The Treatment of Bipolar Depression: Current Status and Future Perspectives

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Abstract

Purpose of Review This paper aims to review current available treatment options and to consider future directions in the treatment of bipolar depression.

Recent Findings There are a limited number of established treatments that have demonstrated varied efficacy in acute bipolar depression including modern antipsychotics (quetiapine, lurasidone, olanzapine ± fluoxetine and recently cariprazine) and mood stabilisers (lamotrigine and valproate). Lithium has a role in protecting against depressive relapses and suicide. Alternative and experimental treatments including pramipexole, modafinil/armodafinil, omega-3 fatty acids and thyroxine may be used to augment the treatment of bipolar depression. Ketamine represents a major breakthrough, producing rapid reductions in depressive symptoms even in cases of treatment-resistance, but challenges remain in how best to maintain response and reduce unwanted side effects.

Summary There remains uncertainty with regard to the relative efficacy and safety of established and experimental treatments for bipolar depression. Further work using consistent and optimal trial designs and further investigation into novel compounds and treatment interventions are warranted.

Keywords Bipolar disorder · Bipolar depression · Antidepressants · Mood stabilisers · Antipsychotics · Experimental treatments

Introduction

Bipolar disorder is a disabling condition characterised by recurrent episodes of depression and mood elevation (mania or hypomania) and mixed states. With respect to symptom duration, depression is typically the predominant phase in bipolar disorder [1], accounting for a greater proportion of impaired social and occupational functioning, morbidity and an excess mortality associated with suicide [2, 3].

Bipolar depression poses a therapeutic challenge, complicated by the need to relieve depressive symptoms without precipitating mania, hypomania or worsening cycle frequency [4]. Despite its high prevalence and clinical importance, until recently there have been relatively few randomised controlled trials (RCTs) in bipolar depression. Although there are a limited number of established treatments demonstrating efficacy in acute episodes, there is a paucity of evidence to decide between different agents and the therapeutic, prophylactic or harmful effects in the long term are less well evaluated.

Bipolar I and II are the most commonly diagnosed subtypes of bipolar disorder. For a diagnosis of bipolar I, criteria must have been met for at least one manic episode which may have been preceded and may be followed by major depressive episodes. To qualify for a diagnosis of bipolar II, the individual must have had at least one hypomanic and at least one major depressive episode [5]. Relative to bipolar I, there has been less research on the safety and efficacy of pharmacological treatments in bipolar II disorder and specifically bipolar II depression [6]. Only a limited number of agents have been examined in both.

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Here, we first review current evidence for recognised treatments in bipolar depression before exploring alternative and experimental treatment options. Finally, we summarise our findings and discuss limitations in this field of research before considering future perspectives in the treatment of bipolar depression.

Antidepressants

Although antidepressants are commonly prescribed for bipolar depression, their use remains controversial [7]. There is a particular lack of placebo-controlled, monotherapy trials examining efficacy of antidepressants in bipolar depression with notable concerns regarding the risk of mood activation, causing a switch to mania or inducing rapid cycling, with the use of ‘unopposed’ antidepressants (i.e. without mood stabiliser or antipsychotic protection).

Two large placebo-controlled trials provided evidence to suggest a potential lack of efficacy of antidepressants in the treatment of bipolar depression. The first, an add-on study, found no additional benefit from adjunctive paroxetine or bupropion as compared with optimised mood stabiliser or antipsychotic treatment [8]. The second, the EMBOLDEN-II study, compared the efficacy of quetiapine with placebo, including paroxetine as a comparator [9]. Although quetiapine was found to be superior to placebo for treating acute depressive episodes in bipolar I and II disorder, paroxetine was not.

Findings from meta-analyses regarding the efficacy of antidepressants have been conflicting. While one found no advantage of antidepressants over placebo [10], three others have suggested greater efficacy of antidepressants compared with placebo in acute bipolar depression [11–13]. In a double-blind comparison trial of venlafaxine versus lithium monotherapy, venlafaxine had significantly greater response and remission rates, without an increase in hypomanic symptoms in bipolar II depression [14]. A further follow-up study of bipolar II patients in remission from a depressive episode demonstrated a lower relapse rate for fluoxetine compared with lithium or placebo, again without an increase in hypomanic symptoms [15].

The frequency and severity of antidepressant-associated mood elevations are significantly higher in bipolar I patients compared with bipolar II [16]. A large naturalistic study found antidepressant monotherapy to be associated with an increased risk of mania in bipolar I patients, while in those also receiving a mood stabiliser, this higher risk was not seen [17]. The risk seems particularly increased with tricyclic antidepressants (TCAs) and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine compared with selective serotonin reuptake inhibitors (SSRIs) [11, 18].

While there may be a role for the cautious use of antidepressant monotherapy in select bipolar II patients who have

previously demonstrated a favourable response, monitoring closely for any adverse reactions such as hypomania or agitation, there is an overall consensus that, especially in bipolar I patients, antidepressants should only be prescribed in combination with antimanic or antipsychotic medications [7]. If an antidepressant is to be prescribed, SSRIs or bupropion is generally recommended, while TCAs are usually best avoided [19].

Mood Stabilisers

Lithium

The use of lithium in treating bipolar depression is supported by a number of early small double-blind trials suggesting superiority of lithium compared with placebo; however, most of these studies had methodological shortcomings [20]. In the only modern, rigorously conducted RCT (EMBOLDEN I), although quetiapine demonstrated superiority over placebo in the treatment of acute bipolar depression, lithium monotherapy did not significantly differ from placebo in reducing depressive symptom scores [21]. It should be noted, in this trial, median serum lithium levels were at the lower end of target range (0.6 mEq/L) and 35% of patients had serum concentrations below this level. Indeed, higher serum levels may be required for sufficient antidepressant effects, but this comes with an increased risk of adverse reactions. Nonetheless, there is evidence that lithium prevents depressive relapse, albeit with more robust protective effects on manic relapse [22, 23], and has an important role in reducing suicide risk in bipolar disorder patients [24].

Lamotrigine

Initial findings from five trials investigating the efficacy of lamotrigine in acute bipolar I and II depression were essentially negative in regard to the primary outcome [25]; however, a subsequent meta-analysis, which pooled data from these trials, determined a modest beneficial effect of lamotrigine on depressive symptoms [26]. Further analysis showed a more substantial effect in those patients with a baseline Hamilton Rating Scale for Depression (HAM-D) score of 24 and above, while in patients with scores below 24 at entry, the high placebo response likely prevented detection of an effect of lamotrigine in individual studies. Add-on studies have shown additional benefits of combining lamotrigine with lithium [27] and with quetiapine [28] treatment in bipolar depression.

Lamotrigine is approved by the FDA as a maintenance treatment in bipolar disorder with evidence for effectiveness in protecting against depressive and manic relapses with more robust effects against depression [29]. Although it may be used in acute bipolar depression, a practical consideration

which may limit clinical utility is the need for cautious dose titration to avoid potential dermatological complications.

Valproate

There are a limited number of small studies of valproate in bipolar depression which have been summarised in two meta-analyses [30, 31]. Taken together, these provide some evidence to support efficacy of valproate monotherapy in bipolar depression although a larger study would be helpful if it confirmed these putative acute benefits. There is also limited evidence to suggest that valproate protects against depressive relapse when used as a maintenance treatment [32], but again this is based on a small number of participants. The BALANCE trial compared valproate, lithium and their combination in a randomised open-label relapse prevention trial [23]. Trial findings demonstrated lithium monotherapy and lithium in combination with valproate were superior to valproate alone in preventing both manic and depressive relapses. Naturally, patients and clinicians need to consider acceptability and potential side-effect burden when deciding between lithium, valproate or their combination as longer term treatments in bipolar disorder.

Carbamazepine

The evidence base concerning the treatment of bipolar depression with carbamazepine is poor. A few early trials exist; however, most are uncontrolled and open label with small numbers of subjects. In one RCT comparing treatment with placebo versus carbamazepine for 12 weeks, although carbamazepine failed to significantly differentiate from placebo in depressive symptom measures at most post-baseline measure points, there was a higher clinical response rate at endpoint compared with placebo ($30/47 = 63.8\%$ vs. $8/23 = 34.8\%$, $p = 0.044$) [33]. In a Cochrane review of oxcarbazepine, a keto derivative of carbamazepine, as an adjunctive to lithium, oxcarbazepine reduced depression rating scale scores more than carbamazepine in a group of manic participants [34]. However, the role of this agent in bipolar depression remains poorly investigated.

Antipsychotics

Several second-generation antipsychotic medications have demonstrated effectiveness in treating bipolar depression. However, efficacy cannot be supported for the class as a whole with evidence instead suggesting a role for specific agents. Notably, these include quetiapine, olanzapine, lurasidone and most recently cariprazine.

Quetiapine

A number of trials have found quetiapine to be effective both as a short-term treatment and for relapse prevention in bipolar depression. Two initial RCTs demonstrated acute effectiveness of quetiapine at doses of 300 mg and 600 mg in bipolar I and II depression as early as week one [35, 36]. In two subsequent RCTs exploring the efficacy and tolerability of quetiapine and active comparators lithium and paroxetine, quetiapine again outperformed placebo in attenuating depressive symptoms while the active comparators did not [9, 21]. Placebo-controlled studies of quetiapine extended release (XR) monotherapy have also consistently demonstrated efficacy in bipolar depression [37–39]. In terms of relapse prevention, in patients with bipolar I disorder previously stabilised on quetiapine, continued maintenance therapy with quetiapine significantly increases time to recurrence of depressive or manic relapse compared with placebo [40], regardless of any combination with lithium or valproate [41]. Although effective in bipolar depression, quetiapine may not always be tolerated, particularly with regard to adverse effects including excess sedation, somnolence and weight gain [42].

Olanzapine ± Fluoxetine

Olanzapine monotherapy has shown superior benefits to placebo in the treatment of bipolar depression with a modest antidepressant effect [43–45]. In a subpopulation analysis of Japanese patients, there was a greater benefit on bipolar depression scores [46]. There is additional evidence to support a prophylactic effect as olanzapine delays relapse into subsequent mood episodes compared with placebo in bipolar disorder patients who have already responded to olanzapine for a manic or mixed episode [47].

In the original RCT, the combination of olanzapine with fluoxetine separated further from placebo than olanzapine monotherapy [43] and the efficacy of this combination has been further supported by findings from comparison studies [48–50]. Compared with lamotrigine, in patients with bipolar I depression, those receiving olanzapine + fluoxetine had significantly greater improvement in depressive symptoms at week 7 and week 25 time points [48, 50]. However, olanzapine + fluoxetine treatment was associated with significantly greater rates of side effects including somnolence, increased appetite, dry mouth, sedation, weight gain and tremor. Additionally, in olanzapine + fluoxetine-treated patients, weight, total cholesterol and triglyceride levels were all significantly elevated compared with those treated with lamotrigine. This suggests that although olanzapine + fluoxetine may be more effective in bipolar depression; lamotrigine shows better tolerability.

Lurasidone

Evidence to support efficacy of lurasidone in the treatment of bipolar depression comes from three large placebo-controlled studies [51–53]. In the first, comparing lurasidone monotherapy versus placebo in bipolar I depression over a 6-week period, lurasidone significantly reduced depressive symptoms compared with placebo [51]. Two further placebo-controlled trials showed significant benefits of lurasidone when used as an adjunct to lithium or valproate in improving depressive symptoms in bipolar depression [52, 53]. It is worth mentioning a final RCT of lurasidone in major depressive disorder with sub-threshold hypomanic symptoms (mixed features) showed lurasidone was also effective in reducing depressive symptoms and overall illness severity in this patient group [54].

Overall, lurasidone seems better tolerated than other antipsychotic medications but notable adverse events include akathisia, somnolence, extrapyramidal symptoms and nausea. Importantly lurasidone produces minimal changes in weight, lipids and measures of glycaemic control [51–53]. When balancing benefits and harms of potential treatment options, although lurasidone may not be quite as efficacious as quetiapine or olanzapine + fluoxetine, it would appear to demonstrate an enhanced tolerability profile, increasing its overall utility [55].

Cariprazine

Cariprazine is a novel antipsychotic that is a selective dopamine D₃ and D₂ partial agonist with higher affinity for the D₃ versus D₂ receptor [56]. An initial 8-week phase IIB study of cariprazine at a dose of 1.5 mg/day demonstrated consistent efficacy compared with placebo in bipolar I depression and was generally well tolerated [57]. A larger phase III study demonstrated that cariprazine at both 1.5 mg/day and 3.0 mg/day was significantly more effective than placebo in improving depressive symptoms in bipolar I depression [58•]. Common adverse events in participants receiving cariprazine were nausea, akathisia, dizziness and sedation while mean changes in weight and metabolic parameters were relatively small and comparable across treatment groups. The use of cariprazine in the treatment of depressive episodes associated with bipolar I disorder has since been approved by the FDA.

Others (Aripiprazole and Ziprasidone)

There is limited evidence from open-label studies to suggest benefits of aripiprazole in bipolar depression as an add-on treatment [59, 60]. However, in two identically designed, 8-week, RCTs of aripiprazole monotherapy in bipolar depression, although significant differences in depressive symptoms were seen during weeks 1–6, aripiprazole did not significantly separate from placebo at week 8 (the primary end point) [61].

Similar to aripiprazole, there are two negative RCTs of ziprasidone in the treatment of bipolar depression [62]. Furthermore, in another large study examining efficacy of adjunctive ziprasidone to pre-existing mood stabiliser in acute bipolar depression, adjunctive ziprasidone treatment failed to separate from mood stabiliser alone in depression ratings at 6 weeks [63].

Taken together, these findings suggest aripiprazole and ziprasidone monotherapy are probably not effective in bipolar depression and should not be used routinely [64].

Alternative and Experimental Treatments

Pramipexole

With study findings supporting efficacy of cariprazine in bipolar depression, dopamine agonism/partial agonism has been suggested as a potential mechanism for antidepressant action [65•]. Pramipexole is a dopamine D₂/D₃ agonist commonly used in the management of Parkinson's disease. There have been two small RCTs of pramipexole combined with existing mood stabiliser treatment both suggesting efficacy and tolerability in bipolar depression [66, 67]. Neither study detected an increased risk of switching to mania/hypomania in the pramipexole-treated groups; however, these are small studies and the data are not sufficient to exclude this potential risk.

Modafinil and Armodafinil

The wakefulness-promoting agent modafinil and its longer lasting R-enantiomer (armodafinil) both act to inhibit dopamine-reuptake and have a potential adjunctive role in bipolar depression [68]. One placebo-controlled trial examining adjunctive modafinil at doses of 100 mg–200 mg/day in bipolar depression found significantly greater improvement in depressive symptoms in the modafinil group at week 2, maintained through to week 6 [69]. A phase II and subsequent phase III study of adjunctive armodafinil 150 mg/day in bipolar I depression again demonstrated significantly improved depressive symptoms compared with placebo and was generally well tolerated [70, 71]. However, in two further double-blind RCTs of adjunctive armodafinil in bipolar I depression, although armodafinil reduced depressive symptoms to a greater extent than placebo, it did not separate from placebo in the primary efficacy outcomes in either study [72, 73]. A recent meta-analysis combining these studies found that compared with placebo, augmentation with modafinil or armodafinil was associated with significantly greater treatment response and remission, encouraging further studies that delineate subtypes of bipolar depression responsive to these novel dopamine enhancing agents [68].

Ketamine

There is growing interest in the potential of ketamine, an uncompetitive N-Methyl-D-Aspartate (NMDA) receptor antagonist, for the treatment of unipolar and bipolar depression. Rapid reductions in depressive symptoms have been reliably demonstrated following a single subanaesthetic ketamine infusion, including in cases of treatment-resistance [74]. Although not fully understood, ketamine's mechanism of antidepressant action is thought to be mediated through NMDA receptor antagonism, resulting in increased cortical glutamate, increased in α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) signalling and with downstream effects on synaptogenic and neuroplastic pathways [75].

In a randomised, placebo-controlled, double-blind, cross-over add-on study of 18 patients with treatment-resistant bipolar depression already receiving lithium or valproate, following a single ketamine infusion (0.5 mg/kg over 40 min) depressive symptoms significantly improved within 40 min compared with placebo and remained significant through day 3 [76]. There was an impressive response rate with 71% of subjects showing a response to ketamine compared with only 6% for placebo. These findings have been replicated in a similarly designed study of 15 patients with treatment-resistant bipolar depression (maintained on lithium or valproate), which demonstrated a comparable rapid and robust antidepressant response following a single ketamine infusion, alongside a significant improvement in suicidal ideation [77]. The most common side effect was acute dissociative symptoms; otherwise, ketamine was generally well tolerated.

Although ketamine may offer a rapid antidepressant effect in cases of bipolar depression, unfortunately the effect is not sustained in the long term. While one option is repeated ketamine infusions [78], the feasibility, accessibility and resources required can limit availability and other routes of administration (oral, sublingual, intranasal, intramuscular, subcutaneous) could prove preferred alternatives for repeat administrations [79]. However, comparatively fewer studies have fully evaluated these alternative routes and further investigation is warranted.

An intranasal formulation of ketamine's (S)-enantiomer, esketamine, was recently approved by the FDA for unipolar depression. Although no trials have specifically examined the use of this formulation in bipolar depression, it could be a potential avenue to consider and explore in the future.

Memantine

Memantine is a non-competitive NMDA antagonist that lacks dissociative side effects associated with ketamine at therapeutic doses and has also been investigated as an adjunctive treatment in bipolar depression. Although results of one RCT suggested an early antidepressant effect of memantine

augmentation to lamotrigine in bipolar depression, this effect failed to separate from placebo at the 8-week trial endpoint [80]. In an RCT examining effects of memantine augmentation to valproate in bipolar II depression, tumour necrosis factor α levels (TNF- α) were significantly lower in the memantine group, suggesting an anti-inflammatory effect, but there was no significant advantage over placebo in terms of antidepressant effect [81]. A meta-analysis of these trials showed no significant benefit of memantine over placebo augmentation in bipolar depression but advised there was not enough evidence to draw meaningful conclusions [82].

Thyroxine/Levothyroxine

Thyroid abnormalities associated with bipolar disorder are a significant problem that can lead to poor outcomes if not recognised and treated [83]. The benefits of adjunctive treatment with thyroid hormones at supraphysiologic doses have been explored in bipolar depression. In a placebo-controlled study, the addition of levothyroxine to continuing treatment with mood stabiliser and/or antidepressant medication in bipolar depression showed no significant benefit over placebo [84]. Interestingly, a secondary analysis revealed a significant difference in female patients only. More recently a double-blind, placebo-controlled trial in 32 patients with treatment-resistant rapid cycling bipolar disorder found that following adjunctive levothyroxine treatment patients spent significantly less time depressed or in a mixed state and greater time euthymic (*within groups*) [85]. *Between groups*, those in the levothyroxine group had a significantly greater increase in time euthymic and decrease in time in the mixed state compared with the placebo group.

Omega-3 Fatty Acids

There is limited evidence for the use of omega-3 fatty acids in bipolar depression and findings of individual studies have not been consistent. While one RCT examining the efficacy of adjunctive ethyl-eicosapentaenoic acid (EPA) in bipolar depression (1–2 g/day) found a significant improvement in HAM-D scores compared with placebo [86], another RCT found no significant difference between adjunctive EPA (6 g/day) and placebo in changes from baseline depressive symptoms [87]. A later meta-analysis, of 5 pooled datasets ($n = 291$), revealed a significant effect in favour of adjunctive omega-3 on the outcome of bipolar depression with a moderate effect size but uncertainty remains regarding optimum formulation and dosage [88].

Mifepristone

At high doses, the progesterone receptor antagonist mifepristone is an antagonist of the glucocorticoid receptor (GR)

subtype of corticosteroid receptor and preliminary evidence demonstrated potential cognitive-enhancing and mood-elevating properties in bipolar disorder [89]. However, in a larger RCT examining adjunctive mifepristone (600 mg/day) for 1 week in 60 patients with bipolar depression, although treatment was well tolerated and a beneficial effect in spatial working memory was demonstrated, there was no significant effect of mifepristone on depressive symptoms [90]. The lack of antidepressant effect may have been dose related as the dose used would not be expected to reliably generate plasma levels within a therapeutic range suggested by previous work in psychotic depression [91].

Non-pharmacological

Although there are limited RCTs of electroconvulsive therapy (ECT) in mania and bipolar depression, there is a wide consensus that ECT is an effective treatment for both acute mania and bipolar depression even in pharmacotherapy-resistant patients [92]. In large sample of drug-resistant bipolar depressed patients, at the end of an ECT course, an antidepressant response was seen in 201 out of 295 individuals (68.1%) [93] and another trial suggests ECT may be more effective than pharmacological treatment in treatment-resistant bipolar depression [94].

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation therapy. There is growing evidence to support its use in bipolar depression with findings from a meta-analysis suggesting rTMS to be a safe, effective treatment option and does not appear to be associated with treatment-emergent affective switches [95]. Efforts to develop the technique are ongoing with encouraging results in bipolar depression using a novel approach called ‘deep’ TMS or (dTMS) to stimulate deeper brain regions [96].

Other non-invasive physical treatments focussing on sleep disturbances and circadian rhythm dysfunction including sleep deprivation, sleep phase advance and light therapy may serve as potential add-on treatment options in bipolar depression to accelerate and sustain antidepressant response [97, 98].

Last, but by no means least, adjunctive psychotherapy has an important role in terms of relapse prevention and episode stabilisation in bipolar disorder [99]. Psychotherapy is an opportunity for psychoeducation and may help to identify and monitor early signs of mood change, develop strategies for relapse prevention, explore and manage relationship between mood, stress and interpersonal difficulties, encourage medication adherence, establish regular sleep-wake cycles and address substance misuse [100]. Although a discussion of different psychotherapy modalities is beyond the scope of this review, in terms of bipolar depression, cognitive behavioural therapy (CBT), family therapy and psychoeducation may be particularly useful in protecting against recurrences [99, 100].

Summary and Future Perspectives

A summary of established and alternative/experimental pharmacological treatments in bipolar depression discussed in this review is provided in Table 1. The development of guidance and expert treatment recommendations for bipolar depression has been largely informed by the strength of evidence for particular drugs or by direct comparative data [19]. However, as shown in Table 2, treatment recommendations are not always consistent, with large variation observed in terms of guideline recommendations and interpretation of available evidence. As one example, the 2017 International College of Neuro-Psychopharmacology (CINP) treatment guidelines recommend aripiprazole and imipramine monotherapy as third-line strategies in bipolar depression [102•]. Uncertainty remains with regard to the relative efficacy and safety of antidepressants, mood stabilisers, antipsychotics and experimental treatments for bipolar depression.

One attempt to address this issue has come from multiple-treatment meta-analyses. In a large network meta-analysis of 29 studies including 8331 subjects, olanzapine + fluoxetine, lurasidone, olanzapine, valproate, SSRIs and quetiapine ranked highest for effect size and olanzapine + fluoxetine also ranked highest for response [64]. A further meta-analysis of 24 trials (7307 subjects) in bipolar depression found statistical superiority over placebo for olanzapine + fluoxetine $\geq$ valproate $>$ quetiapine $>$ lurasidone $>$ olanzapine $>$ aripiprazole and carbamazepine (in order of effect size) [104]. However, these meta-analyses are limited by the small numbers of controlled trials of bipolar depression treatments and by the methods used to assess efficacy meaning certain studies cannot be included as parameters such as outcome and trial duration do not match and cannot be reliably compared with others. This is particularly relevant for early studies of lithium. Furthermore, these network meta-analyses may not be stable as rankings are influenced by inclusion criteria and indirect comparisons sometimes contradict direct comparison findings [65•].

Mindful of these limitations and considering the available evidence, quetiapine is likely the most efficacious established treatment for bipolar depression. Other first-line agents to consider include lurasidone, olanzapine $\pm$ fluoxetine, lamotrigine and valproate. Cariprazine may become more widely used in the future. Lithium is also probably effective in bipolar depression, but the supporting evidence is limited. Alternative treatments including pramipexole, modafinil/armodafinil, omega-3 fatty acids and thyroxine can be used to augment the treatment of bipolar depression. In cases of treatment-resistance, ketamine may provide rapid reductions in depressive symptoms, but challenges remain in considering the most appropriate route of administration and how best to maintain response. Although still highly stigmatised, ECT is another effective treatment and should also be considered in cases of treatment-resistance and high suicidal risk.

Table 1 Summary of established and alternative/experimental pharmacological treatments in bipolar depression

Drug/combination	Summary	Placebo-controlled trials (number in efficacy analysis)	Efficacy	Refs
Established treatments:				
Quetiapine	<ul style="list-style-type: none"> - Five large RCTs have demonstrated clear efficacy for quetiapine monotherapy at 300 mg and 600 mg/day in bipolar I and bipolar II depression. - Two subsequent RCTs in Chinese and Japanese patients demonstrated further efficacy of quetiapine extended release (XR) 300 mg/day in bipolar I and II depression. 	7 (3112)	+++	[9, 21,
Lurasidone	<ul style="list-style-type: none"> - One large RCT showing good effect of lurasidone as monotherapy in bipolar I depression. - Two further RCTs showed significant benefit of lurasidone as an adjunct to mood stabilisers compared with placebo in bipolar I depression. 	Monotherapy: 1 (485) Adjunct: 2 (682) 3 (1282) 1 (437)	+++	[51–53]
Olanzapine	<ul style="list-style-type: none"> - Two large RCTs showing Olanzapine monotherapy is effective in bipolar I depression. - Another small RCT from China demonstrating significantly greater improvements in depressive symptoms relative to placebo. 		++	[43–45]
Olanzapine ± fluoxetine	<ul style="list-style-type: none"> - The combination of olanzapine with fluoxetine separated further from placebo than olanzapine monotherapy in the only placebo-controlled trial. - A double-blind comparison study and 6-month follow-up suggests olanzapine + fluoxetine may be more effective than lamotrigine in bipolar I depression. 		+++	[43]
Cariprazine	<ul style="list-style-type: none"> - In the first RCT which compared cariprazine 0.75 mg/day, 1.5 mg/day and 3.0 mg/day found cariprazine 1.5 mg/day demonstrated consistent efficacy compared with placebo in bipolar I depression. - Subsequent phase III RCT found cariprazine at both 1.5 mg/day and 3.0 mg/day was significantly more effective than placebo in improving depressive symptoms in bipolar I depression. - Modest beneficial effect of lamotrigine in bipolar I and II depression determined from meta-analysis, however numerous failed individual trials. 	2 (1045)	++	[48, 50]
Lamotrigine	<ul style="list-style-type: none"> - Effective in protecting against depressive relapses in bipolar disorder. - Cautious dose titration required to avoid potential dermatological complications. 	5 (1071)	++	[57, 58•]
Valproate	<ul style="list-style-type: none"> - Four small RCTs of valproate in bipolar depression summarised in meta-analyses which support antidepressant efficacy. - Limited evidence suggests valproate protects against depressive relapse when used as a maintenance treatment. 	4 (140)	++	[29]
Lithium	<ul style="list-style-type: none"> - Lithium is likely effective in treating bipolar depression but supporting data has methodological shortcomings. Only one modern rigorously conducted RCT. - Evidence that lithium prevents depressive relapse, however more robust protective effects on manic relapse. 	1 (265)	+ / ++	[30, 31]
Carbamazepine	<ul style="list-style-type: none"> - Important role in reducing suicide risk in bipolar disorder. - In one small RCT, carbamazepine did not significantly differentiate from placebo in measures of depressive symptoms at most post-baseline time points. However, there was a higher clinical response rate at endpoint compared with placebo. 	1 (70)	+	[32]
Alternative/experimental treatments:				
Pranipexole	<ul style="list-style-type: none"> - Two small placebo-controlled trials, one in bipolar I and another in bipolar II depression, suggest efficacy in bipolar depression when used as adjunct to existing mood stabiliser treatment. 		++	[22–24]
Modafinil/armodafinil	<ul style="list-style-type: none"> - One positive RCT of modafinil 100–200 mg/day when used as an adjunct treatment in bipolar depression. - Four RCTs of adjunctive armodafinil in bipolar I depression of which two showed significant benefit over placebo and in the other two did not separate from placebo in primary efficacy outcomes. - Findings combined in recent meta-analysis that suggests augmentation with modafinil or armodafinil is associated with significantly greater treatment response and remission in bipolar depression. 	Adjunct: 2 (43) Adjunct: 5 (1587)	++	[33]
Ketamine (IV)	<ul style="list-style-type: none"> - Two randomised, placebo-controlled, double-blind, crossover trials in treatment-resistant bipolar I and II depressed patients. - High response rate (~ 70%) to single ketamine infusion 0.5 mg/kg over 40 mins in both trials. - Antidepressant effects not long-lasting for most patients. - Most common side-effect was acute dissociative symptoms. 	Adjunct: 2 (33)	++	[66, 67]

Table 1 (continued)

Drug/combination	Summary	Placebo-controlled trials (number in efficacy analysis)	Efficacy Refs
Memantine	<ul style="list-style-type: none"> - One small and one larger RCT failed to show a significant advantage of memantine augmentation (lamotrigine and valproate respectively) over placebo in terms of antidepressant effect in bipolar depression. - One RCT found no significant benefit of adjunct levodopa over placebo in bipolar depression. 	(Crossover trials-subjects received ketamine and placebo) Adjunct: 2 (261) Adjunct: 2 (94)	- [80, 81] + [84, 85]
Thyroxine/levodopa	<ul style="list-style-type: none"> - Another RCT in treatment-resistant rapid cycling bipolar disorder comparing adjunctive levodopa (L-T₄), triiodothyronine (T₃) and placebo found <i>within groups</i>, post-treatment the L-T₄ group spent significantly less time in depressed or in a mixed state and greater time euthymic. <i>Between groups</i>, the L-T₄ group had a significantly greater increase in time euthymic and decrease in time in the mixed state than the placebo group. 		
Omega-3 fatty acids	<ul style="list-style-type: none"> - Meta-analysis of five RCTs of omega-3 in bipolar I and II depression found a significant effect in favour of omega-3 over placebo with moderate effect size. 	Adjunct: 5 (291)	+ + [88]
Mifepristone	<ul style="list-style-type: none"> - Preliminary evidence suggested potential cognitive-enhancing and mood-elevating properties in bipolar disorder. - Larger RCT examining adjunctive mifepristone 600 mg/day in bipolar depression failed to demonstrate significant improvement in depressed mood. Mifepristone treatment was associated with improvement in cognitive function (spatial working memory). 	Adjunct: 1 (60)	± [89] [90]

The rapid improvement in depressive symptoms occurring with ketamine administration, taking place within hours to days rather than weeks to months, represents a paradigm shift in the treatment of depression and now the ultimate goal is the development of rapid acting treatment strategies with a prolonged antidepressant response. An intranasal formulation of the (S)-enantiomer, esketamine, has been developed with promising results following repeated administration in treatment-resistant unipolar depression [105]. Although there have been no trials of intranasal esketamine in bipolar depression completed to date, work is now underway to determine safety and efficacy of an inhaled esketamine formulation in bipolar depression ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03965871) ID: NCT03965871). Alternative and better tolerated ketamine-like agents that affect glutamate neurotransmission may offer future promise in both unipolar and bipolar depression [106, 107]. The psychedelic drug psilocybin, a 5-HT_{2A} partial agonist, is another compound with novel antidepressant mechanisms, currently being investigated in unipolar major depressive disorder ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03775200) ID: NCT03775200, NCT03866174). While this may not be a suitable option to explore in bipolar I depression, due to the potential risk of mania, it may be an interesting avenue to explore in the future in carefully selected bipolar II depressed individuals.

Other novel treatment strategies under investigation in bipolar depression include adjunctive anti-inflammatory agents and probiotics. Several proof-of-concept trials have shown encouraging results for anti-inflammatory agents in the treatment of bipolar depression with moderate effect sizes and good tolerability [101, 103, 108]. Results from trials of probiotics in bipolar depression are awaited ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02155972) IDs: NCT02155972, NCT03349528). Ideally large future studies, using stratified samples enriched with individuals with immune dysfunction or microbiome abnormalities, will establish the role of adjunctive anti-inflammatory agents and probiotics in bipolar depression.

Conclusions

When deciding treatment options in bipolar depression, it is important to balance to potential benefits and harms. The treatments discussed in this review have substantial differences in terms of adverse effect profile, tolerability and acceptability. Considering each case individually and involving the patient in their treatment planning are key.

Despite the severe clinical and socioeconomic impact, research into the treatment of bipolar depression remains limited. Further work using consistent and optimal trial designs and further investigation into novel compounds and treatment interventions are warranted. Together this

Table 2 Selected recent guidelines and treatment recommendations for bipolar depression (within last 5 years)

Guideline	Summary of recommendations
National Institute of Clinical Excellence (NICE) 2014 [101]	<ul style="list-style-type: none"> - First line: olanzapine + fluoxetine or quetiapine - Second line: olanzapine or lamotrigine - If develops depression and already taking lithium: <ul style="list-style-type: none"> - Check plasma levels and increase dose if inadequate - Add olanzapine + fluoxetine or quetiapine first line or lamotrigine second line <ul style="list-style-type: none"> - If develops depression and already taking valproate: <ul style="list-style-type: none"> - Check plasma levels and increase dose if inadequate - Add olanzapine + fluoxetine or quetiapine first line or lamotrigine second line - Additional psychological interventions: cognitive behavioural therapy, interpersonal therapy or behavioural couples therapy * Always consider person's preference and previous response to treatment
British Association for Psychopharmacology 2016 [65•]	<ul style="list-style-type: none"> - Patients not already taking long-term treatment: Consider (a) quetiapine; (b) lurasidone; (c) olanzapine - Lamotrigine plus mood stabiliser or antipsychotic preventing recurrence of mania - If considering antidepressant treatment, co-prescribe with antimanic or antipsychotic, especially in individuals with a history of mania. Olanzapine + fluoxetine has support as a specific treatment combination - If depressive symptoms are less severe, lithium may be considered - Consider ECT in cases of treatment resistance, high risk of suicide, psychosis, not eating or drinking because of depression or severe depression during pregnancy - Additional psychological interventions: cognitive behaviour therapy, family-focused therapy or interpersonal rhythm therapy
International College of Neuro-Psychopharmacology (CINP) treatment guidelines for Bipolar disorder in adults 2017 [102•]	<ul style="list-style-type: none"> - First step: quetiapine or lurasidone. Depending on patient preference and availability, consider cognitive behavioural therapy in addition to medication - Second step: (a) olanzapine ± fluoxetine; (b) mood stabiliser plus lurasidone, modafinil or pramipexole; (c) lithium plus lamotrigine; (d) add escitalopram or fluoxetine to existing treatment - Third step: (a) valproate, aripiprazole, imipramine, phenelzine, carbamazepine or lamotrigine monotherapy; (b) lithium plus L-sulpiride - Fourth step: (a) tranylepromine or lithium monotherapy; (b) venlafaxine plus antimanic; (c) armodafinil or IV ketamine with mood stabiliser; (d) lithium plus fluoxetine or lamotrigine; (e) mood stabiliser plus levothyroxine (L-T4); (f) lithium plus oxcarbazepine - Fifth step: ECT or various medication combinations depending on prescriber's knowledge or personal experience
Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder [103•]	<ul style="list-style-type: none"> - First-line: (a) quetiapine; (b) lurasidone plus lithium or valproate; (c) lithium; (d) lamotrigine; (e) lurasidone; (e) lamotrigine (adj) - Second-line: (a) valproate; (b) SSRIs/bupropion plus antimanic or antipsychotic; (c) ECT; (d) cariprazine; (e) olanzapine + fluoxetine - Third-line: (<i>In alphabetical order</i>) (a) aripiprazole (adj); (b) armodafinil (adj); (c) asenapine (adj); (d) carbamazepine; (e) eicosapentaenoic acid (EPA) (adj); (f) ketamine (IV) (adj); (g) light therapy ± total sleep deprivation (adj); (h) levothyroxine (adj); (i) modafinil (adj); (j) N-acetylcysteine (adj); (k) olanzapine; (l) pramipexole (adj); (m) repetitive transcranial magnetic stimulation (rTMS) (adj); (n) SNRI/MAOI (adj)

This is a summary of each guideline's treatment recommendations, condensed for the purpose of the review. Please refer to individual guidelines for detailed recommendations and further analysis of supporting evidence. ECT, electroconvulsive therapy; adj, adjunctive; SSRIs, selective serotonin reuptake inhibitors; SNRI, serotonin and norepinephrine reuptake inhibitor; MAOI, monoamine oxidase inhibitor

will widen the evidence-based treatment armamentarium in bipolar depression and allow more reliable treatment comparisons to be determined.

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Compliance with Ethical Standards

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards and international/national/institutional guidelines).

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