I	ARP: 99/186 (53) PBO: 122/188 (65)	ARP: 43.2/30.2; PBO:39.0/27.8	*P*=NS$_c$
Aripiprazole	Thase et al, 2008[39]	8 weeks BP-I	ARP: 110/187 (59) PBO: 132/188 (70)	ARP: 44.6/25.7; PBO: 44.3/29.0	*P*=NS$_c$
Olanzapine	Tohen et al, 2003[31]	8 weeks BP-I	OLZ: 179/370 (48) PBO: 145/377 (38)	OLZ: 39.0 / 32.8 PBO: 30.4 / 24.5	OLZ: 15.0[c] PBO: 11.9[c] (*P*=.002)
Quetiapine	Calabrese et al, 2005[33]	8 weeks BP-I or II	QUE: 219/361 (61) PBO: 107/181 (59)	QUE: 58.0 / 52.9 PBO: 36.1 / 28.4	QUE 600 mg/d: 16.73[c] QUE 300 mg/d: 16.39[c] PBO: 10.26 (*P*<.001)
Quetiapine	Thase et al, 2006[34]	8 weeks BP-I or II	QUE: 191/341 (56) PBO: 110/168 (65)	QUE: 59.2 / 52.0 PBO: 44.7 / 37.3	QUE 600 mg/d: 16.00[c] QUE 300 mg/d: 16.94[c] PBO: 11.93c (*P*<.001)
Anticonvulsant monotherapy					
Lamotrigine	Calabrese et al, 1999[21]	7 weeks BP-I	LAM: 88/129 (68) PBO: 47/66 (71)	LAM: 51.0 / NA PBO: 29.0 / NA	LAM 50 mg/d: 11.2[c] LAM 200 mg/d: 13.3[c] PBO: 7.8[c] (*P*<.05)[b,]
Lamotrigine	Calabrese et al, 2008[22]	10 weeks BP-I or II (SCAA2010)	LAM: (66) PBO: (67)	LAM: 50.0 / NA PBO: 49.0 / NA	LAM: 12.0[c] PBO: 12.3[c] (*P*=NS)
Lamotrigine	Calabrese et al, 2008[22]	8 weeks BP-I (SCA40910)	LAM: (61) PBO: (73)	LAM: 46.0 / NA PBO: 39.3 / NA	LAM: 12.2[c] PBO: 11.2[c] (*P*=NS)
Lamotrigine	Calabrese et al, 2008[22]	8 weeks BP-II (SCA100223)	LAM: (73) PBO: (67)	LAM: 45.5 / NA PBO: 40.0 / NA	LAM: 13.4[c] PBO: 12.0[c] (*P*=NS)
Lamotrigine	Calabrese et al, 2008[22]	8 weeks BP-I (SCA30924)	LAM: (60) PBO: (57)	LAM: 54.1 / NA PBO: 45.7 / NA	LAM: 12.6[c] PBO: 11.7[c] (*P*=NS)
Psychostimulant monotherapy					
Modafinil	Frye et al, 2007[55]	6 weeks BP-I or II	MOD: 29/41 (71) PBO: 29/44 (66)	MOD: 43.9 / 22.7 PBO: 39.0 / 18.0	MOD: 10.5[d] PBO: 5.82[d] (*P*=.04)
Combination therapy					
Antidepressant add-on to mood stabilizer	Sachs et al, 2007[15]	26 weeks BP-I or II	MS + AD: 63/179 (35)[e] MS + PBO: 63/187 (34)[e]	MS + AD: 32.4 / 23.5[f] MS + PBO: 38.0 / 27.3[f]	NS
Lamotrigine add-on to lithium	van der Loos et al, 2007[24]	8 weeks BP-I or II	Li + LAM: 52/64 (81) Li + PBO: 50/60 (83)	Li + LAM: 51.6 / NA Li + PBO: 31.7 / NA	Li + LAM: 15.38[c] Li + PBO: 11.03[c] (*P*=.024)
Olanzapine-fluoxetine combination	Tohen et al, 2003[31]	8 weeks BP-I	OFC: 55/86 (64) PBO: 145/377 (38)	OFC: 56.1 / 48.8 PBO: 30.4 / 24.5	OFC: 18.5[c] PBO: 11.9[c] (*P*<.001)

Table I. Pharmacological treatments for bipolar depression: a summary of randomized, double-blind, parallel-group, placebo-controlled trials enrolling ≥40 subjects. ARP, aripiprazole; AST, aspartate aminotransferase; IDS-C, Inventory of Depressive Symptomatology-Clinician Rated Scale; LAM, lamotrigine; MADRS, Montgomery-Asberg Depression Rating Scale; MOD, modafinil; MS, mood stabilizer; NA, data not available; OFC, olanzapine-fluoxetine combination; OLZ, olanzapine; PBO, placebo; QUE, quetiapine; NS, nonsignificant

[a]Defined as a ≥50% reduction in MADRS total score; [b]*P*<.05 only for the lamotrigine 200 mg/day dose; [c]Reduction in MADRS score; [d]Reduction in IDS-C score; [e]Completed 16 weeks of treatment; [f]Responded by week 16

imately 6 months of use in order to avoid cycle acceleration or induction of mood switches above baseline.[43] The negative STEP-BD data now call into question the entire practice of using antidepressants in either the acute or continuation phase treatment of bipolar depression, and unexpectedly do not suggest that antidepressants promote treatment-emergent affective switch. As this trial did not extend beyond 26 weeks, maintenance trials in the magnitude of 1 to 2 years are necessary to explicate the long-term efficacy and safety profile of antidepressant administration.

Disappointingly, there are few trials that address maintenance phase outcomes in bipolar disorder. For example, there are no placebo-controlled maintenance studies of selective serontonin uptake inhibitors (SSRIs), bupropion, or serotonin-norepinephrine uptake inhibitors (SNRIs) in bipolar depression. The only published placebo-controlled, parallel-group maintenance study in a cohort experiencing an index episode of depression involves the anticonvulsant lamotrigine.[44] In this study, patients with BP-I were initially stabilized on lamotrigine for 4 continuous weeks and then randomized to lamotrigine (50, 200, or 400 mg/day), lithium (serum levels 0.8-1.1 mEq/L), or placebo for up to 18 months. Lamotrigine, but not lithium, was superior to placebo in delaying the time to intervention for depressive symptoms. A similar finding was observed in a related 18-month maintenance trial comparing lamotrigine, lithium, and placebo in recently manic or hypomanic subjects with BP-I.[45] In this study, lamotrigine was also superior to placebo in delaying the time to intervention for a depressive episode. Together, these two maintenance trials support the long-term use of lamotrigine in preventing new relapses into depression.

In addition to lamotrigine and lithium, other agents such as olanzapine[46] and aripiprazole[47] have been shown to prolong the time to relapse during maintenance phase treatment. Although a maintenance trial of divalproex did not indicate greater efficacy in preventing the recurrence of mania or depression more so than lithium or placebo,[48] a trend was observed with divalproex in prolonging the time to depressive relapse.[49] In summarizing the collective maintenance trial findings, divalproex, olanzapine, and aripiprazole have not been shown to prolong the time to relapse into a depressive episode. In each of these studies, patients were required to experience a recent manic, hypomanic, or mixed episode as opposed to an episode of major depression. This distinction is notable, as the index mood episode is highly predictive of the polarity to which subjects ultimately relapse.[50] In future investigations, it is imperative that studies be enriched with subjects who have experienced recent episodes of depression to help clarify the most appropriate long-term treatments to prevent depressive relapse and recurrence. Although unpublished at the time of this writing, quetiapine in combination with lithium or divalproex has been studied in two long-term, phase III, placebo-controlled studies. Treatment with quetiapine demonstrated a 70% reduction in the risk of recurrence of a mood event ($P<0.001$) relative to placebo. This effect was also seen separately for the prevention of depression and mania, irrespective of the polarity of the index episode.[51]

Continuation-phase data have also been collected on patients with BP-I depression who participated in the previously reported trial of olanzapine and OFC.[52] At conclusion of the 8-week efficacy trial, subjects were given the option of receiving open-label OFC or olanzapine for up to 24 additional weeks. Although several design features limit the ability to draw firm conclusions regarding maintenance efficacy with these agents, it appears that olanzapine and OFC prolonged the overall time in remission and allowed a majority of patients to achieve remission who at the 8-week end point would otherwise have been designated "nonremitters." Long-term treatment with OFC was not associated with an increased risk for treatment emergent mania.

Future pharmacological considerations for bipolar depression

With the advent of several new antipsychotic agents, it is foreseeable that these compounds will also be tested in patients with bipolar depression. Clinical trials of the dopamine antagonist asenapine have already been conducted in bipolar I mania, where the agent was shown to be superior in reducing manic symptoms in comparison with placebo.[53] Positive results from trials of bifeprunox in the treatment of schizophrenia have been released,[54] but to our knowledge no publicly available data is available regarding this compound's efficacy in bipolar disorder. Bifeprunox is a D_2 partial agonist that possesses high affinity for 5-HT_{1A} receptors, yet demonstrates rather low affinity for 5-HT_{2A}, 5-HT_{2C}, noradrenergic, muscarinic, and histaminergic receptors. If found effective in the short- or long-term relief of bipolar depression, bifeprunox may

offer the advantage of a favorable cardiometabolic profile as compared with currently marketed atypical antipsychotics. Pooled data from four 6-week clinical trials, and one 6-month trial in schizophrenia involving over 1000 subjects found treatment with bifeprunox to be associated with decreases in body weight and improved total cholesterol and triglyceride levels.[55]

Armodafinil, the R-enantiomer of the wakefulness-promoting agent modafinil, is currently being studied in Phase II and III trials as adjunctive therapy for the treatment of major depressive episodes associated with BP-I. Frye and colleagues[56] have demonstrated that the parent compound modafinil at doses up to 200 mg/day, is beneficial for the adjunctive treatment of major depressive episodes in BP-I or II. Subjects enrolled in this trial were inadequately responsive to therapeutic doses or levels of a mood stabilizer, and some had also failed adjunctive antidepressants. Using the Inventory of Depressive Symptoms as the primary outcome measure, nearly twice as many patients showed a response to adjunctive modafinil (44%) as with placebo (23%). Although modafinil is indicated to improve wakefulness, no significant reductions on standardized measures of sleepiness or fatigue were observed, despite the observed antidepressant efficacy.

Other novel treatments that potentially address putative etiologic causes for bipolar disorder are under active investigation. Awaiting analysis and publication are data from a Phase II multicenter, double-blinded placebo-controlled study of an oral formulation of uridine in 80 patients with acute bipolar depression. Uridine is a biological compound vital to the production of DNA, RNA, and multiple other factors needed for cell metabolism. Uridine is synthesized intracellularly within mitochondria. Given the evidence indicating widespread dysregulation of mitochondrial energy metabolism in bipolar disorder and Phase I trial evidence of antidepressant effects for a prodrug of uridine, this unpublished study attempts to explore the utility of this natural nucleoside in bipolar depression.[57]

Conclusions

Limitations to the available literature on bipolar depression include a dearth of combination pharmacotherapy trials and inadequate evidence to demonstrate that atypical antipsychotics or mood stabilizers, with the exception of lamotrigine or quietapine, robustly prevent depressive recurrence. Despite the fact that combination therapy is common practice in bipolar disorder (ie, mean ≥4 psychotropic medications),[58] there is only one placebo-controlled trial to compare combination mood stabilizer treatment (lamotrigine plus lithium) with lithium monotherapy,[24] and there exist no published placebo-controlled trials that compare combinations of mood stabilizers and atypical antipsychotics in acute bipolar depression. Also unanswered is whether particular subgroups of patients do, in fact, respond positively to the addition of an antidepressant. Although the STEP-BD acute antidepressant trial found no benefit with adjunctive paroxetine or bupropion, the use of antidepressants in clinical practice is widespread.[59] Furthermore, investigators have shown that in patients who remit from a depressive episode upon receiving antidepressants, discontinuation of the antidepressant may be associated with higher rates of depressive relapse.[60] Additional studies are therefore necessary to identify specific populations for which antidepressants may be beneficial. Clarification is also needed regarding the likelihood of inducing mania with antidepressants, as there has never been a randomized, placebo-controlled trial to substantiate the assumption that antidepressants induce new mood episodes of opposite polarity or result in cycle acceleration.

Psychosocial treatments also warrant further investigation in treating bipolar depression. Though beyond the scope of this article focused on pharmacological treatments, intensive psychosocial interventions including cognitive behavioral therapy, family focused therapy, and interpersonal social rhythm therapy were recently found to accelerate the time to recovery by 110 days as compared with a collaborative care control group.[61] The psychosocial treatment arm also led to a modest, but significantly greater proportion of subjects who eventually met recovery criteria.

Evidence-based approaches to the treatment of bipolar depression include the first-line use of lithium, lamotrigine, quetiapine, or OFC. Lithium, when at all possible, should be dosed with the goal of attaining a blood level ≥0.8 mEq/L as it appears that higher levels are associated with greater antidepressant efficacy.[18] Among anticonvulsants, only lamotrigine has been thoroughly studied for its efficacy in bipolar depression, with prophylactic benefit potentially outweighing acute antidepressant effects. The most adequately powered studies of bipolar depression to date involve the atypical antipsychotic class of medications. Both OFC and quetiapine have shown clear superiority over placebo and are reasonable first-

choice agents. Of atypical antipsychotics, the data most strongly support quetiapine in the treatment of bipolar depression, with widespread effects across the core symptoms of depression, including an ability to reduce suicidal thinking.[33]

When patients are nonresponsive or only partially responsive to a trial of a single mood stabilizer, considerations include switching to an alternate mood stabilizer/atypical antipsychotic, combining mood stabilizers/atypical antipsychotics, or augmenting with an agent that may possess clinical, but often less empirical evidence, to support its use. Among mood stabilizers, lithium, lamotrigine, and divalproex should be given initial consideration, while among atypical antipsychotics, only olanzapine and quetiapine are substantiated by trial-based assessments. Of moderately sized, multicenter studies, only lamotrigine[24] and modafinil[56] have been shown to reduce depression more effectively than placebo when administered adjunctively to a mood stabilizer. For all agents, it should be kept in mind that an adequate trial consists of at least 6 weeks of treatment.

Over the last decade, we clinicians have witnessed tremendous advances in our ability to manage the depressed phase of bipolar disorder. Nevertheless, even with access to the most novel pharmacological compounds and adherence to research-driven treatment algorithms, bipolar disorder remains a burdensome and chronic illness. In as much, less than one third of patients who achieve recovery are likely to remain well over 2 years of follow-up.[13] These sobering outcomes invite the need for clinical trials seeking to prevent depressive relapse and to explore whether combination treatments provide added efficacy, increased effectiveness, and enhanced recovery. Such trials might employ sequential, adaptive design schemes that incorporate advances in our understanding of genomics and the neurobiological underpinnings of bipolar disorder. It is the expectation that the next generation of clinical trials will provide more personalized and predictive treatment options for those who suffer from this protean disorder. ❑

Dr Kemp has acted as a consultant for Abbott, Bristol-Myers Squibb, and Wyeth; has received an honorarium from Servier; has participated in CME activities by Organon a part of Schering-Plough; and has received research support from the National Institutes of Health and Takeda.
Dr McIntyre has served on the advisory board for Astra-Zeneca, Biovail, BMS, Eli Lilly, France Foundation, GSK, Jannsen-Ortho, Lundbeck, Organon, Pfizer, Shire and Solvay-Wyeth; served on the speakers bureau for Astra-Zeneca, Biovail, Eli Lilly, Lundbeck, and Janssen-Ortho; has participated in CME activities with Astra Zeneca, Bristol-Myers Squibb, France Foundation, I3CME, Physicians' Postgraduate Press, and Solvay/Wyeth; and has received research support from Eli Lilly.
Dr Muzina has received grant support and/or honoraria from Abbott, AstraZeneca, Eli Lilly, GSK, Pfizer, and Repligen.
Dr Calabrese has received grant/research support or has an affiliation/financial interest with Abbott, Astra-Zeneca, BMS, Cleveland Foundation, Department of Defense, France Foundation, GSK, Health Resources Services Administration, Janssen, Johnson & Johnson, Lilly, National Institutes of Mental Health, NARSAD, Repligen, Solvay/Wyeth, and Stanley Medical Research Institute, Cephalon, Dainippon Sumitomo Pharma, Forest Labs, Organon a part of Schering-Plough, OrthoMcNeil, and Supernus Pharmaceuticals.

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Depresión bipolar: reflexiones basadas en ensayos para orientar el tratamiento del paciente

Para la mayoría de los pacientes con trastorno bipolar los episodios depresivos mayores representan la faceta más desgastadora y difícil en el tratamiento de la enfermedad. Los pacientes pasan significativamente más tiempo depresivos que maníacos o hipomaníacos y los intentos suicidas ocurren con mayor frecuencia durante esta etapa de la enfermedad; aun es limitada la disponibilidad de tratamientos. Podría decirse que el descubrimiento de terapias más efectivas para el manejo de los episodios depresivos es la mayor necesidad insatisfecha en el trastorno bipolar. Este artículo proporciona un resumen de terapias farmacológicas basadas en la evidencia tanto para el manejo agudo como longitudinal de la depresión bipolar. Se revisan los resultados de ensayos clínicos de una gran variedad de compuestos, incluyendo estabilizadores del ánimo tradicionales (como litio y divalproato), antipsicóticos atípicos, antidepresivos unimodales y modafinilo. Cuando corresponde, se examinan las diferencias en la eficacia de estos compuestos mediante la discusión de las determinaciones del número necesario a tratar y de la magnitud del efecto. Para el manejo de la fase depresiva del trastorno bipolar se presenta una aproximación clínica pragmática.

Dépression bipolaire : réflexion à partir d'études pour orienter la prise en charge du patient

Les épisodes dépressifs majeurs représentent le versant le plus débilitant et le plus difficile à traiter de la maladie pour la majorité des patients ayant des troubles bipolaires. Les patients sont significativement plus longtemps déprimés que maniaques et hypomaniaques, et c'est pendant cette phase dépressive de la maladie qu'ils font des tentatives de suicide, les traitements restant encore limités. La découverte de traitements plus efficaces pour la prise en charge des épisodes dépressifs reste sans doute le besoin le plus insatisfait dans les troubles bipolaires. Cet article présente un résumé basé sur les preuves concernant les thérapeutiques pharmacologiques pour le traitement aigu et longitudinal de la dépression bipolaire. Les résultats des études cliniques sont revus pour un ensemble de produits, y compris les thymorégulateurs classiques (lithium et divalproex), les antipsychotiques atypiques, les antidépresseurs unimodaux et le modafinil. Le cas échéant, les différences d'efficacité entre les produits sont discutées par rapport au nombre de patients à traiter et à la taille d'effet observée. Une approche clinique pragmatique pour la prise en charge de la phase dépressive du trouble bipolaire est présentée.

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