Bipolar major depression in adults: Investigational and nonstandard approaches to treatment

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Literature review current through: **Oct 2023.**
This topic last updated: **Mar 22, 2022.**

INTRODUCTION

Bipolar disorder is marked by episodes of mania (table 1) and hypomania (table 2) and nearly always includes episodes of major depression (table 3) [1]. Observational studies consistently show that depressive episodes predominate the clinical course of bipolar disorder [2,3]. Compared with manic and hypomanic episodes, bipolar depressive episodes and residual bipolar depressive symptoms account for a greater proportion of long-term morbidity, impaired functioning, and risk of suicide [4,5].

As a result, improved treatment of major depression is a patient priority. An internet-based survey from 11 countries, which asked patients with bipolar disorder (n = 1300) which aspects of care they would most like to see improved, better treatment of depression was endorsed by the largest number (>40 percent) [6]. The second and third leading aspects of care that patients would most like to see improved were avoiding weight gain and preventing relapse of depressive episodes.

This topic reviews investigational approaches to treating bipolar major depression in adults. Other topics discuss choosing treatment for adults with bipolar major depression, the general principles of treating bipolar major depression in adults, the efficacy and adverse effects of antidepressants and second-generation antipsychotics for bipolar major depression in adults, choosing pharmacotherapy for adults with acute mania and hypomania, choosing maintenance treatment for adults, and choosing pharmacotherapy for pediatric bipolar major depression:

- (See "Bipolar major depression in adults: Choosing treatment".)
- (See "Bipolar major depression in adults: General principles of treatment".)
- (See "Bipolar major depression in adults: Efficacy and adverse effects of antidepressants".)
- (See "Bipolar major depression in adults: Efficacy and adverse effects of second-generation antipsychotics".)
- (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)
- (See "Bipolar disorder in adults: Choosing maintenance treatment".)
- (See "Pediatric bipolar major depression: Choosing treatment".)

DEFINITION OF BIPOLAR DISORDER

Bipolar disorder is a mood disorder that is characterized by periods of pathologic mood elevation (mania or hypomania) [1]. Patients with bipolar I disorder experience manic episodes (table 1) and nearly always experience both hypomanic episodes (table 2) and major depressive episodes (table 3). Bipolar II disorder is marked by at least one episode of hypomania (table 2), and one or more major depressive episodes. In addition, psychotic features such as delusions and hallucinations frequently accompany bipolar depressive episodes, particularly in patients with bipolar I disorder [7].

Additional information about the clinical features and diagnosis of bipolar disorder, including bipolar major depression, is discussed separately. (See "Bipolar disorder in adults: Clinical features" and "Bipolar disorder in adults: Assessment and diagnosis".)

INVESTIGATIONAL AND NONSTANDARD APPROACHES

Investigational and nonstandard approaches for bipolar major depression include [8]:

- Armodafinil and modafinil
- Bright light therapy
- Chronotherapy
- Ketamine
- Levothyroxine (T4)
- Methylene blue
- N-acetyl cysteine
- Omega-3 fatty acids
- Pramipexole

These treatments are typically not used due to limited evidence of their efficacy, safety, and tolerability. As an example, some of the treatments have been investigated in small samples or only one trial, and the results need to be replicated before we can suggest using them routinely. For other treatments, the evidence of efficacy was inconsistent, such that some studies indicated the treatment was helpful and other studies did not. Another problem with the treatments is the lack of longer (eg, ≥8 weeks) trials to evaluate the benefits and risks; maintenance treatment generally consists of the regimen used for initial treatment. Some studies were problematic in that they analyzed study completers (per protocol analysis), which can potentially bias the results, rather than analyzing all patients who were randomized (intent to treat analysis).

The investigational treatments have typically been studied as add-on treatments in patients who did not respond to standard drugs such as second-generation antipsychotics (eg, olanzapine or quetiapine), lamotrigine, lithium, valproate, and antidepressants.

Armodafinil and modafinil — Modafinil consists of two stereoisomers that are mirror images of each other and thus not identical in that they cannot be superimposed upon each other (similar to one's hands). One of the stereoisomers is R-modafinil (armodafinil).

Multiple randomized trials suggest that short-term augmentation with armodafinil and modafinil may provide a small benefit for patients with bipolar I or II major depression:

- A meta-analysis of two trials, lasting six or eight weeks, compared add-on armodafinil (150 mg/day) or modafinil (200 mg/day) with placebo in 342 patients [9]. Improvement was greater with armodafinil/modafinil than placebo, and the clinical benefit was small to moderate. In addition, safety, tolerability, and adverse effects were comparable for active treatment and placebo.

- A subsequent eight-week trial compared add-on armodafinil (150 mg/day) with placebo in 393 patients and found that response (reduction of baseline symptoms ≥50 percent) occurred in more patients with armodafinil (56 versus 46 percent) [10]. Discontinuation of treatment due to adverse effects was comparable with armodafinil and placebo (5 and 4 percent).

- Another subsequent eight-week trial compared add-on armodafinil (150 mg/day) with placebo in 393 patients and found that response occurred in more patients with armodafinil (46 versus 34 percent) [11]. Discontinuation of treatment due to adverse effects was comparable with armodafinil and placebo (4 and 5 percent).

However, another eight-week randomized trial in 454 patients with bipolar major depression found that the rate of response to add-on treatment with armodafinil (150 mg/day) or placebo was similar (40 and 39 percent) [12]. In addition, other randomized trials that compared adjunctive armodafinil with placebo for bipolar depression found that the benefit was comparable for the primary outcome [11].

> Augmentation with armodafinil and modafinil for unipolar major depression is discussed separately. (See "Unipolar major depression in adults: Augmentation of antidepressants with stimulants and stimulant-like drugs", section on 'Modafinil and armodafinil'.)

Bright light therapy — Based upon randomized trials, augmentation with bright light therapy may perhaps help bipolar patients with nonseasonal major depression [13]:

- A six-week trial enrolled patients with bipolar I or II major depression who had not responded to pharmacotherapy and randomly assigned them to adjunctive bright light therapy (7000 lux) or placebo (dim red light, 50 lux) [14]. Patients with seasonal affective disorder were not excluded; seasonality traits were present in more than 80 percent of patients, and nearly 75 percent were enrolled during the fall and winter. Bright light therapy or placebo were administered at midday and the target dose was 60 minutes per day by week 4. Among the patients who completed at least one study visit between weeks 4 and 6 (n = 40), remission was greater with add-on bright light therapy than placebo (68 versus 22 percent). In addition, functioning improved more with bright light therapy. None of the study patients switched polarity. However, the study results may have been biased because the analyses included only the patients who completed at least one study visit between weeks 4 and 6 (n = 40), rather than all of the patients who were initially randomized (n = 46).

- A two-week trial enrolled patients with bipolar major depression who had not responded to pharmacotherapy and randomly assigned them to adjunctive bright light therapy (5000 lux) or placebo (dim red light, <100 lux) [15]. Patients with seasonal affective disorder were not excluded, and seasonality traits were not assessed; both inpatients and outpatients were included. Add-on study treatments were administered in the morning for 60 minutes. Among the patients who completed the study (n = 63), response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received bright light therapy than placebo (79 versus 43 percent). One patient in each group became more irritable, but otherwise no manic symptoms emerged, and the treatment was well tolerated. However, the study results may have been biased because the analyses included only the patients who completed the study (n = 63), rather than all of the patients who were initially randomized (n = 74).

- In another two-week trial, investigators enrolled patients with nonseasonal bipolar major depression (n = 50) or unipolar major depression (n = 45) who had not responded to pharmacotherapy and randomly assigned them to adjunctive bright light therapy (10,000 lux) or placebo (sham negative ion generator) [16]. Add-on study treatments were administered in the morning for 30 minutes. Remission occurred in more patients who received bright light therapy than placebo (29 versus 12 percent), and the benefit of active treatment was comparable for bipolar depression and unipolar depression.

By contrast, one study found that bright light therapy was not beneficial for bipolar major depression. An eight-week randomized trial compared bright light therapy (7000 lux) with a placebo control (low density negative ion therapy) as add-on treatment in 38 patients with bipolar I or II depression who were treated pharmacotherapy; study treatments were administered for 7.5 to 45 minutes upon awakening [17]. Improvement in the two groups was comparable. However, the duration of exposure to bright light therapy may have been subtherapeutic, based upon studies in bipolar patients with seasonal affective disorder and patients with nonseasonal unipolar major depression.

Separate topics discuss the efficacy and administration of bright light therapy for seasonal affective disorder, including bipolar disorder with seasonal pattern, and the efficacy of bright light therapy for nonseasonal unipolar major depression. (See "Seasonal affective disorder: Treatment" and "Unipolar depression in adults: Investigational and nonstandard treatment", section on 'Bright light therapy'.)

Chronotherapy — Short-term augmentation with chronotherapy may perhaps improve symptoms of bipolar depression. A seven-week randomized trial compared chronotherapy plus pharmacotherapy with pharmacotherapy alone in patients with bipolar major depression (n = 49) [18]. Chronotherapy consisted of sleep deprivation for one night, bright light therapy (5000 lux for two hours) for three days, and sleep phase advancement (progressively later sleep initiation time) over three nights. Pharmacotherapy included mood stabilizers (eg, lithium) plus antidepressants (eg, sertraline). Response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received chronotherapy plus pharmacotherapy than pharmacotherapy alone (59 versus 22 percent). Two patients treated with chronotherapy switched to hypomania, which resolved within one day without additional medication.

Ketamine — Ketamine is a standard anesthetic drug that may be effective for short-term treatment of bipolar major depression [19]. A meta-analysis of two small randomized trials compared add-on intravenous ketamine (0.5 mg/kg) with saline (placebo) in 33 patients who were hospitalized for treatment-resistant bipolar I or II major depression and treated with lithium or valproate [20]. Study drugs were administered as a single infusion. Response

(reduction of baseline symptoms ≥50 percent) at 24 hours was nearly 12 times more likely with ketamine than placebo (odds ratio 11.6, 95% CI 1.3-107.7). At 72 hours, response was eight times more likely with ketamine, but the difference between the two study drugs was no longer statistically significant. A second meta-analysis of the same two trials also found that improvement of depression was greater with ketamine than placebo, and the clinical benefit was large [21].

Transient side effects that occurred only with ketamine in the two trials included dissociation, feeling strange or bizarre, tachycardia, and increased blood pressure [22], as well as difficulty falling asleep and dizziness or faintness [23]. Among the 33 patients, switching to mania/hypomania occurred in one patient during infusion with placebo [22].

In addition, ketamine may be effective specifically for short-term management of suicidal ideation in bipolar disorder. A six-week randomized trial compared add-on ketamine (0.5 mg/kg) with saline in 52 patients with bipolar disorder who required hospitalization for suicidal ideation in the context of moderate to severe depression [24]. Study drugs were administered intravenously at baseline and at 24 hours, in conjunction with daily antipsychotics, antiepileptics, anxiolytics, and/or antidepressants. At day 3, remission of suicidal ideas occurred in more patients treated with ketamine than placebo (85 versus 28 percent), and the benefit appeared to persist at week 6. Throughout the study, ketamine was well tolerated and none of the study patients developed mania. However, by week 6, the rate of suicide attempts in the ketamine and placebo arms was comparable (8 and 10 percent).

Information about the investigational use of ketamine for unipolar major depression and suicidal ideation is discussed separately. (See "Ketamine and esketamine for treating unipolar depression in adults: Administration, efficacy, and adverse effects".)

Levothyroxine (T4) — Supraphysiologic doses of adjunctive levothyroxine may be useful for bipolar major depression. A six-week randomized trial compared add-on levothyroxine (300 mcg/day) with placebo in 62 patients with bipolar I or II major depression who had not responded to current pharmacotherapy (eg, lithium, lamotrigine, and antidepressants) [25]. The mean change in depression rating scale scores from randomization to week 6 was larger with add-on levothyroxine than placebo. However, several other outcome measures, such as the amount of improvement at week 6 and the number of patients who responded or remitted, were comparable for the two groups. Three patients receiving active drug discontinued treatment due to adverse effects (mild thyrotoxicosis, rash, and switch to mania), compared with none of the patients receiving placebo.

Use of supraphysiologic doses of adjunctive levothyroxine for rapid cycling bipolar disorder is discussed separately. (See "Rapid cycling bipolar disorder in adults: Treatment of major depression", section on 'Refractory patients' and "Rapid cycling bipolar disorder in adults: Treatment of mania and hypomania", section on 'Refractory patients'.)

Methylene blue — Two small, randomized crossover trials suggest that adjunctive methylene blue may help bipolar patients with depressive symptoms:

- One trial compared an active dose of methylene blue (300 mg/day) with low-dose methylene blue (15 mg/day, "placebo") as add-on therapy in 17 patients with bipolar disorder [26]. At study entry, all patients were on lithium and some were receiving other medications. Patients were randomly assigned to active dose or low-dose methylene blue for one year and then crossed over to the other dose for another year. Throughout the two years, the mean number of weeks depressed was less during treatment with active dose methylene blue than low dose (10 versus 19 weeks), whereas the number of weeks manic was comparable. In addition, a combined measure of severity and duration of depressive and manic illness indicated the active dose was superior.

- A subsequent trial compared a therapeutic dose of methylene blue (195 mg/day) with a subtherapeutic dose of methylene blue (15 mg/day) as add-on therapy in 37 patients with bipolar I or II disorder [27]. At study entry, all patients were partially stabilized with lamotrigine, with or without other mood stabilizers. Patients were randomly assigned to a therapeutic or subtherapeutic dose of methylene blue for 13 weeks and then crossed over to the other dose for another 13 weeks (patients thus served as their own controls). Residual depressive symptom scores were lower during treatment with the therapeutic dose than the subtherapeutic dose, regardless of the order of treatment, and the clinical effect of the therapeutic dose was moderate to large. In addition, symptoms of anxiety were lower with the therapeutic dose. Manic/hypomanic symptoms remained low throughout the entire study. Methylene blue was well tolerated, and the most common adverse effects were burning urination, diarrhea, headaches, and nausea.

Methylene blue may be difficult to mask (blind) because it can cause a blue or green tint to urine, feces, or sweat.

N-acetyl cysteine — The benefit of augmentation with N-acetylcysteine (NAC) for treating bipolar depression is not clear. A meta-analysis of five randomized trials compared add-on NAC (1 to 3 grams daily) with placebo in 335 patients acutely ill with bipolar I or II depression, and found that improvement was comparable in the two groups [28]. However, three of the trials (total n = 197) lasted only 16 or 20 weeks, which may not be a sufficient length of treatment. A

24-week randomized trial compared add-on NAC (1 gram twice daily) with placebo in 75 patients with bipolar I or II disorder [29]. On average, the patients were mildly to moderately depressed, such that symptoms did not reach the threshold for major depression. Improvement was greater with NAC than placebo; the superiority of NAC first became apparent at week 20 and became more robust at week 24.

Neuromodulation — Several neuromodulation procedures for treating bipolar major depression have been investigated, including noninvasive therapies such as repetitive transcranial magnetic stimulation, as well as invasive procedures such as deep brain stimulation. (See "Bipolar disorder in adults: Overview of neuromodulation procedures".)

Neuromodulation in the form of electroconvulsive therapy is a standard treatment for bipolar disorder, including bipolar major depression. (See "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy".)

Omega-3 fatty acids — Dietary supplementation with omega-3 fatty acids (n-3 polyunsaturated fatty acids) from fish oils may have modest to moderate benefits for bipolar depression. Given the available data for bipolar depression, other health benefits, and the apparent lack of serious adverse effects, use of omega-3 fatty acids (eg, 1 to 2 grams per day) as an adjunctive treatment is reasonable in patients with bipolar depression, particularly those with increased cardiovascular risk who might also benefit from the effects on elevated triglycerides. (See "Fish oil: Physiologic effects and administration" and "Lipid management with diet or dietary supplements".)

Low-quality, direct evidence supporting the use of adjunctive omega-3 fatty acids for bipolar depression includes a meta-analysis of five randomized trials that compared add-on omega-3 fatty acids with placebo in patients with bipolar I or II disorder (n = 291), including one trial in children (mean age = 13 years; n = 51) [30]. In four trials, omega-3 fatty acids consisted of eicosapentaenoic acid alone or combined with docosahexaenoic acid; one trial used flaxseed oil with alpha-linolenic acid. The trials lasted 12 or 16 weeks. Improvement was greater with omega-3 fatty acids than placebo, and the clinical effect was small to moderate.

Indirect evidence that suggests omega-3 fatty acids may help patients with bipolar depression includes a meta-analysis of 25 randomized trials that compared omega-3 fatty acids with placebo in 1373 patients with unipolar major depression and found a small but statistically significant advantage for active drug [31]. However, the investigators concluded that the effect was probably not clinically meaningful. In addition, heterogeneity across studies was substantial, and it was likely that publication bias skewed the analysis towards finding a beneficial effect for omega-3 fatty acids. Additional information about the use of omega-3 fatty

acids for unipolar major depression is discussed separately. (See "Unipolar depression in adults: Investigational and nonstandard treatment", section on 'Omega-3 fatty acids'.)

Pramipexole — Two small randomized trials suggest that adjunctive pramipexole may perhaps improve bipolar major depression:

- A six-week trial compared add-on pramipexole (average dose 1.7 mg/day) with placebo in 21 patients with bipolar II major depression, and found that response (reduction of baseline symptoms >50 percent) occurred in more patients who received pramipexole (6/10 versus 1/11 [60 versus 9 percent]) [32]. Adverse effects in the two groups were comparable.

- Another six-week trial compared add-on pramipexole (average dose 1.7 mg/day) with placebo in 22 patients with bipolar I or II major depression and found that response occurred in more patients who received pramipexole (8/12 versus 2/10 [67 versus 20 percent]) [33]. Adverse effects in the two groups were comparable.

Augmentation with pramipexole for unipolar major depression is discussed separately. (See "Unipolar major depression in adults: Augmentation of antidepressants with stimulants and stimulant-like drugs", section on 'Pramipexole'.)

TREATMENTS WITH LITTLE TO NO BENEFIT

Randomized trials in patients with bipolar major depression suggest that the following drugs provide little to no benefit:

- Agomelatine [34]
- Celecoxib [35,36]
- Cytidine [20]
- Folic acid [37]
- Infliximab [38]
- Levetiracetam [39]
- Lisdexamfetamine [40]
- Memantine [20]
- Minocycline [36]
- Pregnenolone [41]

However, some of the trials were underpowered. As an example, the trial that compared celecoxib with placebo included only 28 patients [35].

CHOOSING TREATMENT

Choosing a specific treatment regimen for acute episodes of bipolar I or II major depression is discussed separately. (See "Bipolar major depression in adults: Choosing treatment".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Bipolar disorder".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Bipolar disorder (The Basics)" and "Patient education: Coping with high drug prices (The Basics)")
- Beyond the Basics topics (see "Patient education: Bipolar disorder (Beyond the Basics)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)")

SUMMARY

- Investigational and nonstandard treatments for bipolar major depression include armodafinil and modafinil, bright light therapy, chronotherapy, ketamine, levothyroxine (T4), methylene blue, N-acetyl cysteine, neuromodulation, and pramipexole. These

treatments are typically not used due to limited evidence of their efficacy, safety, and tolerability. (See 'Investigational and nonstandard approaches' above.)

- Other investigational treatments for bipolar major depression include omega-3 fatty acids. Omega-3 fatty acids (eg, 1 to 2 grams per day) are a reasonable adjunctive treatment for patients with bipolar depression, given the available data for bipolar depression, their other health benefits, and apparent lack of serious adverse effects. (See 'Omega-3 fatty acids' above.)

- Drugs that appear to provide little to no benefit in treating bipolar major depression include agomelatine, celecoxib, cytidine, folic acid, levetiracetam, lisdexamfetamine, memantine, and pregnenolone. (See 'Treatments with little to no benefit' above.)

- There are several standard treatment options for patients with bipolar major depression. (See "Bipolar major depression in adults: Choosing treatment".)

Topic 115481 Version 10.0

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