



# Recent Advances in Treatment of Bipolar Depression

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## Abstract

1151

Bipolar Disorder (BD) and Major Depressive Disorder (MDD) are two of the most common mental illnesses causing disability in the world. Bipolar depression has been viewed as more endogenous than unipolar depression, based on significant evidence that mania is biologically driven. As a result of this difference in diagnostic categories, mood disorder research tends to focus on either bipolar disorder in general or unipolar depression in particular. Only a few studies have compared unipolar and bipolar depression. If the hypothesis of bipolar depression as distinct is correct, *first*, biological evidence should be more evident in bipolar depression than in unipolar depression. For example, bipolar depression may have a larger genetic contribution than unipolar depression. *Second*, one could expect bipolar and unipolar depression to progress in different ways. *Third*, psychosocial depression triggers should be less pronounced in bipolar depression than in unipolar depression. In conclusion, if unipolar and bipolar depression were distinct illnesses, we would expect biological, course, symptomatology, and psychosocial factors to differ. Pharmacological treatment is fundamental for successfully managing patients with BD. For acute episodes, the objective is symptom reduction, with the ultimate goal of full remission. For maintenance treatment, the goal is to prevent the recurrences of mood episodes. Medications used in the treatment of BD include mood stabilizers (e.g., lithium, valproate, lamotrigine, and carbamazepine), atypical antipsychotics, and conventional antidepressants.

**Keywords:** Bipolar Depression, treatment

**DOI Number:** 10.14704/nq.2022.20.8.NQ44127

**NeuroQuantology 2022; 20(8): 1151:1158**



## Introduction

Bipolar disorder (BD) is a chronic illness associated with severely debilitating symptoms that can have profound effects on both patients and their caregivers. BD typically begins in adolescence or early adulthood and can have life-long adverse effects on the patient's mental and physical health, educational and occupational functioning, and interpersonal relationships. Although not as common as major depressive disorder (MDD), the lifetime prevalence of BD in the United States is substantial (estimated at approximately 4%), with similar rates regardless of race, ethnicity, and gender. Long-term outcomes are persistently suboptimal. The economic burden of BD to society is enormous, totaling almost \$120 billion in the United States in 2009. These costs include the direct costs of treatment and indirect costs from reduced employment, productivity, and functioning. Given the burden of illness to the individual and to society, there is an urgent need to improve the care of patients with BD. (1).

## Recent advances in treatment of bipolar depression

### Antidepressants

Antidepressants are frequently recommended for bipolar depression, but their use is still debatable (2). There is a distinct dearth of placebo-controlled monotherapy trials assessing antidepressant efficacy in bipolar depression, with major concerns about the potential of mood activation, triggering a flip to mania, or inducing rapid cycling, when 'unopposed' antidepressants are used (i.e., without mood stabilizer or antipsychotic protection).

Two major placebo-controlled trials found indications that antidepressants may be ineffective in the treatment of bipolar depression. The first research, a follow-up, demonstrated no additional benefit from supplementary paroxetine or bupropion

medication as compared to optimal mood stabilization or antipsychotic treatment. The EMBOLDEN-II trial assessed the efficacy of quetiapine versus placebo, as well as paroxetine as a control (3).

In bipolar I patients, the frequency and intensity of antidepressant-related mood elevations are much higher than in bipolar II individuals (4). In a large naturalistic investigation, antidepressant monotherapy was linked to a greater risk of mania in bipolar I patients, although this risk was not apparent in those who simultaneously received a mood stabilizer. When compared to selective serotonin reuptake inhibitors (SSRIs), the risk appears to be higher with tricyclic antidepressants (TCAs) and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine. While there may be a role for antidepressant monotherapy in bipolar II patients who have previously shown a favourable response, with close monitoring for any adverse reactions such as hypomania or agitation, there is a general consensus that antidepressants should only be prescribed in combination with antimanic or antipsychotic medications, especially in bipolar I patients. If an antidepressant is needed, an SSRI or bupropion is usually the best choice, whereas TCAs should be avoided (5).

### Mood Stabilizers

#### Lithium

A number of early modest double-blind experiments supporting the use of lithium in the treatment of bipolar depression suggest that it is superior to placebo; nevertheless, most of these studies had methodological drawbacks (6). Although quetiapine showed advantage over placebo in the treatment of acute bipolar depression in the only current, thoroughly conducted RCT (EMBOLDEN I), lithium monotherapy did not substantially differ from placebo in lowering depressive symptom ratings. It's worth noting that median serum lithium levels in this study were at the lower end of the



intended range (0.6 mEq/L), with 35% of patients having serum concentrations below this level. Larger serum levels may be necessary for adequate antidepressant benefits, but this comes with a higher risk of side effects. Nonetheless, there is evidence that lithium inhibits depressive relapse, albeit with a stronger protective impact on manic relapse (7).

### Lamotrigine

The primary outcome of five trials assessing the efficacy of lamotrigine in acute bipolar I and II depression was largely negative however, a subsequent meta-analysis that combined data from these trials revealed that lamotrigine had a moderate positive effect on depressed symptoms (8). Further analysis revealed that patients with a baseline Hamilton Rating Scale for Depression (HAM-D) score of 24 and above had a more significant effect, whereas patients with scores below 24 at entry had a high placebo response, which likely prevented detection of a lamotrigine effect in individual studies. In bipolar depression, studies have indicated that combining lamotrigine with lithium (9) and quetiapine treatment has extra benefits.

The FDA has approved lamotrigine as a maintenance medication for bipolar illness, based on evidence of its efficacy in preventing depressive and manic relapses, with stronger effects against depression (10). Although it can be used to treat acute bipolar depression, the necessity for careful dose titration to minimize severe dermatological problems may restrict its clinical value.

### Valproate

There are a limited number of small studies of valproate in bipolar depression which have been summarized in two meta-analyses. 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 (11).

### Carbamazepine

The evidence foundation for carbamazepine treatment of bipolar depression is limited. There are a few early trials, but the majority are uncontrolled and open label, with small numbers of participants. Although carbamazepine failed to significantly differentiate from placebo in depressive symptom measures at most post-baseline measure points in one RCT comparing treatment with placebo versus carbamazepine for 12 weeks, there was a higher clinical response rate at endpoint compared to placebo ( $30/47 = 63.8$  percent vs.  $8/23 = 34.8$  percent,  $p = 0.044$ ). In a Cochrane study, oxcarbazepine, a keto derivative of carbamazepine, was found to be more effective than carbamazepine at reducing depression rating scale scores in a group of manic participants (27). However, nothing is known about this drug's effect in bipolar depression.

### Antipsychotics

*Several antipsychotic drugs from the second generation have shown to be useful in the treatment of bipolar depression. However, evidence does not indicate efficacy for the class as a whole, instead pointing to a function for specific medicines. Quetiapine, olanzapine, lurasidone, and, most recently, cariprazine are among them. (12).*

### Quetiapine

In a number of studies, quetiapine was proven to be helpful as a short-term treatment and for preventing relapse in bipolar depression. Two early RCTs showed quetiapine's acute effectiveness in bipolar I and II depression as early as week one at doses of 300 mg and 600 mg (12). Quetiapine surpassed placebo in two subsequent RCTs comparing its efficacy and tolerability to active comparators lithium and



paroxetine in reducing depressive symptoms, but the active comparators did not **(13)**.

### **Olanzapine ± Fluoxetine**

Olanzapine monotherapy, which has a mild antidepressant effect, was proved to be superior than placebo in the treatment of bipolar depression. There was a higher benefit on bipolar depression scores in a subgroup analysis of Japanese patients. In bipolar disorder patients who have already reacted to olanzapine for a manic or mixed episode, there is additional evidence to support a preventive benefit, as olanzapine delays relapse into subsequent mood episodes compared to placebo. The combination of olanzapine and fluoxetine was found to be more effective than olanzapine monotherapy in the initial RCT **(14)**.

### **Lurasidone**

Three large placebo-controlled studies show the efficacy of lurasidone in the treatment of bipolar depression. In the first study, lurasidone monotherapy was compared to placebo in bipolar I depression over a 6-week period, and lurasidone significantly reduced depressed symptom. Lurasidone showed significant benefits in alleviating depressive symptoms in bipolar depression when used as an addition to lithium or valproate in two more placebo-controlled trials. It's worth noting that a final RCT of lurasidone in patients with major depressive disorder and subthreshold hypomanic symptoms (mixed characteristics) found that it was likewise beneficial in lowering depressive symptoms and overall illness severity in this patient group **(15)**. Lurasidone appears to be well tolerated compared to other antipsychotic drugs, however it can cause akathisia, somnolence, extrapyramidal symptoms, and nausea. Importantly, lurasidone causes only little changes in weight, lipids, and glycemic control.

### **Cariprazine**

Cariprazine is a new antipsychotic that works as a selective D3 and D2 partial agonist with a higher affinity for the D3 receptor than the D2 receptor. In a preliminary 8-week phase IIB research, cariprazine at a dose of 1.5 mg/day showed consistent efficacy in bipolar I depression when compared to placebo and was generally well tolerated. Cariprazine, at 1.5 mg and 3.0 mg/day, was considerably more effective than placebo in alleviating depressive symptoms in bipolar I depression, according to a larger phase III research **(16)**. Nausea, akathisia, dizziness, and drowsiness were the most common side effects in people using cariprazine, although mean weight and metabolic parameter changes were minor and equivalent across treatment groups. The FDA has since approved cariprazine for the treatment of depressive episodes associated with bipolar I disorder.

### **Alternative and Experimental Treatments**

#### **Pramipexole**

Dopamine agonism/partial agonism has been proposed as a plausible mechanism for antidepressant activity, based on study data supporting cariprazine's efficacy in bipolar depression **(5)**. Pramipexole is a dopamine D2/D3 agonist that is frequently used to treat Parkinson's disease. In bipolar depression, two small RCTs of pramipexole in combination with an existing mood stabilizer therapy showed efficacy and tolerability **(17)**. Neither study found an increased likelihood of mania/hypomania switching in the pramipexole-treated groups; however, they are small trials with insufficient data to rule out this possibility.

#### **Modafinil and Armodafinil**

Both the wakefulness-promoting drug modafinil and its longer-lasting R-enantiomer (armodafinil) inhibit dopamine reuptake and may be used to treat bipolar depression. In a placebo-controlled trial of adjunctive modafinil



at dosages of 100 mg–200 mg/day in bipolar depression, the modafinil group showed significantly higher improvement in depressive symptoms at week 2, which lasted until week 6. **(18)**. In bipolar I depression, a phase II and subsequent phase III research of adjunctive armodafinil 150 mg/day showed significantly better depressed symptoms compared to placebo and was usually well tolerated. However, despite the fact that armodafinil reduced depressed symptoms more than placebo in two more double-blind RCTs of supplemental armodafinil in bipolar I depression, it didn't differentiate from placebo in the primary effectiveness outcomes in either research. A recent meta-analysis of these studies found that augmentation with modafinil or armodafinil was associated with significantly greater treatment response and remission when compared to placebo, encouraging more research into subtypes of bipolar depression that are responsive to these novel dopamine enhancing agents **(19)**.

### **Ketamine**

Ketamine, a non-competitive N-Methyl-D-Aspartate (NMDA) receptor antagonist, is gaining popularity as a treatment for unipolar and bipolar depression. Following a single subanesthetic ketamine infusion, rapid decreases in depression symptoms have been consistently documented, even in cases of treatment resistance. Ketamine's antidepressant action is thought to be mediated through NMDA receptor antagonism, which results in increased cortical glutamate, increased -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) signaling, and downstream effects on synaptogenic and neuroplastic pathways, though the mechanism is not fully understood **(20)**.

### **Memantine**

Memantine is a non-competitive NMDA antagonist that, at therapeutic levels, does not have the dissociative side effects associated with

ketamine. It has also been studied as an additional treatment for bipolar depression. Although one RCT found that adding memantine to lamotrigine had an early antidepressant effect in bipolar depression, the effect failed to distinguish itself from placebo at the 8-week trial's conclusion **(21)**. TNF- levels were considerably lower in the memantine group in an RCT assessing the effects of memantine augmentation to valproate in bipolar II depression, suggesting an anti-inflammatory impact, but there was no significant advantage over placebo in terms of antidepressant effect **(22)**.

### **Omega-3 Fatty Acids**

The use of omega-3 fatty acids in bipolar depression has insufficient evidence, and the results of various research have been inconsistent. 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 when compared to placebo. **(23)**.

### **Mifepristone**

Mifepristone, a progesterone receptor antagonist, is an antagonist of the glucocorticoid receptor (GR) subtype of corticosteroid receptor at high doses, and preliminary research suggests that it may have cognitive and mood-enhancing characteristics in bipolar illness. However, although the treatment was well tolerated and a beneficial effect in spatial working memory was demonstrated in a larger RCT examining adjunctive mifepristone (600 mg/day) for 1 week in 60 patients with bipolar depression, there was no significant effect of mifepristone on depressive symptoms **(13)**. The lack of antidepressant effect could have been due to the dose, as it seemed unlikely that the dose employed would reliably achieve plasma levels within the therapeutic range established by earlier work in psychotic depression **(24)**.



## Non-pharmacological

Despite the lack of RCTs in mania and bipolar depression, there is widespread agreement that ECT is an effective treatment for both acute mania and bipolar depression, especially in pharmacotherapy-resistant patients, however, 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%) and another trial suggests ECT may be more effective than pharmacological treatment in treatment-resistant bipolar depression (25).

rTMS (repetitive transcranial magnetic stimulation) is a type of non-invasive brain

stimulation. There is mounting evidence to support its use in bipolar depression, with data from a meta-analysis indicating that rTMS is a safe and effective therapeutic option that is not linked to treatment-emergent affective changes. The technique is still being developed, with promising results in bipolar depression employing a novel approach dubbed 'deep' TMS or (dTMS) to activate deeper brain regions (26).

**Conflict of Interest:** None

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