Bipolar major depression in adults: Efficacy and adverse effects of second-generation antipsychotics

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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 the efficacy, safety, and tolerability of second-generation antipsychotics for bipolar major depression. 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 for bipolar major depression in adults, investigational 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 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: 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".)

DEFINITION OF BIPOLAR DISORDER

Bipolar disorder is a mood disorder that is characterized by episodes of mania (table 1), hypomania (table 2), and major depression (table 3) [7]. The subtypes of bipolar disorder include bipolar I and bipolar II. Patients with bipolar I disorder experience manic episodes and nearly always experience major depressive and hypomanic episodes. Bipolar II disorder is marked by at least one hypomanic episode, at least one major depressive episode, and the absence of manic episodes. Additional information about the clinical features and diagnosis of bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Clinical features" and "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis'.)

EFFICACY

For outpatients with bipolar major depression and no comorbid substance use disorders, randomized trials have established the efficacy of cariprazine, lurasidone, lumateperone, olanzapine, and quetiapine [8-16]. By contrast, multiple trials have found no benefit in using aripiprazole and ziprasidone [17,18]. Other second-generation antipsychotics including asenapine, clozapine, and risperidone may be helpful, but their benefit has yet to be established. (See 'Other second-generation antipsychotics' below.)

In addition, second-generation antipsychotics are often used as monotherapy or in combination with other drugs for mania, as well maintenance treatment of patients with bipolar disorder. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy" and "Bipolar disorder in adults: Choosing maintenance treatment".)

Quetiapine — Quetiapine monotherapy is efficacious for bipolar I or II major depression, based upon multiple meta-analyses of randomized trials that compared quetiapine with placebo [8,19-22]. As an example, one meta-analysis of five trials (3057 patients treated for eight weeks) compared quetiapine with placebo and found that [10]:

- Remission occurred in more patients who received quetiapine than placebo (odds ratio 2.0, 95% CI 1.7-2.3; 61 versus 42 percent of patients)
- Reduction of anxiety symptoms was greater with quetiapine
- Remission was comparable for quetiapine 300 mg per day and 600 mg per day
- Improvement in quality of life (satisfaction) was superior with quetiapine than placebo
- Remission rates were lower for patients with more severe depressive episodes

A subsequent eight-week randomized trial in patients with bipolar I or II major depression also found that quetiapine 300 mg/day was more efficacious than placebo [23].

In addition, patients with residual symptoms of bipolar major depression may benefit from adjunctive quetiapine. A six-week randomized trial enrolled patients (n = 32) with bipolar I or II disorder who continued to suffer subsyndromal symptoms of depression and/or hypomania, despite ongoing treatment with lithium, lamotrigine, and/or valproate [24]. Patients were randomly assigned to add-on treatment with quetiapine (300 to 600 mg/day) or placebo; improvement of depressive symptoms was greater with quetiapine.

However, quetiapine may be less helpful for patients with bipolar major depression and comorbid psychopathology. A randomized trial compared quetiapine (mean dose 276 mg/day) with placebo as monotherapy or add-on treatment in patients with bipolar I or II major depression (n = 100) [25]. Each patient had comorbid generalized anxiety disorder, and most patients had at least one other comorbid psychiatric disorder. Improvement of depressive symptoms with quetiapine and placebo was comparable.

Quetiapine can cause several adverse effects. Two meta-analyses of five randomized trials (n = 3057) both found that discontinuation of treatment because of side effects occurred in more patients who received quetiapine than placebo (24 versus 6 percent) and was greater for quetiapine 600 mg per day than 300 mg per day [8,10]. Adverse effects that occurred more often with quetiapine than placebo included:

- Sedation
- Weight gain

- Dry mouth
- Headache
- Dizziness
- Nausea
- Constipation
- Extrapyramidal symptoms

Additional information about quetiapine side effects (table 4) is discussed separately. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects", section on 'Adverse effects'.)

The use of quetiapine for maintenance treatment of bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Quetiapine'.)

Bipolar II major depression — Randomized trials for bipolar disorder often exclude patients with bipolar II disorder or combine them with bipolar I patients in the analyses. However, several trials of quetiapine monotherapy included bipolar II patients with major depression and found that the drug was effective for this subgroup:

- Two randomized trials, each lasting eight weeks, compared quetiapine (300 or 600 mg at bedtime) with placebo in patients with bipolar major depression [26]. A pooled analysis of the subgroup of 321 patients with bipolar II depression found that remission was greater with quetiapine 300 or 600 mg/day, compared with placebo (39 and 38 versus 20 percent). This was consistent with the finding that both doses of quetiapine were superior in the total sample of bipolar patients [27]. Among patients with bipolar II depression, discontinuation of treatment due to adverse effects of quetiapine 300 mg/day and 600 mg/day and placebo were 16, 23, and 2 percent; common side effects of quetiapine included dry mouth, sedation, fatigue, and dizziness.

- An eight-week randomized trial compared quetiapine (300 or 600 mg at bedtime) with placebo in patients with bipolar major depression [28]. In the subgroup of 208 patients with bipolar II disorder, symptoms improved more with both doses of quetiapine than placebo; this was consistent with the finding that quetiapine was superior in patients with bipolar I disorder.

Compared with other drugs — Although head-to-head randomized trials seem to suggest that quetiapine monotherapy is superior to lithium monotherapy or paroxetine monotherapy for bipolar major depression, the comparative benefit of quetiapine is not clear due to methodologic problems:

- One eight-week trial assigned patients to quetiapine 300 mg per day (n = 255), quetiapine 600 mg per day (n = 263), or lithium (target serum concentration 0.6 to 1.2 mEq/L [0.6 to 1.2 mmol/L]; n = 136) [29]. Although symptoms improved more with either dose of quetiapine than with lithium, the study was underpowered for lithium [30]. In addition, the mean serum concentration of lithium was 0.61 mEq/L (0.61 mmol/L), and more than a third of the patients treated with lithium had a median serum concentration <0.6 mEq/L (<0.6 mmol/L).

- One eight-week trial assigned patients to quetiapine 300 mg per day (n = 229), quetiapine 600 mg per day (n = 232), or paroxetine 20 mg per day (n = 118) [28]. Although symptoms improved more with either dose of quetiapine than with paroxetine, the study was underpowered for paroxetine. In addition, the paroxetine dose was at the low end of the dose range that is usually used to treat major depression (table 5).

Olanzapine — For patients with bipolar major depression, randomized trials have demonstrated the efficacy of olanzapine monotherapy [20,21,31]. Clinicians can anticipate that among patients treated with olanzapine, approximately 35 percent will remit:

- One six-week trial compared olanzapine (5 to 20 mg per day) with placebo in 514 patients; use of concomitant medication was not reported. Remission occurred in more patients who received olanzapine than placebo (38 versus 29 percent), and discontinuation of treatment due to adverse effects was comparable (9 and 8 percent) [11].

- One eight-week trial compared olanzapine (5 to 20 mg per day) with placebo in 706 patients; benzodiazepines and anticholinergic drugs were allowed as well. Remission occurred in more patients who received olanzapine than placebo (33 versus 25 percent) [9]. However, discontinuation of treatment due to adverse effects occurred in more patients who received olanzapine than placebo (9 versus 5 percent).

- Another eight-week trial compared olanzapine (mean dose 14 mg per day) with placebo in 68 patients; hypnotic and anticholinergic drugs were allowed as well [32]. Remission occurred in more patients who received olanzapine than placebo (35 versus 12 percent).

Subgroup analyses have found that in bipolar major depression with mixed features [33] and bipolar major depression with anxiety symptoms [9], olanzapine is more effective than placebo.

In addition, olanzapine may improve sleep disturbances. A small, four-week randomized trial compared add-on olanzapine (5 to 10 m/day) with placebo in patients with bipolar major depression (n = 25) and assessed patients with home-based sleep recordings; sleep continuity and architecture improved more with olanzapine [34].

Olanzapine can cause serious weight gain and may also cause diabetes mellitus [35-37]. In randomized trials that compared olanzapine with placebo in patients with bipolar major depression, the following adverse effects occurred more often with olanzapine [9,11,32]:

- Sedation
- Weight gain
- Increased appetite
- Dry mouth
- Weakness
- Headache
- Hypercholesterolemia
- Hypertriglyceridemia
- Hyperglycemia
- Alanine aminotransferase abnormally high
- Aspartate aminotransferase abnormally high
- Gamma glutamyl transpeptidase abnormally high
- Hyperprolactinemia
- Neutropenia

Additional information about olanzapine side effects (table 4) is discussed separately. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects", section on 'Adverse effects'.)

Use of olanzapine is limited due to side effects, particularly weight gain and metabolic disease. Although a 12-week randomized trial in patients with schizophrenia found that combining samidorphan with olanzapine can mitigate the weight gain that occurs with olanzapine monotherapy [38], a subsequent 24-week trial found that in nearly 30 percent of patients, the combination caused weight gain ≥7 percent of baseline weight [39]. (Weight change ≥7 percent is regarded as clinically significant.) Patients who completed the 24-week trial were enrolled in a 52-week prospective observational study, which found that weight gain ≥7 percent or weight loss ≥7 percent each occurred in approximately 21 percent of patients who received olanzapine plus samidorphan [40].

Olanzapine plus fluoxetine — The efficacy of olanzapine plus fluoxetine for bipolar major depression is discussed separately. (See "Bipolar major depression in adults: Efficacy and adverse effects of antidepressants", section on 'Acute treatment'.)

Lurasidone — For bipolar I major depression, one randomized trial found that lurasidone monotherapy can be efficacious, and a second trial found that lurasidone can be efficacious as

add-on treatment with lithium or valproate. However, a third trial found that add-on lurasidone was not beneficial [41]:

- **Lurasidone monotherapy** – A six-week trial randomly assigned 505 patients to receive lurasidone 20 to 60 mg per day, lurasidone 80 to 120 mg per day, or placebo [12]. Improvement of symptoms and functional impairment was greater with each lurasidone group than placebo, and the benefit of the two lurasidone dose ranges was similar. As an example, remission was greater with low dose and high dose lurasidone, compared with placebo (42 and 40 versus 25 percent of patients). Lurasidone was also efficacious in the subgroup of patients with bipolar I major depression with mixed features [42]. In addition, discontinuation of treatment due to adverse effects was similar for the three treatment groups (approximately 6 to 7 percent of patients within each group).

- **Lurasidone add-on therapy** – A six-week trial enrolled 348 patients who had not adequately responded to at least one month of treatment with either lithium monotherapy or valproate monotherapy, and randomly assigned them to adjunctive treatment with lurasidone (20 to 120 mg per day) or placebo [13]. Remission occurred in more patients who received add-on lurasidone than placebo (50 versus 35 percent). In addition, improvement of functioning was greater with lurasidone. Discontinuation of treatment due to adverse effects was comparable for lurasidone and placebo (6 and 8 percent of patients).

  However, a second six-week trial (n = 356 patients), using the same methods to compare augmentation with either lurasidone or placebo, found that remission for the two groups was comparable (34 and 28 percent) [41,43].

A prospective, observational study enrolled patients who completed the three randomized trials and followed them for six months, during which all patients (n = 817) received open label treatment with lurasidone (20 to 120 mg/day) [44]. On average, patients showed further improvement of depressive symptoms.

In the three randomized trials, the most frequently reported side effects of lurasidone were [12,13,43]:

- Akathisia
- Headache
- Insomnia
- Nausea
- Sedation
- Extrapyramidal

Based upon our clinical experience, administering lurasidone with food (eg, >350 kilocalories) may limit gastrointestinal side effects. Additional information about lurasidone side effects are shown in the table (table 4).

Cariprazine — Based upon three randomized trials, each lasting six weeks, cariprazine is efficacious for patients with bipolar I major depression:

- One trial (n = 571 patients) compared cariprazine (0.75, 1.5, or 3 mg/day) with placebo [14]. Across multiple outcomes, cariprazine 1.5 mg/day was superior to placebo; as an example, remission occurred in more patients who received cariprazine 1.5 mg/day than placebo (30 versus 16 percent). Cariprazine 3 mg/day was more efficacious than placebo on some outcomes, but not others. Cariprazine 0.75 mg/day provided little advantage over placebo. Discontinuation of treatment due to adverse events was comparable for the four groups. Akathisia was the most common adverse effect of cariprazine, and occurred in a dose-dependent fashion.

- A second trial (n = 480 patients) compared cariprazine (1.5 or 3 mg/day) with placebo [15]. Remission occurred in more patients treated with cariprazine 1.5 or 3 mg/day than placebo (33 and 32 versus 23 percent). Discontinuation of treatment due to adverse effects appeared to be comparable in patients who received cariprazine 1.5 mg/day, 3 mg/day, and placebo (4, 5, and 3 percent). Adverse effects that occurred in at least 5 percent of patients in either cariprazine group, and in at least twice as many patients receiving placebo, were akathisia, dizziness, nausea, and sedation.

- A third trial (n = 493) also compared cariprazine (1.5 or 3 mg/day) with placebo [45]. Cariprazine 1.5 mg/day was more efficacious than placebo on some outcomes, but not others. Cariprazine 3 mg/day provided little to no advantage over placebo. Among patients treated with cariprazine 1.5 mg/day, 3 mg/day, or placebo, discontinuation of treatment due to adverse effects occurred in 3, 7, and 3 percent of patients. Adverse effects that occurred in at least 5 percent of patients in either cariprazine group, and at least twice the rate as placebo, were akathisia/restlessness, fatigue, and nausea.

Lumateperone — Lumateperone appears to be effective in the treatment of acute major depression in the context of either bipolar I or bipolar II disorder. Lumateperone is a novel antipsychotic that modulates serotonin, dopamine, and glutamate neurotransmission that is approved in the United States for the treatment of schizophrenia. It has been US Food and Drug Administration-approved for major depressive episodes in both bipolar I and II disorder, making it the only medication to have indications for both disorders. In one trial, 377 individuals with an acute episode of major depression in the context of bipolar disorder were randomized

to receive six weeks of lumateperone 42 mg/day versus placebo [16]. Lumateperone was associated with greater reduction on the Montgomery Asberg Depression Rating Scale (MADRS), a 60-point clinician rating scale for depression (mean change -16.7; mean difference with placebo 4.6, 95% CI -6.34 to -2.83). Additionally, response rates (defined as >50 percent decline in MADRS) and remission rates (MADRS <12) favored lumateperone over placebo (51 versus 37 percent and 40 versus 34 percent, respectively). Of note, improvements in MADRS scores compared with placebo were noted for both individuals with bipolar I and bipolar II disorder. Furthermore, treatment emergent side effects such as extrapyramidal symptoms, metabolic dysregulation, and weight gain were minimal and similar to placebo. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects", section on 'Adverse effects'.)

Other second-generation antipsychotics — Low quality evidence (eg, indirect outcome, lack of placebo or other control, or small sample), as well as unpublished studies, suggests that monotherapy with other second-generation antipsychotics may possibly be useful for treating bipolar major depression [46]:

- **Asenapine** – A pooled analysis of two randomized trials, each lasting three weeks, compared asenapine (5 or 10 mg twice per day) with placebo in a subgroup of 173 patients with major depression concurrent with mania [47]. Remission occurred in more patients treated with asenapine than placebo (45 versus 24 percent); this was consistent with the finding that asenapine was superior in the total sample of patients with mania. However, among patients with concurrent depression and mania, sedation, dizziness, extrapyramidal symptoms, and weight gain occurred more often with asenapine than placebo.

- **Clozapine** – A retrospective observational study of 326 patients treated with adjunctive clozapine (mean dose 307 mg per day) for up to two years found that the number of hospitalizations and number of days in the hospital were lower during clozapine treatment than the same period of time immediately prior to use of clozapine [48].

- **Risperidone** – One trial enrolled 30 patients with an incomplete response to carbamazepine, lithium, or valproate and randomly assigned the patients to receive adjunctive risperidone, paroxetine, or risperidone plus paroxetine [49]. All three groups improved.

The side effects (table 4) of these drugs are discussed separately. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

Drugs with little to no benefit — For patients with bipolar major depression, multiple randomized trials indicate that there is little to no benefit in using aripiprazole or ziprasidone:

- **Aripiprazole** – Two eight-week trials compared aripiprazole (5 to 30 mg per day) with placebo in a total of 749 patients; a meta-analysis and a pooled analysis each found that the benefits of aripiprazole and placebo were comparable [17,20].

- **Ziprasidone** – Two six-week trials compared ziprasidone (20 to 80 mg twice daily) with placebo in a total of 856 patients; in each trial, ziprasidone demonstrated no advantage [18,20,50]

Rapid cycling bipolar disorder — The efficacy of second-generation antipsychotics to treat bipolar major depression in rapid cycling patients is discussed separately. (See "Rapid cycling bipolar disorder in adults: Treatment of major depression", section on 'Treatment'.)

Geriatric bipolar disorder — The efficacy of second-generation antipsychotics to treat bipolar major depression in geriatric patients is discussed separately. (See "Geriatric bipolar disorder: Treatment of mania and major depression", section on 'First-line treatment'.)

SAFETY AND TOLERABILITY

Side effects — Side effects associated with second-generation antipsychotics include weight gain, hyperglycemia, type 2 diabetes mellitus, hyperlipidemia, sedation, hyperprolactinemia, neuroleptic malignant syndrome, orthostatic hypotension, sudden death, and an increased risk of mortality when used to treat psychiatric symptoms associated with dementia in older adult patients (table 4). Second-generation antipsychotics can also cause extrapyramidal symptoms and tardive dyskinesia, but at rates lower than first-generation drugs. These side effects and their management are described separately. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects" and "Causes of hyperprolactinemia" and "Neuroleptic malignant syndrome" and "Tardive dyskinesia: Etiology, risk factors, clinical features, and diagnosis" and "Tardive dyskinesia: Prevention, treatment, and prognosis" and "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Side effect management'.)

General principles regarding the safety and tolerability of second-generation antipsychotics in bipolar major depression include the following:

- Patients with bipolar depression may be more sensitive to side effects than patients with mania [51,52].

- The risk of extrapyramidal side effects and tardive dyskinesia is thought to be higher in bipolar disorder than schizophrenia [53,54].

- Treatment-emergent mania does not occur in patients who are treated with quetiapine or olanzapine [9-11,55].

In addition, adverse effects can lead to poor adherence [56].

Metabolic effects — The risk of metabolic side effects (eg, weight gain, hyperlipidemia, and hyperglycemia) is increased with some second-generation antipsychotics [57]; this is important given the increased risk of metabolic syndrome [58] as well as cardiovascular morbidity and mortality in patients with bipolar disorder relative to the general population [59-61]. Although most studies of second-generation antipsychotics and metabolic effects involve schizophrenia [57], comparable effects have been found in bipolar disorder [8,55,62,63]. Among second-generation antipsychotics, the greatest risk for metabolic effects is with olanzapine and clozapine, followed by quetiapine and risperidone (table 4) [64]. The risk of clinically significant weight gain for olanzapine monotherapy and olanzapine plus fluoxetine appears to be comparable [9,65]. A review found that in short-term (≤12 weeks) randomized trials, asenapine also causes weight gain, whereas lurasidone does not [66].

Prior to initiating treatment with second-generation antipsychotics, we ask patients about their personal and family history of obesity, diabetes, dyslipidemia, hypertension, cardiovascular disease, and family history of sudden cardiac death [64].

Sedation — Among patients with bipolar major depression, olanzapine and quetiapine often cause somnolence that leads to discontinuation of treatment [52]:

- In an eight-week randomized trial that compared olanzapine with placebo in 706 patients, discontinuation of treatment due to adverse effects occurred in more patients treated with olanzapine than placebo (9 versus 5 percent) [9]. Among patients who discontinued olanzapine because of side effects, the most frequent cause was sedation.

- A meta-analysis of five randomized trials (2477 patients treated for eight weeks) that compared quetiapine with placebo found that discontinuation of treatment due to somnolence was nearly five times more likely in patients who received quetiapine [10].

Monitoring — Bipolar patients who are treated with second-generation antipsychotics should be assessed for [64,67]:

- Metabolic side effects at baseline and periodically thereafter (table 6).

- Extrapyramidal symptoms at baseline and subsequently at every visit. Patients should also be monitored for tardive dyskinesia at baseline, quarterly in the first year, and annually thereafter, using the Abnormal Involuntary Movement Scale (form 1).
- Orthostatic hypotension at baseline and periodically thereafter.
- Prolactin elevation at baseline and periodically thereafter.

In addition, patients may need to be monitored for QT prolongation. Additional information about assessing patients for metabolic side effects, extrapyramidal symptoms, orthostasis, hyperprolactinemia, and QT prolongation is discussed further in the context of schizophrenia. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Monitoring' and "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Side effect management'.)

SUMMARY

- **Effects of bipolar depression** – Depressive episodes predominate the clinical course of bipolar disorder. They account for a greater proportion of long-term morbidity, greater impairment in functioning, and a higher risk of suicide than mania or hypomanic episodes. (See 'Introduction' above.)
- **Treatment selection** – We choose medication regimens for bipolar disorder according to the phase of the illness. Side effect profiles, patient comorbidity, and drug-drug interactions are also considered. This is discussed in detail elsewhere. (See "Bipolar major depression in adults: Choosing treatment" and "Bipolar mania and hypomania in adults: Choosing pharmacotherapy" and "Bipolar disorder in adults: Choosing maintenance treatment".)
- **Efficacy and tolerability** – Trials investigating the efficacy of specific agents in the treatment of bipolar major depression have shown the following:
  - **Quetiapine** – Quetiapine monotherapy is efficacious for short-term treatment of bipolar I or bipolar II major depression. However, side effects such as sedation, weight gain, dry mouth, constipation, extrapyramidal symptoms and QTc prolongation may lead to discontinuation. (See 'Quetiapine' above.)
  - **Olanzapine** – Olanzapine monotherapy may be efficacious for short-term treatment of bipolar I major depression and appears to be effective for bipolar depression with mixed features. However, side effects such as sedation, weight gain, metabolic

dysregulation, hyperprolactinemia, neutropenia, elevated liver functions, and diabetes mellitus may limit its use. (See 'Olanzapine' above.)

- **Olanzapine plus fluoxetine** – The combination is widely studied and is efficacious for short-term treatment of bipolar I major depression. (See 'Olanzapine' above and "Bipolar major depression in adults: Efficacy and adverse effects of antidepressants".)

- **Lurasidone** – Lurasidone is efficacious as monotherapy in the treatment of bipolar I disorder and bipolar I disorder with mixed features. Lurasidone may also be efficacious as add-on therapy with lithium or valproate for bipolar I major depression. Side effects include akathisia, headache, insomnia, nausea, sedation, tremor, and extrapyramidal symptoms. (See 'Lurasidone' above.)

- **Cariprazine** – Cariprazine is efficacious in the treatment of bipolar I major depression. Side effects include weight gain, sedation, and akathisia. (See 'Cariprazine' above.)

- **Lumateperone** – Lumateperone appears to be effective in the treatment of acute major depression in the context of bipolar I or bipolar II disorder. Lumateperone appears to have minimal treatment emergent side effects. (See 'Lumateperone' above.)

- **Other second-generation antipsychotics** – Low-quality evidence or unpublished studies suggest that monotherapy with clozapine, risperidone, or asenapine may be useful for treating bipolar I major depression. (See 'Other second-generation antipsychotics' above.)

- **Drugs with no benefit** – Multiple randomized trials indicate no benefit for either aripiprazole or ziprasidone. (See 'Drugs with little to no benefit' above.)

- **Common adverse effects** – Side effects associated with second-generation antipsychotics include weight gain, hyperglycemia, type 2 diabetes mellitus, hyperlipidemia, sedation, hyperprolactinemia, extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, orthostatic hypotension, sudden death, and an increased risk of mortality when used to treat psychiatric symptoms associated with dementia in older adult patients. Additionally, some agents may cause QTc prolongation. Side effects of specific antipsychotics are discussed above and elsewhere (table 4). (See 'Side effects' above and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

- **Monitoring** – We monitor individuals treated with second generation antipsychotics for bipolar disorder for metabolic side effects (table 6), extrapyramidal symptoms, tardive dyskinesia (form 1), and orthostatic hypotension on a regular basis. We obtain an electrocardiogram prior to starting medication and at regular intervals in all individuals at risk for prolonged QTc or treated with medications with high propensity to cause prolonged QTc. (See 'Monitoring' above and "Schizophrenia in adults: Maintenance therapy and side effect management".)

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