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EXPERT OPINION

Pharmacological Treatment of Bipolar Depression: What are the Current and Emerging Options?

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Nefize Yalin
Allan H Young

Centre for Affective Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, London, UK

Abstract: Depression accounts for the predominant burden associated with bipolar disorder. The identification and management of bipolar depression are challenging, since bipolar depression differs from unipolar depression, responding poorly to traditional antidepressants, which may also induce a switch to hypomania/mania, mixed states and/or cause rapid cycling. Current treatment options for bipolar depression are limited and guidelines vary greatly in their recommendations, reflecting gaps and inconsistencies in the current evidence base. Moreover, some treatment options, such as quetiapine and olanzapine–fluoxetine, although clearly efficacious, may be associated with adverse cardiometabolic side effects, which can be detrimental to the long-term physical health and well-being of patients, increasing the likelihood of treatment non-adherence and relapse. Evidence for some more recent therapeutic options, including lurasidone and cariprazine, suggests that patients' symptoms can be effectively managed without compromising their physical health. In addition, novel agents targeting alternative neurotransmitter pathways and inflammatory processes (such as ketamine and N-acetyl cysteine) are emerging as promising potential options for the treatment of bipolar depression in the future.

Keywords: antidepressant, atypical antipsychotic, bipolar depression, bipolar disorder, pharmacotherapy

Introduction

Depressive symptoms predominate in the clinical course of both bipolar I disorder[1] and bipolar II disorder,[2] accounting for much of the morbidity, mortality and impaired quality of life associated with these conditions.[3–5] While depressive symptoms are three times more frequent than manic/hypomanic symptoms in bipolar I disorder, depression accounts for >90% of patients' symptomatology in bipolar II disorder.[1,2] Suicidality further complicates the depressive presentation of the disease as suicide rates in bipolar disorder are approximately 10 times greater than the general population and depressive episodes and mixed states carry the highest risk for suicidal behavior.[6,7] In addition to these, high suicide rates in bipolar disorder patients could pose a risk to their family and friends as their emotional turmoil may last a long time and, in some cases, may end with their own suicide.[8] The literature on the neurobiology of suicide in bipolar disorder is also ambiguous which makes it difficult for clinicians to take preventative measures.[6] Most of the studies on suicide risk have not included solely bipolar disorder samples or have focused on genetic, cell signaling, neurotransmitter system and neuroimaging measures, which are not a part of daily clinical

Correspondence: Allan H Young
Centre for Affective Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College, London, UK
Tel +020 78485895
Fax +020 78480298,
Email allan.young@kcl.ac.uk

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practice.[6,9] However, there are also studies looking at the relationship between routine clinical measures and suicide risk in mixed psychiatric samples including bipolar disorder patients that showed higher levels of testosterone, lower levels of cholesterol, triglycerides, free triiodothyronine and prolactin could predict suicide attempts.[9,10]

The identification, diagnosis and management of bipolar depression are particularly challenging, since bipolar depression and major depressive disorder (MDD) share certain symptoms, and misdiagnosis leads to inappropriate treatment and poor outcomes.[11] In particular, bipolar depression generally responds poorly to traditional antidepressants, which may also induce a switch to mania and/or cause rapid cycling over the long term.[12] Management of bipolar depression is further complicated by disease- and treatment-related factors, including cardiometabolic problems and immunological abnormalities, which contribute to a substantial reduction in the life expectancy of patients.[13–15]

Pharmacological treatments for bipolar depression are currently limited, although new therapeutic options are emerging, and guidelines vary greatly in terms of the types of pharmacological therapies recommended.[16–22] Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders guidelines (2018) recommend quetiapine, lurasidone + lithium/valproic acid, lithium, lamotrigine, lurasidone and adjunctive lamotrigine,[16] whereas, British Association for Psychopharmacology guidelines (2016) endorse quetiapine, lurasidone or olanzapine as first-line treatments for acute bipolar depression.[17] On the other hand, National Institute for Health and Care Excellence guidelines (2018) recommend olanzapine + fluoxetine, or quetiapine,[18] while the World Federation of Societies of Biological Psychiatry (2010)[19] and German S3 (2012) guidelines[20] only include quetiapine as a first-line agent for the acute treatment of bipolar depression. Finally, the Swiss Society for Bipolar Disorder (2015) recommends monotherapy with lithium (as well as quetiapine/quetiapine XR and lamotrigine),[21] whilst the Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines (2015) classify quetiapine, lurasidone, olanzapine, lithium, lamotrigine and valproate as first-line therapies for the treatment of bipolar depression.[22]

Correct choice of treatment for the individual patient is essential, not only to effectively manage their symptoms but also to ensure that their physical health is not compromised by potential adverse effects of long-term treatment. The objectives of this article are to outline current evidence for pharmacological treatment options for bipolar depression and the implications of this evidence for everyday clinical practice.

Pharmacological Treatment of Bipolar Depression: Available Evidence

The variability between guidelines in the types of pharmacotherapies recommended reflects inconsistencies and gaps in the available evidence. A summary of this evidence is outlined here.

Lithium

The EMBOLDEN I study was a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial in which approximately 800 patients in the acute phase of bipolar depression were randomized to receive 8 weeks of monotherapy with either lithium (600–1800 mg/day), one of two doses of quetiapine (300 or 600 mg/day), or placebo.[23] Reductions in mean Montgomery–Åsberg Depression Rating Scale (MADRS) total score from baseline to Week 8 (the primary endpoint) were significantly greater for both doses of quetiapine versus placebo, but not for lithium versus placebo.[23] Moreover, both doses of quetiapine were significantly more effective than lithium in reducing mean MADRS total score.[23] Similarly, patients treated with quetiapine (both doses), but not lithium, achieved significantly greater MADRS response and remission rates versus placebo, and experienced significantly greater improvements versus placebo on the Hamilton Depression Rating Scale (HAM-D), Clinical Global Impression-Bipolar Version (CGI-BP) severity and change scores, and Hamilton Anxiety Rating Scale.[23] The most common adverse event (AE) with lithium was nausea.[23] The lack of significant treatment effect with lithium observed in EMBOLDEN I may have resulted from only approximately two thirds of patients attaining a minimum lithium serum level of 0.6 mEq/L.[23]

An 8-week, open-label, randomized study demonstrated that lithium was significantly less effective than extended-release quetiapine in treating depressive symptoms and improving sleep quality in patients with bipolar depression.[24]

Nevertheless, in the maintenance setting, there is clear evidence for lithium's efficacy in preventing depressive relapse.[25,26] Furthermore, lithium has been shown to be effectively decreasing the risk of suicide (Odds Ratio(OR)

0.13, 95% Confidence Interval(CI): 0.03–0.66) and the risk of deaths from any cause (OR 0.38, 95% CI: 0.15–0.95) compared to placebo in mood disorders.[27]

Valproate

A meta-analysis of 4 randomized, double-blind and placebo-controlled trials with a total sample of 142 participants showed that valproate monotherapy was superior to placebo in treating acute bipolar depression.[28] The patients on valproate were significantly more likely to meet the response (Relative Risk(RR)=2.10, p=0.02) and the remission (RR=1.61, p=0.04) criteria than those on placebo.[28] The mean response rate was 39.3% for the patients who were prescribed valproate compared to 17.5% for the patients prescribed placebo. The mean remission rates were 40.6% and 24.3% for the patients on valproate and placebo, respectively.[28] The rates for trial completion (RR=1.13, p=0.40) and discontinuation due to side effects (RR=1.44, p=0.72) were not significantly different between valproate and placebo.[28]

Although the results of this meta-analysis are promising, it needs to be noted that all trials included in this meta-analysis had small sample sizes and well-designed clinical trials with large sample sizes are needed to confirm these findings.[28]

A major consideration in the use of valproate is its teratogenic potential during pregnancy.[29]

Antidepressants

A systematic review and meta-analysis of 12 randomized controlled trials of antidepressants in the short-term treatment of bipolar depression, which included data from over 1000 patients, concluded that antidepressants are effective in the short-term treatment of bipolar depression.[30] It also showed that a switch to mania is not commonly observed with short-term treatment (3.8% event rate for antidepressants vs 4.7% for placebo), although the risk is higher with tricyclic antidepressants (10%) than with all other antidepressants (3.2%).[30]

On the other hand, the largest randomized, double-blind, placebo-controlled trial of antidepressants for the treatment of acute bipolar depression, performed as part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), found no differences in efficacy between antidepressant therapy and placebo as an adjunct to a mood stabilizer over a treatment period of up to 6 months (Figure 1).[31] The risk of a switch to mania was found to be similar for antidepressant therapy and placebo.[31] Furthermore, a more recent meta-analysis of six randomized controlled trials of antidepressants for the treatment of acute bipolar depression (<16 weeks) demonstrated that antidepressants were not statistically superior to placebo or other current standard treatments for bipolar depression and they did not increase the risk of a switch to mania in the acute setting.[32] Other studies have demonstrated that the risk of a switch to mania varies

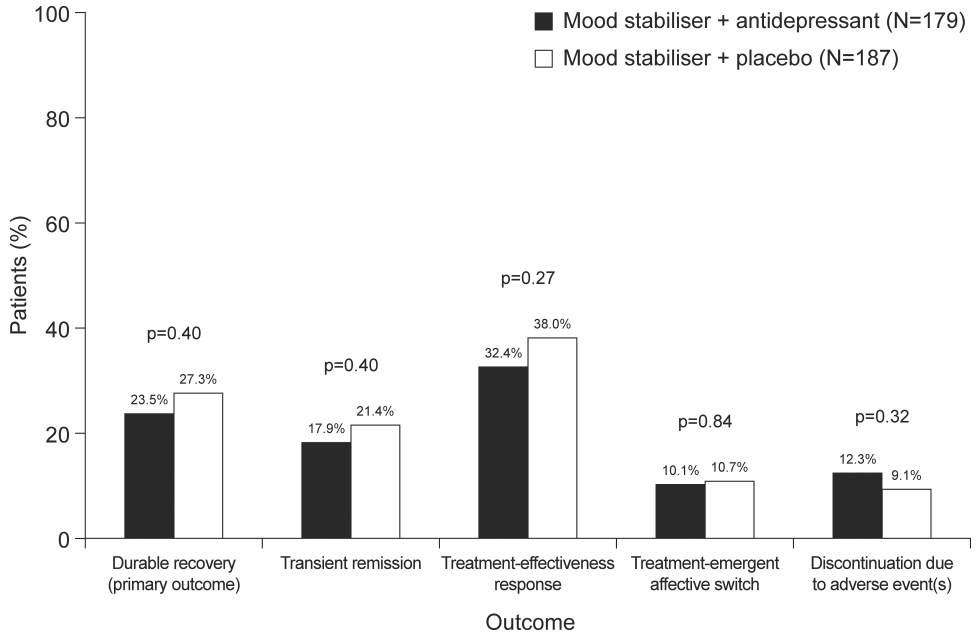

Figure 1 Outcomes according to treatment group in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Data from Sachs et al.[31]

depending on study setting (being higher in retrospective and cross-sectional studies than in randomized controlled trials and open prospective studies),[12,33] which argues against a causal role of antidepressants in the development of manic episodes.

Overall, the possible risk of a switch to mania, together with equivocal evidence regarding efficacy, has led to recommendations for either a cautious approach to antidepressant use in bipolar depression or a total avoidance of antidepressant therapy in this setting.[34–36] The exception to this is fluoxetine, which is approved as a combination therapy with olanzapine in the USA for the treatment of depressive episodes associated with bipolar I disorder[37] (See *Atypical antipsychotics* section for further information).

Lamotrigine

As with antidepressants, evidence for the use of lamotrigine in bipolar depression is equivocal. Results from five double-blind, placebo-controlled clinical trials demonstrated that lamotrigine monotherapy did not differ significantly from placebo on primary efficacy endpoints (17-item HAM-D or MADRS) in the acute treatment of bipolar depression.[38] In one study, lamotrigine (50 or 200 mg/day) was significantly superior to placebo on some secondary efficacy endpoints (including MADRS, Clinical Global Impressions-Severity [CGI-S] and CGI-Improvement), but only rarely separated significantly from placebo on secondary efficacy endpoints in the other studies.[38] By contrast, other trials have demonstrated that lamotrigine was effective in the treatment of bipolar depression when used either as monotherapy or as an adjunct to mood stabilizer therapy in the acute and longer-term settings (Figure 2). [39–41]

An important consideration for the use of lamotrigine is its potential for causing serious adverse skin reactions,[42] although this did not emerge as a common problem in trials of the drug for bipolar depression in the acute setting.[38] The risk of adverse skin reactions may be minimized by initiating lamotrigine at a relatively low dose and up-titrating very slowly.[21]

Atypical Antipsychotics

First-generation antipsychotics have been shown to be ineffective in the treatment of bipolar depression; indeed, continued use of perphenazine as adjunctive therapy to a mood stabilizer following remission from an acute manic episode was found to shorten time to depressive relapse and increase rates of dysphoria, depressive symptoms and extrapyramidal symptoms, in comparison with placebo.[43]

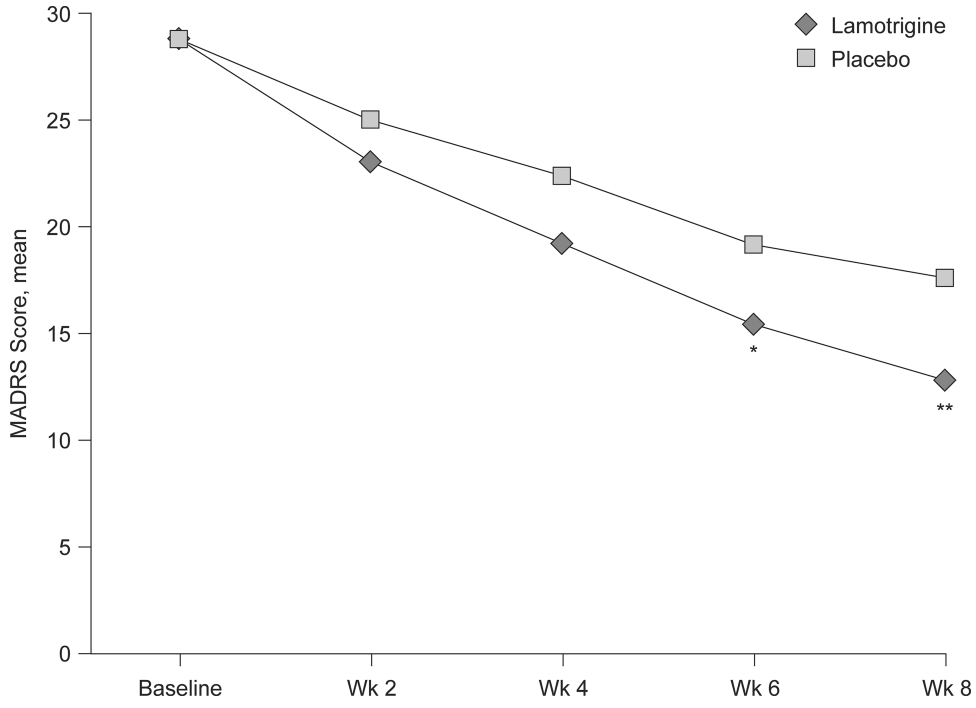

Figure 2 MADRS total score over 8 weeks of double-blind treatment with lamotrigine (titrated to 200 mg/day) or placebo in the LamLit study. *p=0.031 versus placebo; **p=0.006 versus placebo. (MADRS, Montgomery–Åsberg Depression Rating Scale; Wk, week). van der Loos ML, Mulder PG, Hartong EG, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *J Clin Psychiatry.* 2009;70(2):223–231,. Copyright 2009, Physicians Postgraduate Press. Reprinted by permission.[40]

Several atypical antipsychotics have been investigated for the treatment of bipolar depression, but quetiapine is currently the only antipsychotic to be approved for this condition in Europe.[44] In the USA, the Food and Drug Administration has approved olanzapine–fluoxetine combination therapy for the treatment of depressive episodes associated with bipolar I disorder[37] and lurasidone for the treatment of bipolar depression, as monotherapy or as adjunctive therapy to lithium or valproate.[45] An important issue to consider when assessing the potential use of atypical antipsychotics is the great variability between agents in their propensity for causing adverse cardiometabolic effects, including sudden cardiac death, weight gain, dyslipidemia and glucose dysregulation.[46,47]

Quetiapine

Among the approved treatments for bipolar depression, quetiapine has the largest evidence base. A systematic review and meta-analysis of eleven randomized controlled trials that compared quetiapine with placebo or active treatments in patients with acute bipolar depression demonstrated that quetiapine monotherapy (300 or 600 mg/day) is effective for acute bipolar depression and the prevention of mania/hypomania switching.[48] Compared with placebo, the mean difference (95% CI) for average change in depressive scores (MADRS or Children's Depression Rating Scale, Revised) was −4.66 (−5.59 to −3.73).[48] For quetiapine versus placebo, the risk ratios (RR) (95% CI) for response rate at endpoint, remission rate at endpoint and treatment-emergent mania were 1.31 (1.23–1.40), 1.36 (1.24–1.49) and 0.58 (0.37–0.91), respectively.[48] Quetiapine treatment was also associated with significant improvements in clinical global impression, quality of life, sleep quality, anxiety and functioning.[48]

Compared with placebo, quetiapine caused more AEs of somnolence (RR, 3.74; 95% CI, 2.86–4.90), dry mouth (RR, 3.65; 95% CI, 3.04–4.40), sedation (RR, 3.32; 95% CI, 2.71–4.06), extrapyramidal side effects (RR, 2.77; 95% CI, 2.12–3.62), increased appetite (RR, 2.81; 95% CI, 1.58–5.01), weight gain (RR, 2.33; 95% CI, 1.34–4.03), dizziness (RR, 2.18; 95% CI, 1.73–2.74), constipation (RR, 2.05; 95% CI, 1.50–2.81) and fatigue (RR, 1.57; 95% CI, 1.16–2.13).[48]

Olanzapine–Fluoxetine Combination Therapy

In the 8-week, randomized, double-blind, placebo-controlled United States registration trial, combined olanzapine–fluoxetine treatment (6 and 25, 6 and 50, or 12 and 50 mg/day olanzapine and fluoxetine, respectively) was shown to be significantly more effective than both placebo and olanzapine alone (5–20 mg/day) in the treatment of bipolar I depression, without increasing the risk of developing manic symptoms (Figure 3).[49] At Week 8, MADRS total scores were lower than at baseline by 11.9, 15.0, and 18.5 points in the placebo, olanzapine, and olanzapine–fluoxetine groups, respectively.[49] Corresponding values for remission were 24.5%, 32.8% and 48.8%, respectively, and, for treatment-emergent mania, they were 6.7%, 5.7% and 6.4%, respectively.[49]

AEs were similar for olanzapine and olanzapine–fluoxetine, except that diarrhea and nausea were significantly more common with olanzapine–fluoxetine than with olanzapine.[49] The most frequently reported AEs with olanzapine–fluoxetine (occurring in ≥10% of patients and ≥2-times more frequently than with placebo) were weight gain (17.4% vs 2.7%; p<0.001), increased appetite (12.8% vs 5.0%; p<0.001), dry mouth (16.3% vs 6.1%; p=0.02), asthenia (12.8% vs 3.2%; p<0.001) and diarrhea (18.6% vs 6.6%; p=0.001).[49]

A subsequent analysis of data from this trial demonstrated that the number needed to harm (NNH) for clinically significant weight gain (defined as ≥7% increase from baseline) was six for olanzapine–fluoxetine versus placebo.[50]

Lurasidone

The effectiveness of lurasidone in bipolar depression has been investigated in the Program to Evaluate the Antidepressant Impact of Lurasidone (PREVAIL). PREVAIL 1 was a 6-week, randomized, double-blind, placebo-controlled trial that evaluated lurasidone's efficacy as adjunctive therapy to lithium or valproate.[51] Lurasidone (20–120 mg/day), compared with placebo, significantly reduced mean MADRS total score (−17.1 vs −13.5; effect size, 0.34) and CGI-Bipolar Version (CGI-BP) depression severity score (−1.96 vs −1.51; effect size, 0.36) at week 6.[51] Lurasidone treatment also resulted in significantly greater improvements in anxiety symptoms and patient-reported measures of quality of life and functionality.[51] The incidence of treatment-emergent mania was similar for lurasidone versus placebo (1.1% vs 1.2%).[51] The only AE reported by ≥5% of patients in the lurasidone group and ≥2-times more frequently than with placebo was somnolence (8.7% vs 4.3%).[51] Akathisia occurred in 7.7% of patients treated with lurasidone and 4.3% of those treated with placebo and the incidence of extrapyramidal events was 15.3% versus 9.8%.[51]

PREVAIL 2 was a 6-week, randomized, double-blind, placebo-controlled trial, which demonstrated that

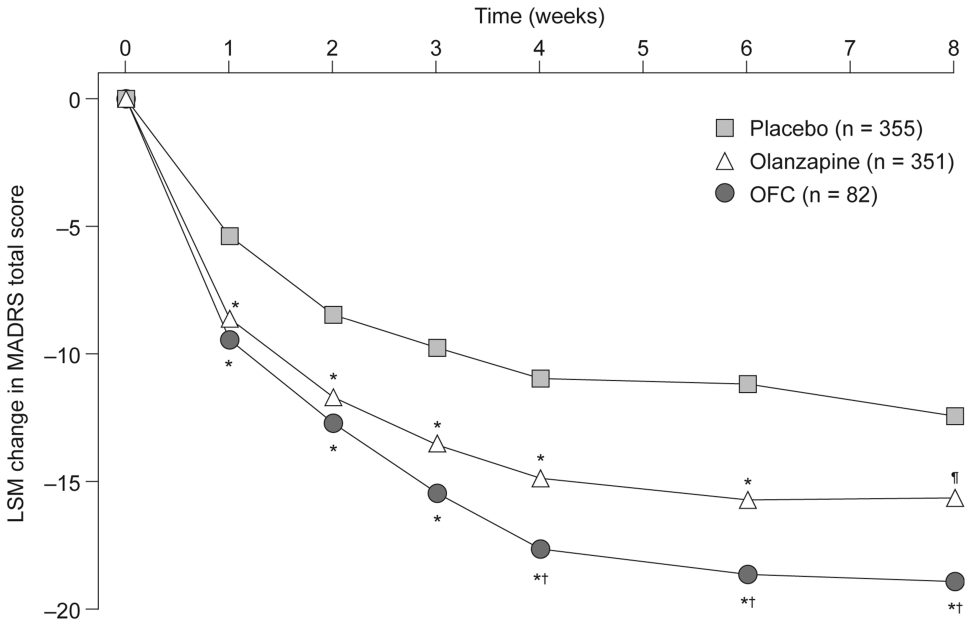

Figure 3 MADRS total score over 8 weeks of treatment with olanzapine–fluoxetine combination therapy (6 and 25, 6 and 50, or 12 and 50 mg/day olanzapine and fluoxetine, respectively), compared with olanzapine alone (5–20 mg/day) and placebo. *p<0.001 versus placebo; †p<0.05 versus olanzapine; ¶p=0.002 versus placebo. (LSM, least squares mean; MADRS, Montgomery–Åsberg Depression Rating Scale; OFC, olanzapine–fluoxetine combination). Reproduced with permission from Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry.* 2003;60(11):1079–1088. Copyright (2003) American Medical Association. All rights reserved.[49]

lurasidone monotherapy was significantly more effective than placebo in decreasing MADRS total and CGI-BP depression severity scores, with progressive improvement observed from week 2 onwards (Figure 4).[52] Mean changes in MADRS total scores from baseline to week 6 for lurasidone 20–60 mg/day, lurasidone 80–120 mg/day and placebo were −15.4, −15.4 and −10.7, respectively (effect sizes for both lurasidone groups vs placebo, 0.51).[52] Corresponding values for mean changes in CGI-BP depression severity scores were −1.8 (effect size, 0.61), −1.7 (effect size, 0.50) and −1.1, respectively.[52] As in the adjunctive setting, there were also significant improvements in both lurasidone groups, compared with placebo, in anxiety symptoms and patient-reported measures of quality of life and functionality.[52] Treatment-emergent mania occurred in 3.7%, 1.9% and 1.9% of patients in the lurasidone 20–60 mg, lurasidone 80–120 mg and placebo groups, respectively.[52] The most frequently reported AEs with lurasidone (≥5% of patients in either group and ≥2-times more frequent than with placebo) were nausea (10.4%, 17.4% and 7.7% for lurasidone 20–60 mg, lurasidone 80–120 mg and placebo groups, respectively), akathisia (7.9%, 10.8% and 2.4%), extrapyramidal events (4.9%, 9.0% and 2.4%), sedation (3.0%, 7.2% and 1.8%) and vomiting (2.4%, 6.0% and 1.8%).[52]

PREVAIL 3 was another 6-week, randomized, double-blind, placebo-controlled trial that evaluated lurasidone's efficacy as adjunctive therapy to lithium or valproate.[53] Unlike PREVAIL 1, which only included patients treated retrospectively with lithium or valproate,[51] PREVAIL 3 included patients treated either retrospectively or prospectively with a mood stabilizer.[53] In PREVAIL 3, improvements in MADRS total score and CGI-BP depression severity score from baseline to week 6 were not significant for lurasidone versus placebo, although there was a significant separation in favor of lurasidone versus placebo on MADRS total score from weeks 2–5 and on CGI-BP depression severity score from weeks 3–5.[53] A pre-planned analysis demonstrated that improvement in MADRS total score was significantly greater in patients treated with a mood stabilizer retrospectively versus prospectively.[53] The most frequently reported AEs with lurasidone (≥5% of patients and ≥2-times more frequent than with placebo) were akathisia (14.1% vs 5.3%) and somnolence (11.9% vs 4.7%).[53] The incidence of extrapyramidal events was 12.4% in patients treated with lurasidone versus 7.6% in patients treated with placebo.[53] In all the PREVAIL trials, lurasidone treatment was associated with minimal changes in weight, lipids, and measures of glycemic control.[51–53]

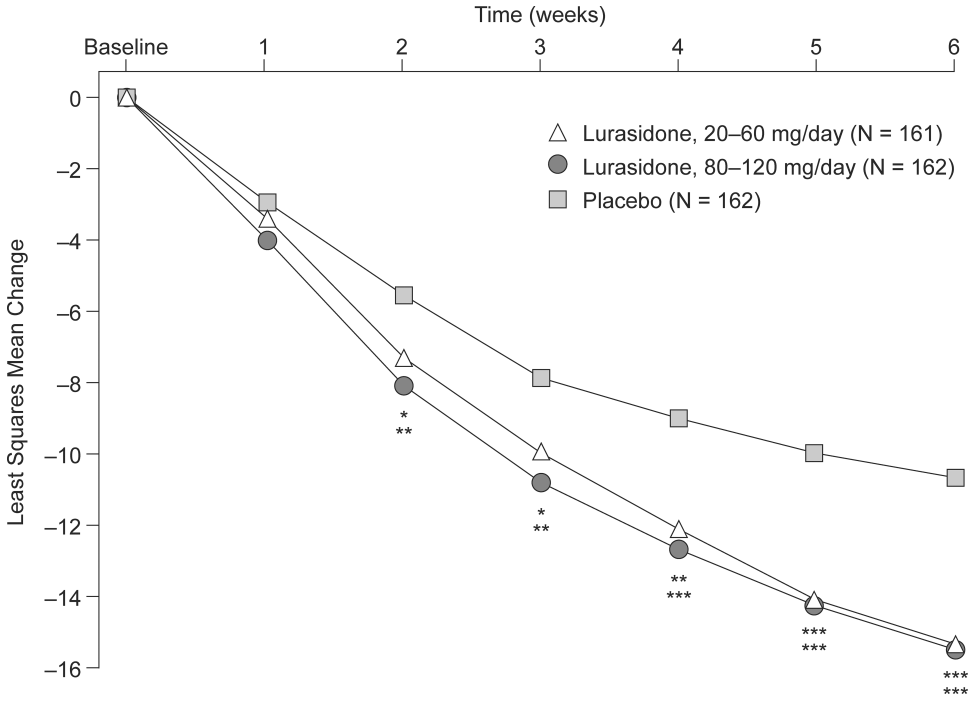

Figure 4 MADRS total score following 6 weeks of treatment with lurasidone monotherapy versus placebo in PREVAIL 2. *p<0.05 versus placebo; **p<0.01 versus placebo; ***p<0.001 versus placebo. (MADRS, Montgomery–Åsberg Depression Rating Scale.) Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*. 2014;171(2):160–168. Reprinted with permission from the *American Journal of Psychiatry*, (Copyright © 2014). American Psychiatric Association. All Rights Reserved. [52]

A post hoc analysis of PREVAIL 1 and 2, based on number needed to treat (NNT) and NNH analyses, revealed that the benefits associated with lurasidone treatment (in terms of response and remission) were comparable to those of quetiapine and olanzapine–fluoxetine, with less risk of sedation, compared with quetiapine and less risk of clinically significant weight gain compared with olanzapine–fluoxetine (Table 1).[54] Lurasidone is currently not approved for the treatment of bipolar depression in Europe.

Aripiprazole

The effectiveness of aripiprazole monotherapy (5–30 mg/day) in bipolar depression was evaluated in two identically designed, 8-week, multicenter, randomized, double-blind, placebo-controlled trials.[55] Statistically significant differences were observed during Weeks 1 to 6 on both MADRS total score (the primary endpoint) and CGI-BP depression severity score (a key secondary endpoint); however, aripiprazole was not significantly superior to placebo at endpoint for either of these outcome measures.[55] The most frequently reported AEs with aripiprazole (≥10% of aripiprazole patients in either study and ≥2-times more frequent than with placebo) were akathisia, insomnia, nausea, fatigue, restlessness and dry mouth.[55] In both studies, there were no clinically significant differences between aripiprazole and placebo in terms of serum prolactin, fasting serum glucose, lipid levels and weight gain.[55]

A post hoc analysis of the two monotherapy trials, based on baseline severity of core depressive symptoms, suggested that aripiprazole may provide some improvements in core symptoms of depression in patients who are severely depressed (Bech-6 Total score >15), although statistical significance was not demonstrated.[56] In the long-term setting, aripiprazole has been shown to be more effective than placebo in delaying manic relapse, but not depressive relapse, when administered as either monotherapy[57] or as adjunctive therapy with a mood stabilizer.[58]

Cariprazine

Cariprazine is an atypical antipsychotic that acts as a partial agonist at dopamine D_2 and D_3 receptors (with higher binding affinity for D_3) and serotonin 5-HT_{1A} and 5-HT_{2A} receptors.[59] In a Phase 2, 8-week, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose trial, conducted in adult patients with bipolar I disorder experiencing a current major depressive episode, treatment with cariprazine 1.5 mg/day resulted in significantly greater improvement than placebo on change from baseline to Week 6 in MADRS total score (the primary endpoint), whereas treatment with cariprazine 3.0 mg/

Table 1 Summary of NNT (MADRS Responder; MADRS Remitter) and NNH (Clinically Significant Weight Gain; Somnolence) Values for Adjunctive Lurasidone and Lurasidone Monotherapy, Compared with Quetiapine Monotherapy and Olanzapine–Fluoxetine Combination Monotherapy. Lurasidone Data are Pooled from the PREVAIL I and II Trials

Parameter	Adjunctive Lurasidone 20–120 mg/day	Lurasidone Monotherapy 20–60 mg/day	Lurasidone Monotherapy 80–120 mg/day	Quetiapine IR or XR Monotherapy	Olanzapine–Fluoxetine Combination Monotherapy
NNT MADRS response[a]	7	5	5	6	4
NNT MADRS remission[b]	7	6	7	6	5
NNH clinically relevant weight gain[c]	42	29	5550	16	6
NNH somnolence[d]	19	130	14	3[e]	NR

Notes: Data from Citrome et al.[54] [a]Response defined as ≥50% reduction from baseline in MADRS total score. [b]Remission defined as a MADRS total score of ≤12 at last observation carried forward endpoint. [c]Clinically significant weight gain defined as ≥7% increase from baseline in body weight. [d]Includes hypersomnia, sedation and somnolence. [e]Rounded up from 2.4.

Abbreviations: IR, immediate release; MADRS, Montgomery–Åsberg Depression Rating Scale; NNH, number needed to harm; NNT, number needed to treat; NR, not recorded; XR, extended release.

day was not significantly superior to placebo when adjusted for multiple comparisons.[60] A similar pattern of significance was observed on the CGI-S.[60]

In a subsequent Phase 3, 6-week, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose trial, conducted in adult patients with bipolar I depression, cariprazine 1.5 and 3.0 mg/day were both significantly superior to placebo on change from baseline to Week 6 in MADRS total score (the primary endpoint): the least squares mean differences were −2.5 (95% CI, −4.6 to −0.4; adjusted p=0.033; effect size, 0.28) for cariprazine 1.5 mg/day and −3.0 (95% CI, −5.1 to −0.9; adjusted p=0.010; effect size, 0.34) for cariprazine 3.0 mg/day.[61] Both cariprazine dosages were associated with lower CGI-S scores than placebo.[61] The most frequently reported AEs with cariprazine (≥5% of patients and ≥2-times more frequent than with placebo) were nausea (0.6%, 3.8% and 9.1% for placebo, cariprazine 1.5 mg/day and cariprazine 3.0 mg/day, respectively), akathisia (3.2%, 6.4% and 5.5%), dizziness (1.9%, 5.1% and 3.6%) and sedation (1.3%, 5.1% and 3.0%).[61] Mean changes in weight and metabolic parameters were comparable across groups and not considered clinically significant.[61] Cariprazine is currently not approved for the treatment of bipolar depression in Europe.

Novel Treatment Options

Current treatment options for bipolar depression, such as atypical antipsychotics, generally target central dopaminergic and serotonergic systems. However, several novel therapeutic targets are emerging as potential alternative treatment approaches. These include ketamine, which is thought to exert antidepressant effects through antagonism of N-methyl-D-aspartate receptors and, possibly, by inhibiting the function of norepinephrine and serotonin transporters;[62] and riluzole, a glutamatergic modulator that inhibits glutamate release and enhances glutamate reuptake, and additionally enhances α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid trafficking.[63] Furthermore, the high prevalence of medical comorbidities in bipolar disorder, such as cardiovascular disease and immune dysfunction, has led to speculation that it may represent a "multi-system inflammatory disease",[64] which has resulted in several anti-inflammatory agents being investigated as potential therapeutic options for bipolar depression, including N-acetyl cysteine[65] and the antibiotic minocycline.[66] In addition, brexpiprazole, modafinil/armodafinil and pramipexole as well as triiodothyronine (T3) could be other promising agents in the treatment of bipolar depression.[67–71] A summary of evidence for these and other novel treatment approaches for bipolar depression is outlined in Table 2.

Limitations of Article

This article has attempted to provide an overview of current evidence for pharmacological treatment options for bipolar depression and a commentary on the implications of this evidence for everyday clinical practice. However, the evidence it includes was not collected via systematic review of the literature and its contents are therefore by no means definitive; rather, they represent the authors' opinions of the current treatment landscape for bipolar depression, based on their interpretation of published data and personal clinical experience.

Summary

Although depression predominates the clinical course of bipolar disorder, current treatment options for bipolar depression

Table 2 Novel Treatments for Bipolar Depression

Agent	Pharmacological Details	Summary of Evidence in Bipolar Depression
Ketamine	• NMDA receptor antagonist; dissociative anesthetic agent[72] • Thought to exert antidepressant effects via NMDA receptor antagonism and possible inhibitory effects on norepinephrine and serotonin transporter function[62]	• Several RCTs and open-label retrospective studies have demonstrated rapid improvement of depression, suicidal ideation and anhedonia following single low (subanesthetic) intravenous doses, compared with placebo[73–78] ○ Response rate for depression was statistically significant versus placebo for up to approximately 3 days[74,75] • Some evidence of improvement in fatigue for up 2 weeks following single intravenous dosing[79] • AEs include dizziness, blurred vision, restlessness, nausea/vomiting and headache; AEs are usually transient and mild; no serious AEs reported[73,77,80] • Use may be limited by need for administration by an anesthesiologist and hospitalization post-administration[81] ○ Potential use as a longer-term treatment is currently unclear[81]
Modafinil/ armodafinil	• Wakefulness-promoting, low-affinity dopamine transport inhibitor[68] • Armodafinil is the active R-enantiomer of modafinil[68]	• A 6-week placebo-controlled study demonstrated that modafinil added to a mood stabilizer ± an antidepressant resulted in significantly greater response and remission rates than placebo[69] ○ Incidence of treatment-emergent hypomania/mania was similar between groups[69] • Three 8-week studies of armodafinil as an adjunctive treatment in bipolar depression have been inconsistent in their findings[68,82,83] ○ In a 6-month, open-label extension study of patients completing these trials, armodafinil improved depressive symptoms and patient functioning and was generally well tolerated[84] ○ Most frequently reported AEs were headache, insomnia and anxiety
Pramipexole	• D_2/D_3 receptor agonist[70]	• Two small, 6-week RCTs have investigated the effectiveness of pramipexole as an adjunct to mood stabilizers in bipolar depression (n=22; n=21)[70,85] ○ In one, improvements from baseline in HAM-D score and CGI severity were significantly greater with pramipexole versus placebo, as was HAM-D responder rate[70] ○ In the other, ANOVA for MADRS total score showed a significant treatment effect, and MADRS responder rate was significantly higher with pramipexole versus placebo[85] • In both trials, pramipexole was well tolerated and not associated with an increased incidence of hypomania/mania[70,85] • Additional limited evidence supporting the use of adjunctive pramipexole for bipolar depression from open studies[86,87]
Riluzole	• Inhibits glutamate release and enhances glutamate reuptake and AMPA trafficking[63] • Inhibits voltage-dependent sodium channels[88]	• In an 8-week, open-label study conducted in 14 acutely depressed bipolar patients (MADRS ≥20), riluzole added to existing lithium treatment resulted in significant improvement in MADRS total score and no switch to hypomania/mania was observed[89] • Interim analysis of an 8-week, placebo-controlled RCT of riluzole monotherapy, conducted in 19 patients with bipolar depression, demonstrated that there were no significant differences on MADRS or HAM-D scores for riluzole versus placebo, and anxiety scores (HAM-A) were significantly lower for placebo versus riluzole[90] ○ The trial was subsequently stopped[90]
N-acetyl cysteine	• Acetyl derivative of the amino acid cysteine[91] • Increases glutathione levels in the brain, which may decrease oxidative stress and inflammation[91]	• In a 24-week, multicenter RCT, conducted in patients with bipolar disorder in the maintenance phase, N-acetyl cysteine (as an adjunct to usual treatment) resulted in significant improvements on MADRS versus placebo[92] • A subsequent RCT of N-acetyl cysteine as an adjunctive maintenance treatment for bipolar disorder yielded inconclusive results due to low event rates[93] • A 20-week placebo-controlled RCT will assess the effects of adjunctive N-acetyl cysteine treatment on depressive symptoms in patients diagnosed with bipolar depression[94] ○ Primary outcome will be mean change from baseline on MADRS

(*Continued*)

Table 2 (Continued).

Agent	Pharmacological Details	Summary of Evidence in Bipolar Depression
Other anti-inflammatory agents	• Bipolar disorder has been proposed to be a multisystemic inflammatory disease due to high levels of comorbid medical conditions and adjunctive anti-inflammatory medication may, therefore, be a rationale therapeutic strategy[64]	• A systematic review and meta-analysis of 10 RCTs assessing treatment with adjunctive non-steroidal anti-inflammatory drugs, omega-3 polyunsaturated fatty acids, N-acetylcysteine and pioglitazone demonstrated a moderate and statistically significant antidepressant effect[65] ○ No switching to hypomania/mania or clinically significant AEs were reported[65] • In an 8-week, open-label pilot study of adjuvant therapy with the antibiotic, minocycline, conducted in 20 patients with bipolar disorder experiencing acute depressive symptoms, 50% were MADRS responders and 40% were MADRS remitters[66] ○ Higher baseline glutathione levels were associated with significantly greater improvement in MADRS score[66] • In another 8-week, open-label pilot study, conducted in 29 patients with bipolar I/II depression, adjunctive minocycline resulted in significant reductions on MADRS, HAMD-17 and CGI-severity[95] • A Phase IIa, 2×2, placebo-controlled RCT evaluated augmentation therapy with minocycline and/or aspirin for bipolar depression[96] ○ MADRS responder rates were significantly higher for aspirin + minocycline versus placebo + placebo, and for aspirin + minocycline and aspirin + placebo versus minocycline + placebo and placebo + placebo[96] ○ Patients with higher baseline levels of IL-6 responded better to minocycline than those with lower levels[96] • An 8-week, placebo-controlled RCT demonstrated that addition of the cyclooxygenase-2 inhibitor, celecoxib, to escitalopram therapy in patients with bipolar depression resulted in significantly greater improvements on HAMD-17 than placebo[97] ○ CRP levels decreased significantly more with celecoxib versus placebo[97] ○ Baseline CRP levels were significantly higher in patients with bipolar depression versus healthy controls, indicating that CRP may be a useful biomarker for bipolar depression[97] • A multicenter, 3-month, placebo-controlled RCT with factorial design will investigate the effectiveness of minocycline and/or celecoxib added to usual therapy for the treatment of depressive symptoms in patients experiencing a DSM-5 bipolar I or II disorder and a current major depressive episode[98] ○ Primary outcome will be mean change from baseline to Week 12 on HAM-D[98] ○ CRP levels will be measured at baseline and end of treatment[98]
T3	• Active form of thyroid hormone thyroxine[67] • The thyroid hormones affect the function of serotonin, catecholamine and dopamine systems in the brain[67]	• In one retrospective chart review, 84% of the patients with bipolar disorder (n=159) who were treatment-resistant showed improvement with add-on T3 and approximately one third (33%) went into remission[99] • In a comparative study, bipolar subgroup revealed a mean of 15 points decrease on the HAM-D with T3 after 1 week compared to only 6 points in the control group[100] • In an open-label study, add-on T3 treatment was effective in 5 out of the 7 patients (72%) with bipolar depression[67]
Brexpiprazole	• Serotonin and dopamine receptor modulator[101] • Sub-nanomolar potency as an antagonist at serotonin 5-HT_{2A} and adrenergic α1A receptors[71] • A partial agonist at serotonin 5-HT_{1A} and dopamine D_2 receptors[71]	• In an open-label study, treatment with brexpiprazole 4 mg/day for 8 weeks resulted in decreases in MADRS total and Inventory of Depressive Symptomatology Self-report scores at Weeks 4 and 8 in 21 patients with bipolar depression[71] ○ An increase in Quality of Life in Bipolar Disorder score from baseline to Week 8, with no significant changes in Young Mania Rating Scale and cognitive scores were also reported[71]

Abbreviations: AE, adverse event; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANOVA, analysis of variance; CGI, Clinical Global Impression; CRP, C-reactive protein; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; HAMD-17, 17-item Hamilton Depression Rating Scale; IL-6, interleukin-6; MADRS, Montgomery–Åsberg Depression Rating Scale; NMDA, N-methyl-D-aspartate; RCT, randomized controlled trial: T3, triiodothyronine, 5-HT_{1A}, serotonin 1A receptor: $5HT_{2A}$, serotonin 2A receptor.

are limited; in particular, because traditional antidepressants have equivocal efficacy in bipolar depression and may induce a switch to mania and/or rapid cycling over the long term. Moreover, some pharmacological agents that are effective in treating bipolar depression, such as quetiapine and olanzapine–fluoxetine, may be associated with important cardiometabolic side effects (especially weight gain) over the long term, which compromise patients' physical health, increasing the risk of morbidity and mortality, and/or the likelihood of treatment non-adherence and associated relapse. More recently, evidence for certain atypical antipsychotics, such as lurasidone and cariprazine, has demonstrated that it may be possible to effectively manage bipolar depression without unduly compromising patients' long-term physical health. Furthermore, although most of the current treatment options for bipolar depression generally target central dopaminergic and serotonergic systems, emerging evidence for several novel therapeutic targets, including the glutamatergic system and inflammatory processes, indicates the potential for alternative pharmacological treatment approaches for bipolar depression in the future. Bipolar depression causes substantial mortality, morbidity and impairment of quality of life, and its effective management currently represents an important unmet need. It is hoped that new and emerging pharmacological treatments for this challenging condition will help address this need.

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