Bipolar major depression in adults: Choosing treatment

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Literature review current through: **Oct 2023.**
This topic last updated: **May 19, 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 bipolar 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 choosing treatment for adults with bipolar major depression. Other topics discuss 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, investigational and nonstandard approaches to treating bipolar major depression in adults, choosing pharmacotherapy for adults with acute mania and hypomania, choosing maintenance treatment for adults, and choosing pharmacotherapy for pediatric and geriatric bipolar major depression.

- (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 major depression in adults: Investigational and nonstandard approaches to treatment".)
- (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)
- (See "Bipolar disorder in adults: Choosing maintenance treatment".)
- (See "Pediatric bipolar major depression: Choosing treatment".)
- (See "Geriatric bipolar disorder: Treatment of mania and major depression", section on 'Bipolar major depression'.)

DEFINITIONS

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 characterized 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".)

Antimanic drug — We use the term antimanic drug to refer to medications that can reduce acute symptoms of mania/hypomania, without causing a switch to the opposite polarity. Examples include lithium, antiepileptics such as carbamazepine and valproate, and second-generation antipsychotics such as aripiprazole, cariprazine, lurasidone, olanzapine, quetiapine, and risperidone.

By contrast, lamotrigine does not reduce acute symptoms of mania/hypomania and is thus not an antimanic drug per se. However, lamotrigine can prevent episodes of mania. (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Lamotrigine'.)

GENERAL PRINCIPLES

The general principles and issues that are involved in treating bipolar major depression in adults include the following:

- Initial assessment
- Goals
- Setting
- Pharmacotherapy
- Duration of an adequate drug trial
- Monitoring
- Adjunctive psychotherapy
- Comorbidity

These general principles are discussed in detail separately. (See "Bipolar major depression in adults: General principles of treatment".)

Pharmacotherapy plus psychotherapy — Although the cornerstone of treatment for acute bipolar major depression is pharmacotherapy, we frequently prescribe adjunctive psychotherapy to improve outcomes [8]. At minimum, all patients should be educated about their illness to improve acceptance of the diagnosis and need for treatment, optimize adherence to treatment, and facilitate recognition and responses to early warning signs of relapse [9]. Psychoeducation also includes information about self-management, such as creating structure and adopting daily routines, being physically active, monitoring symptoms, and avoiding potentially mood destabilizing activities such as alcohol misuse and use of cannabis and other drugs.

Evidence-based, adjunctive psychotherapies for managing acute bipolar major depression include cognitive-behavioral therapy, interpersonal and social rhythm therapy, group psychoeducation, and family-focused therapy. (See "Bipolar major depression in adults: General principles of treatment", section on 'Adjunctive psychotherapy'.)

BIPOLAR I MAJOR DEPRESSION, NO ANTIMANIC DRUG THERAPY

This section describes acute treatment of patients who present with bipolar I major depression in the absence of antimanic drug therapy. (See 'Antimanic drug' above.)

Choosing pharmacotherapy — We suggest that acute treatment of bipolar I major depression in patients who are currently not treated with an antimanic drug (see 'Antimanic drug' above) proceed according to the sequence described in the subsections below. Patients start with first-

line medications and depending upon symptom improvement and tolerability, either continue the treatment regimen or progress to the next step [9]:

- First-line medications – Monotherapy with quetiapine or lurasidone.
- Second-line medications – If quetiapine monotherapy and lurasidone monotherapy are each ineffective or intolerable, next step treatment options include:
  - Olanzapine plus fluoxetine
  - Valproate (divalproex) monotherapy
  - Combination therapy with quetiapine or lurasidone plus lithium or valproate
  - Combination therapy with lithium plus valproate or lamotrigine
- Third-line medications – If second-line medication regimens are not effective or tolerable, next step treatment options include:
  - Monotherapy with lamotrigine, lithium, or olanzapine
  - Monotherapy with carbamazepine or cariprazine
  - Combination therapy with olanzapine plus lithium or valproate
  - Other antimanic drug combinations (eg, lithium plus carbamazepine)
  - Combination therapy with lithium or valproate plus an antidepressant such as a selective-serotonin reuptake inhibitor (SSRI; eg, fluoxetine) or bupropion
  - Combination therapy with a second generation antipsychotic (usually quetiapine, lurasidone, or olanzapine) plus an antidepressant
- Treatment-refractory patients – Electroconvulsive therapy (ECT)

ECT frequently provides a rapid clinical response and may thus be indicated as initial treatment in urgent clinical situations that are life-threatening, such as persistent suicidal behavior or gross impairment of functioning (eg, dehydration and malnutrition secondary to refusal of liquids and food) [9-11]. In addition, ECT is reasonable as next step treatment for patients with bipolar major depression who are severely ill (eg, persistent suicidal ideation with a plan) and do not respond to or tolerate multiple (eg three to five) medication trials.

The specific treatment choice depends upon prior treatment history, treatment side effects (table 4 and table 5 and table 6 and table 7), comorbid illnesses, patient preferences, and cost. As an example, clinicians often avoid quetiapine in patients who are overweight and avoid lurasidone in patients sensitive to dyspepsia.

The duration of an adequate trial for a particular medication regimen is discussed separately. (See "Bipolar major depression in adults: General principles of treatment", section on 'Duration of an adequate drug trial'.)

First-line medications — For patients with acute bipolar I major depression who are not taking an antimanic drug, we suggest either quetiapine or lurasidone as initial pharmacotherapy [9,12]. We generally start with quetiapine because it has been more widely studied than lurasidone in acutely depressed patients. In addition, using quetiapine to treat bipolar I major depression is advantageous in that the drug has demonstrated efficacy for maintenance treatment. However, no published head-to-head trials have compared quetiapine with lurasidone, and it is reasonable to start with lurasidone first. Multiple practice guidelines recommend treating bipolar depression with quetiapine or lurasidone, either as initial treatment or next step treatment [10,11,13-17].

- **Quetiapine** – Quetiapine is typically administered at bedtime because it frequently causes sedation. The drug is generally started at a dose of 50 mg at bedtime and titrated up by increments of 50 to 100 mg/day over one week to a target dose of 300 mg/day [18-21]. There is no compelling evidence supporting a target dose less than 300 mg/day [22]. Patients who are sensitive to adverse effects may start with 25 mg at bedtime, and increase the dose more slowly. The efficacy of immediate- and extended-release quetiapine for acute bipolar major depression is comparable [23].

  Randomized trials indicate that doses of quetiapine 600 mg/day are no more effective than 300 mg/day [24]. Nevertheless, in our clinical experience, larger doses (eg, 800 mg/day) may be required for patients with an incomplete response at lower doses. In patients who have difficulty tolerating a relatively large single dose, the drug can be administered twice daily, with most of the drug given at night (eg, 100 mg in the morning and 500 mg at bedtime).

  The efficacy of quetiapine for acute bipolar I or II major depression is well established, based upon multiple meta-analyses of randomized trials. The efficacy and adverse effects of quetiapine in acute treatment are discussed separately, as are the maintenance treatment efficacy data. (See "Bipolar major depression in adults: Efficacy and adverse

effects of second-generation antipsychotics", section on 'Quetiapine' and "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Quetiapine'.)

- **Lurasidone** – Lurasidone is started at 20 mg once daily in the evening and is taken with a meal (eg, >350 calories) or 30 minutes thereafter to ensure adequate bioavailability and to limit gastrointestinal side effects [25,26]. The dose can be increased every two to seven days by increments of 20 mg per day to optimize effectiveness and tolerability. The target dose range is 20 to 120 mg per day. Side effects that may limit dose increases include headache, nausea, and akathisia. One potential advantage of lurasidone is that it typically does not cause weight gain and adverse metabolic effects, including elevation of blood glucose [27].

  The efficacy and adverse effects of lurasidone in patients in acute bipolar I major depression are discussed separately. (See "Bipolar major depression in adults: Efficacy and adverse effects of second-generation antipsychotics", section on 'Lurasidone'.)

For patients with bipolar I major depression who do not respond to treatment with quetiapine, or do not tolerate the drug, we suggest tapering and discontinuing the failed medication over one to two weeks at the same time that lurasidone is started and titrated up. Response is defined as substantial improvement in the number, intensity, and frequency of symptoms and is often operationalized in studies as reduction of baseline symptoms ≥50 percent. The failed medication is generally tapered by the same amount for each dose decrease. As an example, quetiapine 300 mg/day is decreased by 50 mg per day, every one to three days. In the same manner, patients who start with lurasidone and do not respond are switched to quetiapine.

In addition, ECT frequently provides a rapid clinical response and may thus be indicated as first-line treatment in certain urgent clinical situations that are life-threatening or characterized by gross impairment of functioning. (See 'Treatment-refractory patients' below.)

Second-line medications — Patients with bipolar I major depression may not respond to or tolerate initial treatment with quetiapine monotherapy and lurasidone monotherapy. For these patients, we suggest olanzapine plus fluoxetine, valproate (divalproex) monotherapy, combination therapy with quetiapine or lurasidone plus lithium or valproate, and combination therapy with lithium plus valproate or lamotrigine. [9,12]. Using these drugs for bipolar major depression is consistent with multiple treatment guidelines [10,11,13-17].

- **Olanzapine plus fluoxetine** – The efficacy of olanzapine plus fluoxetine is well established, based upon randomized trials that compared the combination with active treatments (eg, olanzapine monotherapy and lamotrigine monotherapy), as well as placebo. As an example, a network (multiple treatment) meta-analysis of 29 randomized

trials evaluated the efficacy of 13 medication regimens in patients who were treated for 4 to 16 weeks (n >8000) [28]. The analysis ranked the efficacy of medications by using results from direct comparisons between the drugs, as well as indirectly comparing drugs through their relative effect with a common comparator (typically placebo). The most efficacious drug regimen among those studied was olanzapine plus fluoxetine.

However, olanzapine plus fluoxetine is reserved for treatment-resistant patients because of problematic weight gain and metabolic disorders. In addition, the adverse effects of olanzapine often preclude using the drug as a maintenance treatment, and we recommend that antidepressants be avoided as maintenance treatments in bipolar disorder. The efficacy and adverse effects of the drug combination for acute bipolar major depression are described elsewhere, as are the efficacy and adverse effects of olanzapine monotherapy for maintenance treatment. (See "Bipolar major depression in adults: Efficacy and adverse effects of antidepressants", section on 'Acute treatment' and "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Olanzapine'.)

Clinicians can prescribe olanzapine plus fluoxetine as two separate pills or a as a single pill. Individual pills are generally recommended because of cost and flexibility in dosing each medication. If each drug is prescribed as a separate pill, the starting dose of olanzapine is typically 5 mg once daily at bedtime [29,30]. The dose can then be titrated up by increments of 5 mg/day every one to seven days, depending upon efficacy and tolerability; the maximum dose is to 15 mg/day. For patients sensitive to adverse effects, the dose can be started at 2.5 mg/day, titrated up to 5 mg/day within one to seven days, and further titrated by 2.5 or 5 mg/day every one to seven days. Concurrent with administration of olanzapine, fluoxetine is usually started at 20 mg/day at bedtime. The dose can then be titrated up by increments of 10 or 20 mg/day every one to seven days, depending upon efficacy and tolerability; the maximum dose is to 50 mg/day.

If olanzapine plus fluoxetine is prescribed as a single pill (olanzapine-fluoxetine combination), the starting dose is 6 and 25 mg/day [29]. The dose can then be titrated up to 6 and 50 mg/day after one to seven days, depending upon efficacy and tolerability; subsequently, the dose can be increased to 12 and 50 mg/day.

If a patient treated with olanzapine plus fluoxetine switches to mania or hypomania, clinicians should immediately discontinue the fluoxetine [31]. Abruptly stopping the drug should not cause discontinuation symptoms because the half-life of fluoxetine is long. (See "Discontinuing antidepressant medications in adults", section on 'SSRIs'.)

- **Valproate (divalproex)** – Using valproate monotherapy to treat acute bipolar I major depression is advantageous in that the drug has demonstrated efficacy for maintenance treatment. However, the drug is often avoided in women of childbearing age due to concerns about teratogenicity [9]. (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Valproate' and "Risks associated with epilepsy during pregnancy and the postpartum period", section on 'Valproate'.)

  For patients with bipolar disorder, valproate is usually started at a dose of 250 mg two or three times per day. The dose is increased by 250 mg to 500 mg every one to three days as tolerated to reach a therapeutic serum level, which generally occurs with 1500 mg to 2500 mg per day [32-35]. Valproate is usually administered twice daily (although a once-a-day formulation is available in the United States).

  We suggest drawing valproate serum levels three to five days after each dose increase and prescribing the drug to achieve a target serum level between 50 and 125 mcg/mL [32,34,35]. Levels should be drawn 12 hours after the last dose and generally collected in the morning, before the first dose of the day. After target serum levels have been achieved, levels should be checked at 6- to 12-month intervals and are particularly useful in patients receiving medications that affect valproate concentrations and to confirm adherence. Some patients may not require regular valproate levels, and one review concluded that clinical observation of efficacy and toxicity can be used to guide some dose adjustments [36].

  Common side effects of valproate include weight gain, nausea, vomiting, hair loss, easy bruising, and tremor (table 5); divalproex is a formulation of valproate that can minimize gastrointestinal distress. In addition, valproate is rarely associated with hepatic failure and thrombocytopenia (table 6); liver function tests and platelets should thus be monitored at 6- to 12-month intervals in all patients taking the drug [37-39]. (The US Food and Drug Administration [FDA] recommends checking liver function tests prior to initiating treatment and at frequent intervals thereafter, especially during the first six months.) Valproate rarely causes pancreatitis; symptoms of abdominal pain and vomiting should prompt an assessment that includes a serum amylase and lipase. In women of reproductive potential, valproate is associated with a higher risk of menstrual disturbances and polycystic ovary syndrome, compared with lithium or lamotrigine [40,41].

  Additional information about the pharmacology of valproate, its adverse effects, and available preparations are discussed separately, as well as problems using valproate in

women of childbearing age. (See "Bipolar disorder in women: Contraception and preconception assessment and counseling".)

Evidence supporting the use of valproate includes multiple meta-analyses of randomized trials [28,42,43]. As an example, a meta-analysis of four small trials, lasting six or eight weeks, compared valproate with placebo in 142 patients with bipolar I or II depression (total n = 142) [44]. Remission occurred in more patients who received valproate than placebo (relative risk 1.61, 95% CI 1.02-2.53; 41 versus 24 percent of patients). In addition, a pooled analysis found that discontinuation of treatment due to side effects was comparable for valproate and placebo (4 and 3 percent of patients).

- **Combination therapy with quetiapine or lurasidone plus lithium or valproate** – We reserve combination therapy for cases in which monotherapy with quetiapine or lurasidone yields insufficient benefit. Monotherapy is associated with better adherence and fewer adverse effects than combination therapy. Although lurasidone plus lithium or valproate has been approved for acute bipolar I major depression, we nevertheless recommend combined lurasidone and mood stabilizer treatment as a second-line treatment option.

  The use of quetiapine or lurasidone plus lithium or valproate is discussed elsewhere in this topic. (See 'Add-on pharmacotherapy' below.)

- **Combination therapy with lithium plus valproate or lamotrigine** – The use of these medication regimens is discussed elsewhere in this topic. (See 'Add-on pharmacotherapy' below.)

In addition, for patients with bipolar major depression who are severely ill (eg, persistent suicidal ideation with a plan) and have not responded to multiple (eg, three to five) pharmacotherapy trials, electroconvulsive therapy may be indicated. (See 'Treatment-refractory patients' below.)

Third-line medications — Patients with bipolar I major depression may not respond to or tolerate initial and next step treatments with quetiapine, lurasidone, olanzapine plus fluoxetine, valproate (divalproex), combination therapy with quetiapine or lurasidone plus lithium or valproate, and combination therapy with lithium plus valproate or lamotrigine. For these patients, we suggest monotherapy with lamotrigine or lithium [9]. However, for patients who were not previously treated with olanzapine plus fluoxetine during the current depressive episode (eg, patients with a prior history of poor response to adjunctive antidepressants), olanzapine monotherapy is a reasonable alternative. Other reasonable alternatives include monotherapy with carbamazepine or cariprazine, and combination therapy with olanzapine

plus lithium or valproate. In addition, it is reasonable to prescribe other antimanic drug combinations (eg, lithium plus carbamazepine), as well as combination therapy with lithium or valproate plus an antidepressant such as an SSRI (eg, fluoxetine) or bupropion, and combination therapy with a second generation antipsychotic (usually quetiapine, lurasidone, or olanzapine) plus an antidepressant. The use of lamotrigine, lithium, olanzapine, carbamazepine, cariprazine, or combination pharmacotherapy is consistent with multiple treatment guidelines [10,11,13-15,17].

- **Lamotrigine** – Using lamotrigine monotherapy to treat acute bipolar I major depression is advantageous in that the drug is generally well tolerated and has demonstrated efficacy for maintenance treatment [9,45]. However, a disadvantage in using lamotrigine as an acute treatment is that its efficacy is modest and clinicians need to titrate the dose slowly to reduce the risk of life-threatening skin rashes.

  The starting dose of lamotrigine is usually 25 mg once per day for two weeks, which is then increased to 25 mg twice per day for weeks 3 and 4 [46,47]. The dose is then titrated up, depending upon symptomatic improvement and tolerability, by 25 to 50 mg/day, one week at a time for each increase. The target dose ranges from 100 to 400 mg/day; in many studies, the target dose was 200 mg/day. An extended-release formulation is available for once a day dosing. The starting dose of lamotrigine must be lower and the dose-titration schedule more conservative for patients already taking valproate (which can interfere with the conjugation of lamotrigine and therefore increase the risk of severe rash).

  The slow titration of lamotrigine appears to reduce the risk of serious and life-threatening skin rash, defined as any rash associated with hospitalization, discontinuation of lamotrigine, or Stevens-Johnson syndrome (toxic epidermal necrolysis). In four acute and four maintenance randomized trials that slowly titrated the dose of lamotrigine in 827 patients with bipolar disorder, no cases of serious rash occurred; among the 685 patients who received placebo, there was one case of serious rash [47].

  Lamotrigine can be efficacious for treating acute bipolar I or II major depression, but the clinical effect is generally modest, and the benefit appears to be greater in patients with more severe symptoms [28]. Evidence for the efficacy of lamotrigine includes a meta-analysis of patient level data from five randomized trials (n = 1072) that compared lamotrigine (100 to 400 mg per day) with placebo for 7 to 10 weeks [46]. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received lamotrigine than placebo (44 versus 35 percent). In subgroup analyses, the benefit of lamotrigine was comparable for bipolar I and bipolar II major depression; however, lamotrigine was superior to placebo for severe depression at baseline but not for

moderate depression. The modest benefit found in these randomized trials may be due in part to the six-week dose-titration schedule required to reach the target dose, in trials that generally lasted only eight weeks [12].

The tolerability of lamotrigine in patients with bipolar disorder is generally good [48]. Pooled analyses from four acute and four maintenance randomized trials (total n = 1512 patients) found that discontinuation of treatment due to adverse events was comparable for lamotrigine and placebo (12 and 10 percent), and the incidence of any specific side effect that occurred was also comparable for the two groups [47]. The most common side effects of lamotrigine and placebo were as follows:

- Headache – 25 and 21 percent
- Nausea – 14 and 15 percent
- Infection – 11 and 11 percent
- Dizziness – 9 and 8 percent
- Any rash – 9 and 8 percent
- Somnolence – 9 and 6 percent
- Pain – 9 and 7 percent

In patients with pre-existing cardiac disease, lamotrigine may be associated with an increased risk of arrythmias. Following reports of abnormal electrocardiographic findings, chest pain, loss of consciousness, and cardiac arrest in patients treated with lamotrigine, the FDA conducted in vitro studies of the drug at therapeutically relevant serum concentrations [49]. The results prompted the agency to issue a warning that lamotrigine can slow ventricular conduction (widen QRS) and increase the risk of serious, potentially life-threatening arrythmias in patients with clinically important structural or functional cardiac disease (eg, heart failure, valvular heart disease, or conduction system disease), patients with multiple risk factors for coronary artery disease, or patients using other sodium channel blockers. Although the benefits of lamotrigine in patients with bipolar major depression and underlying heart disease may outweigh the risks, we suggest that clinicians attempt to avoid the drug in these patients.

Additional information about the side effects (table 5 and table 6) of lamotrigine is discussed separately in the context of epilepsy. (See "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Lamotrigine'.)

The efficacy of lamotrigine as maintenance therapy for bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Lamotrigine'.)

- **Lithium** – Although evidence supporting the use of lithium monotherapy for bipolar I major depression is not compelling, administering lithium is consistent with multiple treatment guidelines [11,50-52]. Using lithium is advantageous in that the drug has demonstrated efficacy for maintenance treatment and may reduce the risk of suicide [9]. (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Lithium'.)

  The starting dose and dose-titration schedule for lithium, as well as the use of lithium serum concentrations to adjust the dose, are discussed separately. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Prescribing lithium'.)

  Evidence supporting the use of lithium for treating bipolar major depression includes a review of nine small controlled trials (total n = 163) that were conducted in 1960s and 1970s; eight of the nine studies found that lithium was superior to placebo [53]. However, methodologic problems beyond the small sample sizes include the use of a nonrandom crossover design in many of the studies. As an example, the largest study was a crossover trial in which hospitalized patients with bipolar I or II disorder (n = 40) were initially treated with placebo for at least six days, followed by lithium for a minimum of two weeks, which was then followed by a second round of placebo; patients and clinical raters were both blind to the prescribed study drug [54]. Depressive symptoms were greater during treatment with placebo than lithium.

  However, other studies indicate that lithium may not be beneficial for bipolar major depression. As an example, a relatively large and recent eight-week randomized trial compared lithium with placebo in patients with bipolar I or II disorder (n = 265) [18]. Improvement of depressive symptoms, as well as response and remission, were each comparable for lithium and placebo. It appears that problems with adverse effects (eg, dry mouth, nausea, and tremor) limited the benefit of lithium; although the target serum concentration was 0.6 to 1.2 mEq/L (0.6 to 1.2 mmol/L), the average lithium serum concentration was only 0.6 mEq/L.

- **Olanzapine** – The efficacy of olanzapine monotherapy for acute bipolar I major depression is well established, based upon randomized trials that compared the drug with placebo [9,28]. As an example, a network meta-analysis of 29 randomized trials evaluated the efficacy of 13 medication regimens in patients who were treated for 4 to 16 weeks (n >8000) [28]. The analysis ranked the efficacy of medications by using results from direct comparisons between the drugs, as well as indirectly comparing drugs through their relative effect with a common comparator (typically placebo). The second most efficacious drug regimen was olanzapine. In addition, using olanzapine is advantageous in that the

drug has demonstrated efficacy for maintenance treatment. However, olanzapine monotherapy is less effective than olanzapine plus fluoxetine [29].

Olanzapine is reserved as a third-line treatment for bipolar major depression because of problematic metabolic side effects. We typically do not use olanzapine monotherapy in patients who have not responded to olanzapine plus fluoxetine. (See 'Second-line medications' above.)

The starting dose of olanzapine is typically 5 mg once daily at bedtime [29,30]. The dose can then be titrated up by increments of 5 mg/day every one to seven days, depending upon efficacy and tolerability; the maximum dose is to 20 mg/day. For patients sensitive to adverse effects, the dose can be started at 2.5 mg/day, titrated up to 2.5 or 5 mg/day within one to seven days, and further titrated by 5 mg/day every one to seven days.

The efficacy and adverse effects of olanzapine for acute bipolar major depression and for maintenance treatment are discussed separately. (See "Bipolar major depression in adults: Efficacy and adverse effects of second-generation antipsychotics", section on 'Olanzapine' and "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Olanzapine'.)

- **Carbamazepine** – Carbamazepine monotherapy may help patients with acute bipolar I major depression, and has also been used as maintenance treatment [9,11]. However, its clinical use is limited by the potential for severe adverse effects (eg, rash, aplastic anemia, and liver toxicity) and significant drug-drug interactions due to induction of cytochrome P450 enzymes.

  The administration of carbamazepine, the use of serum concentrations to guide dosing, and side effects (table 5 and table 6) are discussed separately in the context treating bipolar mania and treating epilepsy. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Carbamazepine' and "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Carbamazepine'.)

  Specific interactions of carbamazepine with other medications may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

  Evidence supporting the use of carbamazepine for acute bipolar I major depression includes a 12-week randomized trial, which compared carbamazepine (mean dose 452 mg/day) with placebo in patients with bipolar I or II major depression (n = 74) [55]. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients who

received carbamazepine than placebo (64 versus 35 percent). In addition, discontinuation of treatment was comparable for carbamazepine and placebo (4 and 0 percent).

Evidence supporting the use of carbamazepine as maintenance treatment is discussed separately. (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Carbamazepine'.)

- **Cariprazine** – For acute treatment of bipolar I major depression, cariprazine monotherapy is started at 1.5 mg/day. If patients do not respond after one to two weeks and are tolerating the drug, increase the dose to 3 mg/day; the maximum dose is 3 mg/day [56].

  Evidence supporting the use of cariprazine for bipolar I major depression is discussed separately. (See "Bipolar major depression in adults: Efficacy and adverse effects of second-generation antipsychotics", section on 'Cariprazine'.)

- **Combination therapy with olanzapine plus lithium or valproate** – The use of these medication regimens is discussed elsewhere in this topic. (See 'Add-on pharmacotherapy' below.)

- **Other antimanic drug combinations (eg, lithium plus carbamazepine)** – The use of these medication regimens is discussed elsewhere in this topic. (See 'Add-on pharmacotherapy' below.)

- **Combination therapy with lithium or valproate plus an antidepressant such as an SSRI (eg, fluoxetine) or bupropion** – The use of these medication regimens is discussed elsewhere in this topic. (See 'Add-on pharmacotherapy' below.)

- **Combination therapy with a second-generation antipsychotic (usually quetiapine, lurasidone, or olanzapine) plus an antidepressant** – The use of these medication regimens is discussed elsewhere in this topic. (See 'Add-on pharmacotherapy' below.)

Treatment-refractory patients — For patients with bipolar major depression who are severely ill (eg, persistent suicidal ideation with a plan) and have not responded to multiple (eg, three to five) pharmacotherapy trials, we suggest ECT [9-12,14,15,57]. However, there are no established criteria for the number or duration of unsuccessful drug trials prior to initiating ECT. The use of ECT for bipolar major depression is consistent with multiple practice guidelines [10,11,14-16].

ECT frequently provides a rapid clinical response and may thus be indicated as initial treatment in urgent clinical situations that are life-threatening or characterized by gross impairment of functioning, including patients with [9-11]:

- Severe suicidal behavior, such as patients who survive a suicide attempt and wish they had succeeded – (See "Suicidal ideation and behavior in adults".)

- Severe psychosis, such as patients with persistent auditory hallucinations characterized by commands to kill oneself – (See "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation", section on 'Clinical manifestations'.)

- Malignant catatonia, which is characterized by signs of catatonia (table 8 and table 9) along with fever, autonomic instability, delirium, and rigidity – (See "Catatonia in adults: Epidemiology, clinical features, assessment, and diagnosis", section on 'Malignant catatonia' and "Catatonia: Treatment and prognosis", section on 'Malignant catatonia'.)

- Dehydration and malnutrition in patients with fluid and food refusal secondary to depressive illness.

ECT may be less risky than antidepressant and antipsychotic medication for certain patients, including those who are debilitated and older (eg, ≥65 years). Pregnant and lactating patients worried about teratogenesis and other medication side effects can also be effectively and safely treated with ECT. Patients may prefer ECT and request it as a first-line treatment if, for example, the patient has a history of a depressive episode that was successfully treated with ECT after failing multiple medication trials.

Separate topics provide an overview of ECT (including pre-ECT evaluation, use of concurrent medications, treatment course, and adverse effects), and discuss the indications for and efficacy of ECT in bipolar major depression, the medical consultation for ECT, and the technique for performing ECT. (See "Overview of electroconvulsive therapy (ECT) for adults" and "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy" and "Medical evaluation for electroconvulsive therapy" and "Technique for performing electroconvulsive therapy (ECT) in adults".)

ANXIETY, INSOMNIA, OR AGITATION

Managing bipolar I or II major depressive episodes that include prominent symptoms of anxiety (eg, ruminative thoughts, worrying, and panic attacks), insomnia, or mild to moderate psychomotor agitation depends upon the primary (foundational) pharmacotherapy regimen that is prescribed:

- If patients are not receiving a sedating medication, such as quetiapine or olanzapine, we generally add a benzodiazepine, such as lorazepam 0.5 to 1 mg one to three times/day, on

a temporary basis (eg, 6 to 12 weeks). If the anxiety, insomnia, or mild to moderate psychomotor agitation do not resolve within a few weeks (eg, two to three), we suggest discontinuing the benzodiazepine in favor of add-on pharmacotherapy with a different drug. (See 'Add-on pharmacotherapy' below.)

- If patients are receiving a sedating medication, we typically titrate up the dose of the drug within the therapeutic range, until the symptoms resolve. If the anxiety, insomnia, or mild to moderate psychomotor agitation do not resolve within a few weeks, we suggest add-on pharmacotherapy with a different drug. (See 'Add-on pharmacotherapy' below.)

Anxiety symptoms that are part of a depressive syndrome are distinguished from anxiety disorders. Treatment of anxiety disorders is discussed separately.

Treatment of patients with bipolar disorder and acute, severe agitation is discussed separately in the context of mania. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Agitation'.)

PARTIAL RESPONSE

Patients with bipolar I or II major depression who are treated with an antimanic drug may achieve a partial, clinically meaningful response, but continue to suffer significant symptoms. For these patients we suggest add-on pharmacotherapy. (See 'Add-on pharmacotherapy' below.)

BREAKTHROUGH BIPOLAR I MAJOR DEPRESSION DESPITE ONGOING ANTIMANIC DRUG THERAPY

New episodes of major depression can occur in patients with bipolar I disorder who previously responded to and continued antimanic drug therapy (see 'Antimanic drug' above) [58].

General approach — For bipolar I major depressive episodes that occur despite ongoing antimanic drug therapy (see 'Antimanic drug' above), management begins with a clinical evaluation that identifies and addresses common reasons for breakthrough episodes [9-11,15,59-62]:

- Poor adherence to treatment – Identify and address barriers to adequate adherence. (See "Bipolar disorder in adults: Managing poor adherence to maintenance pharmacotherapy", section on 'Management'.)

- Inadequate dose of the antimanic drug – Optimize dose of the antimanic drug. (See 'Optimize dose of the antimanic drug' below.)

- Drug-drug interactions may render antimanic drugs less effective or increase adverse effects – Specific interactions of antimanic drugs with other medications may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

- Substance abuse may destabilize the patient's mood – Identify and address substance abuse; multiple topics in UpToDate discuss management of substance use disorders. (See "Substance use disorders: Clinical assessment".)

- Concomitant medications may destabilize the patient's mood – Discontinue medications that may induce mood instability (eg, antidepressants, caffeine, steroids, stimulants, and sympathomimetics), particularly if the medications have not been clearly effective or are correlated in time with depression onset or worsening.

- Increases in psychosocial stress or significant disruption of regular social rhythms and daily routine – Adjunctive psychotherapy can be useful for targeting problems that provoked the current depressive episode, including difficulties with relationships or stress at work, dysfunctional thoughts and/or behavior, and disruption of social rhythms. (See "Bipolar major depression in adults: General principles of treatment", section on 'Adjunctive psychotherapy'.)

- Thyroid disease in patients treated with lithium. (See "Lithium and the thyroid", section on 'Thyroid disease in lithium-treated patients'.)

- Insufficient antidepressive efficacy of the current antimanic drug – In many cases, monotherapy with the current antimanic drug at therapeutic doses does not provide sufficient antidepressive efficacy, and add-on treatment is needed. (See 'Add-on pharmacotherapy' below.)

- Suboptimal efficacy of the antimanic drug with regard to preventing recurrence of major depression – Patients who respond to treatment of an acute mood episode with an antimanic drug typically continue that drug as maintenance therapy. However, the drug may fail as maintenance therapy or may initially prevent recurrences of mood episodes and subsequently fail. Choosing maintenance therapy, after successfully treating the breakthrough episode of bipolar I major depression, is discussed separately. (See "Bipolar disorder in adults: Choosing maintenance treatment".)

Optimize dose of the antimanic drug — For patients taking carbamazepine, lithium, or valproate, serum concentrations should be measured to evaluate adherence and adequacy of dosing [9,10,13,17]. If the serum concentration is subtherapeutic and the patient has had reasonably good adherence (eg, taking 80 percent of prescribed doses), the dose of carbamazepine, lithium, or valproate should be increased to achieve serum levels that are within the therapeutic range. The dose and therapeutic range of serum concentrations are discussed separately in the context of treating acute mania. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Medication doses and side effects'.)

For patients with bipolar major depression who are taking low doses of second-generation antipsychotic drugs (eg, quetiapine, lurasidone, or olanzapine), we suggest increasing the daily medication dose to the minimum dose found to be effective for new bipolar depressive episodes in randomized trials, and if the depressive episode persists, to progressively titrate the dose up to the maximum tolerated within the therapeutic dose range. The administration of second-generation antipsychotics is discussed elsewhere in this topic. (See 'First-line medications' above and 'Third-line medications' above.)

For patients with bipolar I major depression who are treated with second-generation antipsychotics or lamotrigine, therapeutic serum concentrations have not been established [9].

Add-on pharmacotherapy — Many patients suffer breakthrough episodes of bipolar I major depression because of insufficient antidepressive efficacy of the current antimanic drug. For these patients, we suggest adjunctive pharmacotherapy rather than other approaches, such as switching medications [9].

For bipolar patients with either breakthrough major depression or major depression unresponsive to monotherapy, choosing a specific drug for add-on pharmacotherapy depends upon the current (ongoing) antimanic drug therapy, ie, whether patients are currently treated with:

- A second-generation antipsychotic, or
- Another antimanic drug (eg, lithium or valproate) or lamotrigine

Relatively few randomized trials have studied breakthrough bipolar major depression or major depression unresponsive to monotherapy; thus, selecting a drug for augmentation is typically based upon studies conducted in patients who present with acute bipolar I major depression in the absence of current antimanic drug therapy. (See 'Bipolar I major depression, no antimanic drug therapy' above.)

Observational studies consistently show that many patients with bipolar disorder receive psychotropic polypharmacy [63]; one retrospective study of patients hospitalized with bipolar depression (n >2200) over a 15-year period found that nearly 85 percent received at least two concurrent psychotropic drugs [64]. However, adherence to treatment may be worse with medication combinations than monotherapy [65,66].

Currently treated with a second-generation antipsychotic — For patients who are currently treated with a second-generation antipsychotic and require a second drug to manage acute bipolar major depression, we suggest add-on treatment with lamotrigine, lithium, or valproate [9]. This approach is consistent with multiple practice guidelines [11,14,15].

- **Lamotrigine** – For patients with bipolar major depression who are treated with a second-generation antipsychotic and require a second drug, augmentation with lamotrigine can be beneficial. In addition, lamotrigine has established efficacy as maintenance therapy for bipolar disorder. Thus, if an acutely ill patient responds to lamotrigine plus another drug (eg, quetiapine or lithium), but the other drug proves to be intolerable during maintenance therapy, the other drug can readily be discontinued, leaving the patient with lamotrigine monotherapy for maintenance therapy [67].

  The starting dose, dose-titration schedule, and adverse effects of lamotrigine are discussed elsewhere in the topic. (See 'Third-line medications' above.)

  Evidence supporting augmentation of second-generation antipsychotics with lamotrigine includes a study that enrolled 202 patients with bipolar I or II depression who had not responded to pharmacotherapy (eg, quetiapine monotherapy, valproate, lithium, and antidepressants) and treated them with open-label quetiapine (target dose 300 mg/day) for one to two weeks [67]. Patients were then randomly assigned to add-on lamotrigine (target dose 200 mg/day) or placebo for 12 weeks, during which both groups continued to receive quetiapine. In addition, medications prescribed at the time of enrollment were continued if clinically indicated. Remission occurred in more patients treated with adjunctive lamotrigine than placebo (31 versus 16 percent), and the benefit of lamotrigine was maintained at the 52-week follow-up assessment.

  The efficacy of lamotrigine as maintenance therapy for bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Lamotrigine'.)

- **Lithium** – The starting dose and dose-titration schedule for lithium, as well as the use of lithium serum concentrations to adjust the dose, are discussed separately. (See "Bipolar

disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Prescribing lithium'.)

If lithium is used as add-on treatment for bipolar major depression, clinicians should try to achieve a serum concentration between 0.8 and 1.2 mEq/L (0.8 and 1.2 mmol/L). Serum levels should generally not exceed 1.2 mEq/L due to potential toxicity. Patients who cannot tolerate a level of 0.8 mEq/L may respond to a level of 0.6 mEq/L (0.6 mmol/L); however, serum concentrations less than 0.6 mEq/L often appear to be ineffective. As an example, a six-month, open-label randomized trial enrolled 283 acutely ill patients with bipolar I or II disorder who were suffering primarily symptoms of depression despite ongoing pharmacotherapy and randomly assigned them to add-on treatment with lithium or to no add-on treatment [68]. Throughout treatment with adjunctive lithium, serum concentrations averaged 0.4 to 0.5 mEq/L (0.4 and 0.5 mmol/L), and improvement of depressive symptoms in the group that received lithium and the control group was comparable. Additional information about serum lithium concentrations is discussed separately. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Lithium dose and serum concentrations'.)

- **Valproate** – The administration of valproate is discussed separately. (See 'Second-line medications' above.)

  Clinicians using adjunctive valproate should note that the drug can inhibit enzymatic metabolism of other drugs. Specific interactions of valproate with other medications may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Augmentation with lamotrigine, lithium, or valproate may be declined due to either a prior history of poor response or to potential side effects that are unacceptable; a reasonable alternative to these three drugs is add-on treatment with an antidepressant, such as a serotonin reuptake inhibitor (eg, fluoxetine) or bupropion [9]. We suggest that clinicians avoid using antidepressants in patients with bipolar major depression who have previously experienced poor outcomes with antidepressant treatment, including patients with a history of treatment-emergent switching to mania/hypomania, rapid cycling, or suicidal ideation and behavior. In addition, we generally avoid antidepressants in patients with concurrent manic symptoms, substance use disorders, early age of onset of bipolar disorder, and a recent history of mania or hypomania. Although the use of antidepressants to treat bipolar I major depression is controversial, there is a limited role for these drugs as adjuncts to antimanic drugs in some patients. The role of antidepressants in treating bipolar I major depression, including their efficacy and potential adverse effects, including the potential risk of switching to mania, is

discussed separately. (See "Bipolar major depression in adults: Efficacy and adverse effects of antidepressants".)

If a patient treated with an adjunctive antidepressant switches to mania or hypomania, clinicians should immediately discontinue the antidepressant [31]. However, abruptly stopping the antidepressant may cause discontinuation symptoms. (See "Discontinuing antidepressant medications in adults".)

For patients with bipolar I major depression who are treated with a second-generation antipsychotic, we suggest avoiding augmentation with another second-generation antipsychotic. Although no high quality studies have evaluated this approach, a prospective observational study followed patients with bipolar I or II disorder who were treated with either second-generation antipsychotic monotherapy (n = 1796) or multiple concurrent second-generation antipsychotics (n = 162); the average length of follow-up was 21 months [69]. The use of multiple concurrent second-generation antipsychotics did not appear to confer any benefit and was associated with increased side effect burden, including dry mouth, tremor, sedation, sexual dysfunction, and constipation.

Currently treated with other antimanic drugs or lamotrigine — For bipolar patients who are currently treated with carbamazepine, lamotrigine, lithium, or valproate, and who require a second drug to manage acute major depression, we suggest add-on treatment with a second-generation antipsychotic [9]. Our order of preference is:

- Quetiapine
- Lurasidone
- Olanzapine

Augmentation with a second-generation antipsychotic is consistent with practice guidelines [11]. The administration, efficacy, and adverse effects of quetiapine, lurasidone, and olanzapine in patients with bipolar major depression is discussed elsewhere. (See 'First-line medications' above and 'Third-line medications' above and "Bipolar major depression in adults: Efficacy and adverse effects of second-generation antipsychotics".)

Patients with bipolar I major depression may decline adjunctive second-generation antipsychotics, due to either a prior history of poor response or to potential side effects that are unacceptable. A reasonable alternative to second-generation antipsychotics is add-on treatment with an antidepressant, such as a serotonin reuptake inhibitor (eg, fluoxetine) or bupropion [9]. Although the use of antidepressants to treat bipolar I major depression is controversial, there is a limited role for these drugs as adjuncts to antimanic drugs. The role of antidepressants in bipolar I major depression, as well as their efficacy and potential adverse

effects, including the risk of switching to mania, is discussed separately. (See "Bipolar major depression in adults: Efficacy and adverse effects of antidepressants".)

If a patient treated with an adjunctive antidepressant switches to mania or hypomania, clinicians should immediately discontinue the antidepressant [31]. However, abruptly stopping the antidepressant may cause discontinuation symptoms. (See "Discontinuing antidepressant medications in adults".)

For bipolar patients who are currently treated with carbamazepine, lamotrigine, lithium, or valproate, and who require a second drug to manage acute major depression, it is also reasonable to combine two of these drugs, such as [9,11,14,15]:

- Lamotrigine and lithium
- Lamotrigine and valproate
- Lithium and valproate
- Carbamazepine and lithium

Caution is required when combining lamotrigine and valproate due to the increased risk of lamotrigine-induced severe skin rashes, including Stevens-Johnson syndrome. Valproate can inhibit enzymatic metabolism of other drugs, including lamotrigine. If the two drugs are combined, doses of lamotrigine must be lower (eg, by 50 percent) and the dose-titration schedule for the adjunctive drug must be more conservative. Specific interactions of valproate with other medications may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate. Information about prescribing lamotrigine, valproate, carbamazepine, and lithium is discussed elsewhere in this topic. (See 'Second-line medications' above and 'Third-line medications' above.)

Multiple randomized trials indicate that add-on therapy with lamotrigine can be efficacious for bipolar major depression [70]:

- An eight-week trial enrolled patients with bipolar I or II major depression who had not responded to lithium (n = 124) and randomly assigned them to add-on treatment with lamotrigine (target dose of 200 mg/day by week 7) or placebo [71]. Response (reduction of baseline symptoms ≥50 percent) was greater with add-on lamotrigine than placebo (52 versus 32 percent). The incidence of each side effect that occurred (eg, headache, fatigue, nausea, flu-like symptoms, or any rash) was comparable in the two groups.

- A 16-week, open-label trial enrolled patients with bipolar I or II major depression (n = 66) who had not responded to combined treatment with antimanic drugs plus antidepressants and randomly assigned them to add-on treatment with lamotrigine

(target dose 150 to 250 mg/day), risperidone (0.5 to 6 mg/day), or inositol (target dose 10 to 25 mg/day) [72]. Patients were allowed to refuse randomization to any one of the three options. Improvement of depressive symptoms and functioning was greater with lamotrigine than risperidone or inositol.

Limited evidence supports the combination of lithium plus valproate (divalproex). A six-week randomized trial enrolled 27 patients who suffered a breakthrough episode of bipolar I or II major depression despite maintenance treatment with lithium or divalproex monotherapy and randomly assigned them to either lithium plus divalproex or to add-on paroxetine (lithium plus paroxetine or divalproex plus paroxetine) [73]. Improvement of depressive symptoms and functioning with lithium/divalproex and with paroxetine augmentation was comparable. However, the small sample and lack of a placebo arm limits interpretation of the results.

BIPOLAR II MAJOR DEPRESSION

Choosing treatment — We treat bipolar II major depression in the same manner as bipolar I major depression. Thus:

- Treatment for patients with bipolar II major depression who not currently receiving antimanic drug therapy (see 'Antimanic drug' above) is the same as it is for bipolar I patients. (See 'Bipolar I major depression, no antimanic drug therapy' above.)
- Treatment for patients with breakthrough episodes bipolar II major depression despite ongoing antimanic drug therapy is the same as it is for bipolar I patients. (See 'Breakthrough bipolar I major depression despite ongoing antimanic drug therapy' above.)

Treatment of bipolar II major depression follows the practices established for bipolar I major depression because the large majority of patients in treatment studies had bipolar I disorder rather than bipolar II disorder [9]. As an example, in a pooled analysis of 24 randomized trials that compared active drugs (eg, quetiapine, lamotrigine, or valproate) with placebo for treating bipolar major depression (n >7000 patients), more than 85 percent had bipolar I disorder [42].

Drug studies specific for bipolar II major depression — Relatively few randomized trials have focused upon bipolar II major depression, compared with bipolar I major depression [42]. In addition, many of the bipolar II trials had methodologic shortcomings, such as open-label administration of study drugs and lack of a placebo arm, which makes it difficult to interpret the results.

The following drugs have been studied in randomized trials that focused upon patients with bipolar II major depression [74]:

- **Quetiapine compared with placebo** – Multiple randomized trials in patients with bipolar II major depression have demonstrated that quetiapine (300 or 600 mg at bedtime) is efficacious. (See "Bipolar major depression in adults: Efficacy and adverse effects of second-generation antipsychotics", section on 'Bipolar II major depression'.)

- **Lamotrigine compared with placebo** – An eight-week randomized trial compared lamotrigine (target dose 200 mg/day) with placebo in patients with bipolar II depression (n = 214); improvement with lamotrigine and placebo was comparable, such that response (reduction of baseline symptoms ≥50 percent) occurred in roughly 50 percent of patients in each group [45]. However, the lack of benefit seen with lamotrigine may have been due to the six-week dose-titration schedule required to reach the target dose, in a trial that lasted only eight weeks.

- **Lamotrigine compared with lithium** – An open-label, 16-week randomized trial compared lamotrigine (target dose 100 to 200 mg/day) with lithium (target serum concentration 0.6 to 1.2 mEq/L [0.6 to 1.2 mmol/L]) in 90 patients with bipolar II depression [75]. Remission was comparable with lamotrigine and lithium (66 and 55 percent of patients). Although discontinuation of treatment was identical in each group (20 percent), the mean number of side effects was lower with lamotrigine than lithium (four versus nine). Interpretation of this study is limited by the large number of patients who discontinued treatment for any reason (56 percent overall) and lack of a placebo arm.

- **Lithium compared with venlafaxine** – An open-label, 12-week randomized trial compared lithium (target serum concentration 0.5 to 1.5 mEq/L [0.5 to 1.5 mmol/L]) with venlafaxine (37.5 to 375 mg/day) in 83 patients with bipolar II major depression [76]. Improvement of depression was greater with venlafaxine than lithium, and switching to hypomania was comparable for the two groups (one patient in each group).

- **Lithium compared with lithium plus sertraline** – A 16-week randomized trial compared lithium plus placebo with lithium plus sertraline in patients with bipolar II major depression (n = 97) [77]. The mean serum lithium concentration in both groups was approximately 0.6 mEq/L (0.6 mmol/L); the minimum target dose of sertraline was 100 mg/day. Response (reduction of baseline symptoms ≥50 percent) was comparable in patients who received lithium alone and lithium plus sertraline (67 and 48 percent). Although the difference between treatments was not statistically significant, a difference of this magnitude, if real, would be clinically meaningful. Switching to hypomania was

comparable with lithium and lithium plus sertraline (19 and 13 percent of patients), as was discontinuation of treatment due to side effects.

- **Adjunctive antidepressant compared with placebo** – A 26-week randomized trial found that response to antidepressants plus antimanic drugs (eg, lithium or valproate) was comparable in patients with bipolar II depression (n = 54) and patients with bipolar I depression (n = 118; 20 and 25 percent) [78].

  In addition, other studies suggest that adjunctive antidepressants may be less likely to induce switching to mania or hypomania in patients with bipolar II major depression than patients with bipolar I major depression. (See "Bipolar major depression in adults: Efficacy and adverse effects of antidepressants", section on 'Clinical risk factors'.)

BIPOLAR I OR II MAJOR DEPRESSION WITH PSYCHOTIC FEATURES

Episodes of major depression in bipolar I disorder or bipolar II disorder can include psychotic features, such as delusions or hallucinations [1]. (See "Bipolar disorder in adults: Clinical features", section on 'Psychosis'.)

For treatment of bipolar I or II major depression with psychotic features, standard treatment consists of a regimen that includes an antipsychotic drug [11,79]. The specific choice of an antipsychotic is discussed elsewhere in this topic. (See 'Bipolar I major depression, no antimanic drug therapy' above and 'Add-on pharmacotherapy' above.)

Treatment-resistant bipolar major depression with psychotic features that does not respond to multiple trials of pharmacotherapy is treated with electroconvulsive therapy [11]. However, electroconvulsive therapy frequently provides a rapid clinical response and may thus be indicated as initial treatment in certain urgent clinical situations that are life-threatening or characterized by gross impairment of functioning. (See 'Treatment-refractory patients' above.)

RAPID CYCLING BIPOLAR DISORDER

Treatment of major depression in patients with rapid cycling bipolar disorder is discussed separately. (See "Rapid cycling bipolar disorder in adults: Treatment of major depression".)

BIPOLAR I OR II MAJOR DEPRESSION WITH SEASONAL PATTERN

We treat bipolar I and bipolar II major depression with seasonal pattern in the same manner as bipolar I major depression without seasonal pattern. Thus:

- Treatment for patients with bipolar major depression with seasonal pattern who are not currently receiving antimanic drug therapy (see 'Antimanic drug' above) is the same as it is for bipolar I patients. (See 'Bipolar I major depression, no antimanic drug therapy' above.)

- Treatment for patients with breakthrough episodes of bipolar major depression with seasonal pattern despite ongoing antimanic drug therapy is the same as it is for bipolar I patients. (See 'Breakthrough bipolar I major depression despite ongoing antimanic drug therapy' above.)

However, for patients with bipolar major depression with seasonal pattern who do not respond to standard treatments, it is reasonable to attempt a trial of adjunctive bright light therapy. (See "Seasonal affective disorder: Treatment", section on 'Bipolar disorder with seasonal pattern'.)

SPECIAL POPULATIONS

Pregnant patients — Treatment of bipolar major depression during pregnancy and the teratogenic and postnatal risks of pharmacotherapy for bipolar disorder are discussed separately. (See "Bipolar disorder in pregnant women: Treatment of major depression" and "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy" and "Risks associated with epilepsy during pregnancy and the postpartum period", section on 'Effects of ASMs on the fetus and child'.)

Postpartum patients — Treatment of postpartum patients with bipolar major depression, including patients who are breastfeeding, is discussed separately, as is the safety of infant exposure to psychotropic drugs through breastfeeding. (See "Bipolar disorder in postpartum women: Treatment", section on 'Breastfeeding patients' and "Breastfeeding infants: Safety of exposure to antipsychotics, lithium, stimulants, and medications for substance use disorders" and "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding".)

Pediatric patients — Treatment of pediatric bipolar major depression is discussed separately. (See "Pediatric bipolar major depression: Choosing treatment".)

Geriatric patients — Treatment of geriatric bipolar major depression is discussed separately. (See "Geriatric bipolar disorder: Treatment of mania and major depression", section on 'Bipolar

major depression'.)

INVESTIGATIONAL AND NONSTANDARD APPROACHES

Investigational and nonstandard approaches for treating bipolar major depression are discussed separately. (See "Bipolar major depression in adults: Investigational and nonstandard approaches to 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 AND RECOMMENDATIONS

- **General principles** – The general principles and issues that are involved in treating bipolar major depression include the initial assessment, goals of treatment, setting, pharmacotherapy, duration of an adequate drug trial, monitoring, adjunctive psychotherapy, and comorbidity. (See "Bipolar major depression in adults: General principles of treatment".)

- **Bipolar I major depression in patients who are not receiving antimanic drugs**

  - **Initial treatment**

    - Usual approach – Patients with bipolar I disorder often present with major depression in the absence of antimanic drug therapy. For these patients, we suggest initial treatment with quetiapine or lurasidone rather than other medications (**Grade 2C**). Patients unresponsive to the first drug are switched to the other drug. (See 'First-line medications' above and "Bipolar major depression in adults: Efficacy and adverse effects of second-generation antipsychotics".)

    - Life-threatening illness – Electroconvulsive therapy frequently provides a rapid clinical response and may thus be indicated as initial treatment in life-threatening clinical situations. (See 'Treatment-refractory patients' above.)

  - **Treatment-resistant illness** – Patients with bipolar I major depression may not respond to or tolerate quetiapine monotherapy and lurasidone monotherapy. Second-line treatment options for these patients include:

    - Olanzapine plus fluoxetine
    - Valproate monotherapy
    - Combination therapy with quetiapine or lurasidone plus lithium or valproate
    - Combination therapy with lithium plus valproate or lamotrigine

    (See 'Second-line medications' above and 'Add-on pharmacotherapy' above.)

  - **Highly resistant/refractory illness**

    - Usual approach – Patients with bipolar I major depression may not respond to first and second-line medications. For these patients, treatment options include monotherapy with lamotrigine, lithium, olanzapine, carbamazepine, or cariprazine; combination therapy with olanzapine plus lithium or valproate; other antimanic drug combinations (eg, lithium plus carbamazepine); combination therapy with lithium or valproate plus an antidepressant; and combination therapy with a

second-generation antipsychotic plus an antidepressant. (See 'Third-line medications' above and 'Add-on pharmacotherapy' above.)

- Severe illness – Patients with bipolar major depression who are severely ill and do not respond to first-, second-, or third-line medications are treated with electroconvulsive therapy. (See 'Treatment-refractory patients' above.)

- **Breakthrough episodes of bipolar I major depression despite ongoing antimanic drug therapy**

  - **General approach** – New episodes of major depression can occur in patients with bipolar I disorder who previously responded to and continued antimanic drug therapy. Initial management includes a clinical evaluation that identifies and addresses common reasons for breakthrough episodes, such as poor adherence, inadequate dose of the antimanic drug, substance abuse, psychosocial stress, and insufficient antidepressive efficacy of the current antimanic drug. (See 'General approach' above.)

  - **Add-on pharmacotherapy** – For breakthrough episodes of bipolar I major depression that are due to insufficient antidepressive efficacy of the current antimanic drug, we suggest add-on pharmacotherapy rather than switching (**Grade 2C**). The specific choice depends upon the current antimanic drug therapy:

    - Patients who are currently treated with a second-generation antipsychotic are generally prescribed add-on lamotrigine, lithium, or valproate. (See 'Currently treated with a second-generation antipsychotic' above.)

    - Patients who are currently treated with an antimanic drug other than a second-generation antipsychotic generally receive an adjunctive second-generation antipsychotic. Our order of preference is quetiapine, lurasidone, and olanzapine. (See 'Currently treated with other antimanic drugs or lamotrigine' above.)

- **Other patients with bipolar major depression**

  - **Bipolar II major depression** – We treat bipolar II major depression in the same manner as bipolar I major depression. (See 'Bipolar II major depression' above.)

  - **Seasonal pattern** – We treat bipolar I or II major depression with seasonal pattern in the same manner as bipolar I major depression without seasonal pattern. (See 'Bipolar I or II major depression with seasonal pattern' above.)

- **Psychotic features** – Standard treatment of bipolar I or II major depression with psychotic features includes an antipsychotic drug. Patients who do not respond to pharmacotherapy or who have life-threatening symptoms may require electroconvulsive therapy. (See 'Bipolar I or II major depression with psychotic features' above.)

- **Rapid cycling** – (See "Rapid cycling bipolar disorder in adults: Treatment of major depression".)

- **Pregnancy** – (See "Bipolar disorder in pregnant women: Treatment of major depression".)

- **Postpartum** – (See "Bipolar disorder in postpartum women: Treatment", section on 'Bipolar major depression'.)

- **Pediatric** – (See "Pediatric bipolar major depression: Choosing treatment".)

- **Geriatric** – (See "Geriatric bipolar disorder: Treatment of mania and major depression", section on 'Bipolar major depression'.)

ACKNOWLEDGMENT

The editorial staff at UpToDate acknowledges Jeffrey Stovall, MD, who contributed to an earlier version of this topic review.

Topic 15267 Version 44.0

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