Essential Pharmacotherapies for Bipolar Disorder

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Abstract

Purpose of Review The evidence basis for treatment of bipolar disorder, both for adults and children, is fairly varied and while Federal Drug Administration (FDA) approval provides one marker of evidence, many psychotropic medications are used for off-label indications. Primary care providers are increasingly at the forefront of initiating treatment for patients with mental health disorders. The purpose of this review is to discuss the current state of evidence for medications treating bipolar disorder, highlighting the evidence, exploring contraindications, side effects, and monitoring requirements for each of the major agents available.

Recent Findings Currently, there are three major classes of medication to treat bipolar disorder: lithium, anti-seizure drugs, and a growing range of second-generation antipsychotics. The guiding principle in initiation of treatment is to target treatment to the primary phase of illness while balancing side effect profiles with patient characteristics and comorbidities.

Summary While FDA approval of medications for the treatment of bipolar disorder is somewhat limited for both children and adults, in practice, a wider range of medications have shown to be useful. Increasing second-generation antipsychotic medications can be used as first-line agents for both bipolar mania and bipolar depression.
**Introduction**

Bipolar disorder is a psychiatric illness characterized by episodes of mania and hypomania and depression. Mood stabilization is the mainstay of pharmacotherapy with regimens targeted to the presenting episode and then adjusted as needed for maintenance. Because bipolar disorder is relatively prevalent among primary care samples as compared with the general public and the depressive episodes tend to be longer-lasting depression is more likely to be the presenting phase of the illness when patients seek help from their primary care providers [1]. Once the need for mood stabilization is recognized, the provider should start a regimen that is tailored to the patient’s symptoms and comorbidities. Given that access to psychiatric care frequently involves significant wait times, treatment initiation is reasonable in the primary care setting. There are three main classes of medications for treating bipolar disorder: lithium, antiepileptic drugs, and second-generation antipsychotic, with various indications and evidence for phase of illness and adult versus pediatric populations in each. Medical comorbidity, side effect profile, cost, and monitoring requirements should also be considered when picking an agent. In general, generic medications are the least expensive and most likely to be covered by insurance. Since insurance coverage is highly variable and relative cost unpredictable under cost, we have noted whether or not the medication is available in a generic form as a relative marker for cost. In the following paper, we discuss the evidence behind use of the major common medications for the treatment of bipolar disorder and explore the major contraindications, side effects, and indications in pediatric populations. Furthermore, we classify the information according to the quality of the evidence based on a ranking system (Table 1) adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [2]. After evaluating all the information, we based conclusions and recommendations using an adaptation of the Taxonomy for Strength of Recommendation for Treatment Statements (SORT) [3] (Tables 2, 3 and 4).

**Pharmacologic treatment**

**Lithium**

Experience with lithium monotherapy in treating acute mania spans over four decades; however, differences in methodology make it difficult to draw specific conclusions regarding older studies. There are at least five recent RCTs

| Grade of evidence* | Type of study                                      |
|-------------------|---------------------------------------------------|
| A                 | High-quality RCTb or meta-analysis                 |
| B                 | Low-quality RCTc or OL study                      |
| C                 | Case series, retrospective chart review            |
| D                 | Case reports, expert opinion                      |

*aOnce initial grade of individual study is determined:
- Decrease grade of evidence if study presents: imprecise data [-1]; dropout/loss to follow-up rate > 35% [-1]; serious limitations to the study [-2]; no intention to treat analysis [-1]; negative result in DBPC [-3]; inconsistent results [-1]
- Increase grade if study presents: large effect size response Cohen’s $h > 0.80$ or remission Cohen’s $h > 0.60$ [+1]; consistent evidence in two or more OL [+1]

bPlacebo control trial and adequately powered
cActive comparison group or inadequately powered
comparing lithium to placebo [4–8]. Overall, lithium monotherapy has been consistently superior to placebo with a number needed to treat (NNT) for lithium in acute mania of around five with a therapeutic effect usually achieved after a week of treatment.

In terms of bipolar depression, lithium failed to separate from placebo in the only more recent rigorously conducted RCT [9]. Of note, lithium levels in this study tended to be on the lower end of the spectrum (mean lithium level 0.61 mEq/L) and there appeared to be a relatively large placebo response in that population.

There are six methodologically sound RCTs exploring the efficacy of lithium monotherapy compared to placebo in relapse prevention [10–15]. Results from these studies are varied; however, a systematic review and meta-analysis that pooled the data from these six studies found lithium to be significantly superior to placebo in preventing mood episodes, both manic and depressive [16]. Of note, these studies were not all sampled from a pool of subjects already known to be lithium responders.

**Side effects and contraindications**

The most common adverse events with lithium are nausea, vomiting, dizziness, headache, insomnia, asthenia, constipation, diarrhea, tremor, and weight gain. More severe and less common side effects include abnormal T waves on ECG, hypothyroidism, nephrotoxicity, and neurotoxicity.

**Dosing and monitoring**

Starting dose is usually 300 mg twice daily, titrated every 5 days usually to 900 to 1800 mg per day or a serum level of 0.8–1.2 mEq/L. Lithium levels should be checked 5 to 7 days after a dose change (draw blood 10–14 h after last dose) and once on a steady dose, every 6 to 12 months. In addition to serum levels, patients on lithium therapy should have renal and thyroid function assessed before treatment, every 2 to 3 months in the first 6 months of treatment and every 6 to 12 months thereafter. An electrocardiogram should be evaluated prior to treatment and after major dosing changes occur or if paired with a medication known to affect QTc interval.

| Definition                                                      | Evidence required                                                                 |
|-----------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Level 1: Strong recommendation based on high-quality evidence;  | Based on consistent findings from 2 or more studies that reach grade A evidence   |
| further research is unlikely to change the confidence of the    |                                                                                  |
| evaluated intervention                                           |                                                                                  |
| Level 2: Moderate recommendation, further research is likely    | Based on results of 1 grade A study or on inconsistent (mixed) findings from 2   |
| to have an important impact on the confidence of               | or more grade A studies                                                           |
| recommendation                                                  |                                                                                  |
| Level 3: Weak recommendation, further research is very likely   | Based on studies whose highest level of evidence is B                             |
| to have an important impact on confidence                       |                                                                                  |
| Level 4: Effect of intervention is uncertain                    | Based on grade C evidence or lower                                               |

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**Table 2. Level of recommendation, definition, and criteria**

| Definition                                                      | Evidence required                                                                 |
|-----------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Level 1: Strong recommendation based on high-quality evidence;  | Based on consistent findings from 2 or more studies that reach grade A evidence   |
| further research is unlikely to change the confidence of the    |                                                                                  |
| evaluated intervention                                           |                                                                                  |
| Level 2: Moderate recommendation, further research is likely    | Based on results of 1 grade A study or on inconsistent (mixed) findings from 2   |
| to have an important impact on the confidence of               | or more grade A studies                                                           |
| recommendation                                                  |                                                                                  |
| Level 3: Weak recommendation, further research is very likely   | Based on studies whose highest level of evidence is B                             |
| to have an important impact on confidence                       |                                                                                  |
| Level 4: Effect of intervention is uncertain                    | Based on grade C evidence or lower                                               |
| Medication      | Dose range                      | Generic | FDA approved | Level of evidence |
|-----------------|---------------------------------|---------|--------------|-------------------|
| **Mania**       |                                 |         |              |                   |
| Mood stabilizers|                                 |         |              |                   |
| Lithium         | 900–1800 mg/day                 | Yes     | Yes          | Level 1           |
| Serum: 0.8–1.2 mEq/L |                                  |         |              |                   |
| Divalproex      | 1500–2500 mg/day                | Yes     | Yes          | Level 2           |
| Carbamazepine   | 600–1800 mg/day                 | Yes     | Yes          | Level 1           |
| Serum: 4–12 mg/mL|                                  |         |              |                   |
| **Antipsychotics**|                                |         |              |                   |
| Olanzapine      | 5–20 mg/day                     | Yes     | Yes          | Level 1           |
| Risperidone     | 1–6 mg/day                      | Yes     | Yes          | Level 1           |
| Risperidone LAI| 25–50 mg/fortnight, IM         | No      | Yes          | Level 1           |
| Paliperidone    | 3–12 mg/day                     | Yes     | No           | Level 2           |
| Paliperidone LAI| Monthly 117–234 mg/month IM maintenance | No    | No           | Level 2\(^1\)   |
|                 | Trimonthly 273–819 mg/3 month IM maintenance | No    | No           | Level 2\(^1\)   |
| Quetiapine      | 400–800 mg/day                  | Yes     | Yes          | Level 1           |
| Quetiapine XR   | 400–800 mg/day                  | Yes     | Yes          | Level 1           |
| Aripiprazole    | 15–30 mg/day                    | Yes     | Yes          | Level 1           |
| Aripiprazole LAI| 300–400 mg/4 weeks IM maintenance | No    | No           | Level 3           |
| Ziprasidone     | 80–160 mg/day, often BID        | Yes     | Yes          | Level 1           |
| Cariprazine     | 3–6 mg/day                      | No      | Yes          | Level 1           |
| Asenapine       | 5–20 mg/day                     | No      | Yes          | Level 1           |
| Iloperidone     | 6–12 mg/day                     | No      | No           | Level 4           |
| Lurasidone      | 20–120 mg/day                   | No      | No           | Level 4           |
| Clozapine       | 300–600 mg/day, often BID       | Yes     | No           | Level 2           |
| **Bipolar depression**|                            |         |              |                   |
| Mood stabilizers|                                 |         |              |                   |
| Lithium         | 900–1800 mg/day                 | Yes     | No           | Level 3           |
| Serum: 0.8–1.2 mEq/L |                                  |         |              |                   |
| Divalproex      | 1500–2500 mg/day                | Yes     | No           | Level 3           |
| Carbamazepine   | 600–1800 mg/day                 | Yes     | No           | Level 3           |
| Serum: 4–12 mg/mL|                                  |         |              |                   |
| Lamotrigine     | 100–400 mg/day                  | Yes     | No           | Level 2           |
| **Antipsychotics**|                                |         |              |                   |
| Olanzapine      | 5–20 mg/day                     | Yes     | No           | Level 3           |
| Olanzapine/Fluoxetine| Olanzapine: 3–12 mg/day        | No\(^2\)| Yes          | Level 1           |
|                 | Fluoxetine: 25–50 mg/day        |         |              |                   |
| Quetiapine      | 300–600 mg/day                  | Yes     | Yes          | Level 1           |
| Quetiapine XR   | 300–600 mg/day                  | Yes     | Yes          | Level 1           |
| Lurasidone      | 20–120 mg/day                   | No      | Yes          | Level 1           |
Table 3. (Continued)

| Medication    | Dose range           | Generic | FDA approved | Level of evidence |
|---------------|----------------------|---------|--------------|-------------------|
| Aripiprazole  | 15–30 mg/day         | Yes     | No           | Level 4           |
| Cariprazine   | 3–6 mg/day           | No      | No           | Level 2           |
| Asenapine     | 5–20 mg/day          | No      | No           | Level 4           |
| Iloperidone   | 6–12 mg/day          | No      | No           | Level 4           |

**Maintenance/prevention of relapse**

**Mood stabilizers**

| Medication     | Dose range           | Generic | FDA approved | Level of evidence |
|----------------|----------------------|---------|--------------|-------------------|
| Lithium        | 900–1800 mg/day      | Yes     | Yes          | Level 1           |
| Serum: 0.8–1.2 mEq/L |
| Divalproex     | 1500–2500 mg/day     | Yes     | Yes          | Level 1           |
| Carbamazepine  | 600–1800 mg/day      | Yes     | No           | Level 3           |
| Serum: 4–12 mg/mL |
| Lamotrigine    | 100–400 mg/day       | Yes     | Yes          | Level 1           |

**Antipsychotics**

| Medication     | Dose range           | Generic | FDA approved | Level of evidence |
|----------------|----------------------|---------|--------------|-------------------|
| Olanzapine     | 5–20 mg/day          | Yes     | Yes          | Level 1           |
| Risperidone    | 1–6 mg/day           | Yes     | No           | Level 2<sup>2</sup>|
| Risperidone LAI| 25–50 mg/fortnight, IM| No      | Yes          | Level 1           |
| Paliperidone   | 3–12 mg/day          | Yes     | No           | Level 2           |

**Paliperidone LAI**

| Medication     | Dose range           | Generic | FDA approved | Level of evidence |
|----------------|----------------------|---------|--------------|-------------------|
| Monthly        | 117–234 mg/month IM maintenance | No | No | Level 2<sup>1</sup> |
| Trimestruently | 273–819 mg/3 months IM maintenance | No | No | Level 2<sup>1</sup> |
| Quetiapine     | 400–800 mg/day       | Yes     | Yes          | Level 1           |
| Quetiapine XR  | 400–800 mg/day       | Yes     | Yes          | Level 1           |
| Aripiprazole   | 15–30 mg/day         | Yes     | Yes          | Level 1           |
| Aripiprazole LAI| 300–400 mg/4 weeks IM maintenance | No | Yes | Level 1          |
| Ziprasidone    | 80–160 mg/day, often BID | Yes | No | Level 2          |
| Asenapine      | 5–20 mg/day          | No      | No           | Level 1           |
| Clozapine      | 300–600 mg/day, often BID | Yes | No | Level 3          |

<sup>1</sup>Level of evidence assigned based on extrapolation from riperidone studies

<sup>2</sup>Level of evidence assigned based on extrapolation from LAI risperidone studies

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**Cost**

Available as a generic medication.

**Valproate**

Older studies indicated the usefulness of valproate monotherapy in the treatment of acute mania [17–19]; however, due to methodological issues, limited data can be extracted from these studies. The efficacy of valproate monotherapy in the treatment of acute mania has recently been studied in at least six modern RCTs using a placebo comparator [4, 20–24]. Results from these trials are mixed with three positive studies [4, 20, 23] and three studies failing to separate from placebo [21, 22, 24]. In a meta-analysis using a random effect model and
pooled placebo subjects, it showed valproate to be overall superior to placebo in the treatment of acute mania, albeit with a small effect size [25]. The NNT for response is around 10 and the therapeutic effect is present after 5 to 15 days.

Evidence supporting the efficacy of valproate monotherapy in depressive episodes is inconsistent. There are three, albeit small, positive studies [26–28] and a negative study (unpublished but available through a meta-analytical paper [29]).
Overall, these studies suggest that there is some data regarding the efficacy of valproate monotherapy in the treatment of bipolar depression (NNT \( \sim 7 \)).

For relapse prevention, there are two studies comparing valproate with placebo \([11, 12]\), four studies comparing valproate with lithium \([11, 30–32]\), and one comparing valproate to olanzapine \([33]\). Follow-up for these studies was between 6 and 24 months. In a meta-analysis summarizing these studies \([34]\), valproate was determined to be more effective than placebo in preventing withdrawal due to any mood episode (NNT 8) or a depressive episode (NNT 13); no strong evidence suggested that valproate is superior to placebo in preventing a manic episode. Furthermore, the meta-analysis also found no strong evidence suggesting valproate to be superior to lithium or olanzapine.

### Side effects and contraindications

The most frequent adverse events were somnolence, nausea, dizziness, asthenia, constipation, twitching, weight gain, hair loss, and vomiting. More serious and rare side effects include thrombocytopenia and liver failure. Valproate has also been linked to polycystic ovaries and is well known to be teratogenic; thus, extreme caution should be exercised in women of childbearing age.

### Dosing and monitoring

Valproate target dose is usually between 1500 and 2500 mg per day. Serum valproate levels are recommended to be checked 2 to 5 days after each dose increase (obtaining sample 12 h after last dose); valproate target serum level is recommended between 50 and 125 \( \mu \text{g/mL} \). Patients on a steady dose should have their levels measured every 6 to 12 months. In addition, complete blood count, renal function, and liver function tests should be checked every 6 to 12 months.

### Cost

Available in a generic formulation.

### Carbamazepine

Studies published in the 1980s suggested carbamazepine’s efficacy in the treatment of acute mania \([35, 36]\). Recent studies using current standard methodology also demonstrate carbamazepine monotherapy is superior to placebo in acute mania \([37–39]\). The NNT for response to acute mania is of five with a therapeutic effect expected after 2 weeks.

Aside from a handful of open studies and older withdrawal studies \([35, 40]\), there is relatively little data regarding the efficacy of carbamazepine in bipolar depression. Only one RCT compared carbamazepine with placebo in bipolar depression treated over 12 weeks \([39]\); in this study, carbamazepine was superior to placebo in terms of response and remission.

There is only one small placebo-controlled study exploring carbamazepine’s efficacy in relapse prevention. Although carbamazepine prevented a mood episode in 60% of cases relative to 22% in the placebo group, the differences were not significant likely due to lack of power.
Side effects and contraindications

Common carbamazepine-related adverse events include dizziness, nausea, somnolence, pruritus, rash, and drowsiness. Less common side effects are double or blurred vision, dizziness, sedation, ataxia, vertigo, gastrointestinal disturbances, cognitive impairment, hematological effects, and Stevens-Johnson syndrome including its related dermatologic effects.

Dosing and monitoring

The typical dosage of carbamazepine in the treatment of bipolar disorder is 600 to 1800 mg/day (serum concentration 4–12 mg/mL). After several weeks under carbamazepine, an induction of hepatic enzymes (CYP 3A4) occurs and the drug levels drop and may require additional upward dose titration.

Cost

Available in generic formulation.

Lamotrigine

There is no evidence lamotrigine monotherapy is effective in the treatment of acute mania. In two unpublished studies (accessible in sponsor study register website), lamotrigine failed to separate to placebo in both 3-week and 6-week follow-up [41, 8].

For bipolar depression, lamotrigine monotherapy was studied in four unpublished [42–45] and one published RCTs [46]. Lamotrigine monotherapy failed to separate from placebo 8-week fixed dose (200 mg) RCT in patients with bipolar disorder type I [42, 43] and type II [45] with acute depression, and in a 10-week flexible dose (100–400 mg) RCT [44]. Lamotrigine monotherapy did separate from placebo in a 7-week 200 mg a day RCT [46]. Overall, evidence supporting lamotrigine monotherapy efficacy in treating bipolar depression is negligible, though possibly a weak signal may be present (NNT around 10).

There are three RCTs comparing placebo and lamotrigine in relapse prevention; all studies were enriched for lamotrigine tolerability [12, 13, 47]. Overall, lamotrigine seems to be more effective than placebo in preventing depressive episodes but not manic episodes.

Side effects and contraindications

Common side effects include nausea, dyspepsia, pain, insomnia, and non-serious skin rash. More serious side effects include SJS, multi-organ hypersensitivity, and aseptic meningitis.

Dosing and monitoring

Dose target for lamotrigine is 100 to 400 mg per day. The most significant drawback of lamotrigine treatment is the need to initiate it at 25 mg/day for 2 weeks, then 50 mg/day for another 2 weeks, and then by increments of 25 to 50 mg/day thereafter to avoid a moderately high incidence of rash [48].
Available in a generic formulation.

**Antipsychotics**

The use of “antipsychotic” medications to treat aspects of bipolar disorder dates back many years. The first psychiatric patient to receive chlorpromazine, the earliest modern antipsychotic medication, was reportedly suffering from psychotic mania, and in 1973, chlorpromazine became only the second medication to be officially sanctioned by the Food and Drug Administration (FDA) for bipolar mania, at a recommended starting dose for outpatients ranging from 30 to 75 mg administered in divided doses [49, 50]. Chlorpromazine and other first-generation antipsychotic medications (FGAs), haloperidol in particular, have been found to be as effective for mania as the second-generation antipsychotic medications (SGAs) [51]. However, their use has been limited by a host of potential short- and long-term adverse effects including parkinsonian symptoms, elevated prolactin, weight gain, sedation, anti-cholinergic effects, and the potential for neuroleptic malignant syndrome and tardive dyskinesia. In addition, low-potency FGAs have been associated with significantly prolonged QTc [52, 53]. Moreover, these medications have not been found to be effective for bipolar depression or maintenance therapy [51]. As a result, FGAs have been largely displaced in the bipolar pharmacopeia by the newer SGAs.

Since olanzapine became the first SGA to be FDA-approved for mania, the use of SGAs to treat patients with bipolar disorder has grown to rival that of both anti-seizure drugs and lithium. While not all of these medications have been aggressively tested for efficacy in acute mania, virtually all of the SGAs studied have been observed to be effective [54]. Data on the use of these medications for maintenance has also been generally positive—and even where data is lacking, clinical recommendations are usually to continue treatment with therapeutics found to be effective for acute episodes [55, 56]. In contrast, findings have been far more mixed with regard to the use of these medications for bipolar depression [57, 58].

Because SGA medications are pharmacologically quite diverse, adverse effects differ a great deal. A metabolic syndrome potentially manifesting with weight gain, elevated blood sugar, and increased cholesterol has been deemed a class effect, though the incidence appears to vary between individual SGA medications [53]. Guidelines recommend baseline and repeat measurements of weight, blood pressure, and waist circumference, as well as fasting glucose and plasma lipids; individuals at increased risk of diabetes should be followed particularly closely [59]. Many of these medications may also be associated with prolonged QTc, and other potential adverse effects including neuroleptic malignant syndrome and tardive dyskinesia while more prevalent with FGAs have been reported in patients treated with SGAs as well [53]. Guidelines for the management of SGAs in children and adolescents may differ to some degree due to evidence of disparate vulnerabilities to these medications [60].

**Olanzapine**

Olanzapine was the first SGA FDA-approved for mania, for which multiple large, DBPC studies have found it to be effective, both alone and in
combination with lithium or valproate [54, 61]. Moreover, a recent network analysis found olanzapine to be more effective in treating mania than lithium, anti-seizure drugs, and most other SGAs [62]. The NNT in adults with acute mania is five with response occurring as early as days 2 to 7. Olanzapine has also shown to be effective in adolescent acute mania with a NNT of four [63]. Olanzapine is FDA-approved for bipolar maintenance in adults as well, with efficacy demonstrated by double-blind studies of olanzapine alone and in combination with lithium or valproate [55, 56]. For patients with bipolar depression, two DBPC trials found the response to olanzapine monotherapy to be statistically but not clinically significant. The NNT of 11.3 in monotherapy arms contrasted with the NNT of 3.89 observed in patients who received a combination of olanzapine with fluoxetine. As a result only, the latter, marketed as a single combination medication, was FDA-approved for bipolar depression in both adults and adolescents [64–65].

**Side effects and contraindications**

Common adverse effects include weight gain, dyslipidemia, glucose dysregulation, sedation, and elevated prolactin. The incidence of weight gain and metabolic syndrome appears to be particularly high with olanzapine. There is also a black box warning for increased risk of death in elderly patients with dementia-related psychosis [53].

**Dosing and monitoring**

Recommended dosing ranges from 5 to 20 mg once daily for mania and maintenance treatment. For depression, the recommended dose is 5 to 12.5 mg in combination with 20 to 50 mg of fluoxetine.

**Cost**

Olanzapine is available as a very inexpensive generic. However, the orally dissolving tablet formulation is less inexpensive, and the long-acting injectable formulation (FDA-approved only for schizophrenia) is quite expensive. Symbyax is also expensive but can be replicated more cheaply by combining generic olanzapine and fluoxetine.

**Risperidone/paliperidone**

Based on multiple large, DBPC studies, risperidone has been FDA-approved for mania in adults, either as monotherapy or in combination with lithium or valproate. In addition, risperidone is available as a long-acting injectable which has also been found to be effective as monotherapy for mania [54, 61]. Moreover, a network analysis of anti-manic agents found risperidone to be associated with the greatest likelihood of therapeutic response [62]. In children, risperidone monotherapy for mania is FDA-approved for ages 10–17 years. In addition to a DBPC study demonstrating efficacy in adolescents [66], an additional study has also
shown significant symptomatic improvements in younger children, age 3–7 years [67, 68]. In patients whose mania responded to treatment with risperidone, the long-acting injectable (LAI) was found to delay manic relapse in adults as monotherapy and in combination with treatment-as-usual (TAU) [55, 56]. Risperidone was not found to be effective in a network analysis of efficacy in bipolar depression, but only limited data was available [69].

Paliperidone is an active metabolite of risperidone. Although not FDA-approved for bipolar disorder, it has also been found to be effective as monotherapy for bipolar mania and maintenance in DBPC studies [70–72]. In addition, a small open-label study found it to be effective for manic symptoms in “bipolar spectrum” children [73]. Paliperidone is also available as monthly and trimonthly LAI formulations; the former was found to be effective in maintenance of three bipolar patients in a small case series [74]. Paliperidone has not been studied as a treatment for bipolar depression.

Dosing and monitoring

Recommended dose of oral risperidone is from 1 to 6 mg daily in adults and 0.5 to 2.5 mg daily in children. LAI should be dosed at 25 to 50 mg injected intramuscularly fortnightly. Paliperidone oral doses may range from 3 to 12 mg daily; monthly and trimonthly LAI formulations are also available.

Side effects and contraindications

Common adverse effects with risperidone and paliperidone may include weight gain, glucose dysregulation, and elevated prolactin; elevated prolactin and potentially parkinsonian symptoms may become more likely with increasing doses—the former may also be associated with galactorrhea. There is a black box warning for increased risk of death in elderly patients with dementia-related psychosis.

Cost

Risperidone is available as a very inexpensive generic, with the orally dissolving tablet formulation only slightly less so. The long-acting injectable formulation is quite expensive. Oral paliperidone is available as a generic but remains expensive. Paliperidone LAI formulations are very expensive.

Quetiapine

Quetiapine, both immediate and extended-release, is FDA-approved for the treatment of bipolar mania, as monotherapy and in combination with lithium or valproate; as monotherapy for depression; and as monotherapy or in combination with lithium or valproate to maintain response. These indications in adults are
supported by multiple, large DBPC studies [55, 56, 61, 64]. Quetiapine was found to be somewhat less effective than other SGA medications in meta-analyses comparing efficacy for mania [62]. However, it showed a strong NNT of 5.62 for bipolar depression and was found in one meta-analysis to be the only SGA superior to lithium in preventing relapse in some patients [56, 64]. Quetiapine is FDA approved for mania in children 10–17 years of age, based on a DBPC study [75]. Furthermore, in a head-to-head, randomized, double-blind study comparing quetiapine to divalproex [76]; quetiapine was found to be superior to divalproex with regard to rates of response (84% vs. 56%) and remission (60% vs. 28%). Another RCT study comparing quetiapine/divalproex combination to divalproex alone [77] found response rates were significantly higher in the combination group than the mono-therapy group (87% vs. 53%), but that the combination was also associated with greater weight gain (4.2 kg ± 3.2 vs. 2.5 kg ± 2.1). Quetiapine is not FDA-approved for bipolar depression in children, and separate DBPC studies showed quetiapine and extended-release quetiapine did not separate from placebo [78, 79]. Quetiapine is also not FDA-approved for maintenance therapy in children and adolescents; however, open-label extension studies in adolescents suggest that longer-term treatment with quetiapine in this population may be well tolerated [80–82].

**Side effects and contraindications**

Common adverse effects include weight gain, dyslipidemia, glucose dysregulation, orthostasis, and sedation. Sedation and orthostasis may become particularly acute with higher doses. Quetiapine may be an especially good choice in patients vulnerable to parkinsonian effects because of its low dopamine receptor binding. There are black box warnings for increased risk of death in elderly patients with dementia-related psychosis and for increased risk of suicidal thoughts and behaviors in patients under age 25 years.

**Dosing and monitoring**

Quetiapine and quetiapine XR adult dosing recommendations for bipolar mania and maintenance treatment are 400 to 800 mg daily, 300 mg daily for bipolar depression, with some patients requiring up to 600 mg daily. Recommendations for bipolar depression and maintenance are to take quetiapine once daily, typically at bedtime. While FDA-approved guidelines for treating mania call for split dosing, quetiapine is usually prescribed as a single bedtime dose. Dosing recommendations in children range from 400 to 600 mg daily.

**Cost**

Quetiapine is available as a very inexpensive generic, with the extended-release formulation only slightly less so.

**Aripiprazole**

With multiple DBPC studies showing efficacy, aripiprazole has been FDA-approved as a treatment for bipolar mania in both adults [62] and
Aripiprazole is approved for use in children 10–17 years old [83–84], and is effective as monotherapy or adjunctively with lithium or valproate [85]. Aripiprazole is also approved for maintenance treatment in adults [86]. The monthly LAI formulation has not been studied in acute mania, but has been shown to be effective for maintenance therapy in adults [87]. Despite some promising open-label findings, DBPC studies in adults did not find aripiprazole to be effective for bipolar depression [88].

**Side effects and contraindications**

Aripiprazole has been associated with less weight gain and metabolic adverse effects than many other SGAs. Parkinsonian symptoms are also rare, though akathisia may be problematic, particularly with higher doses. There are black box warnings for increased risk of death in elderly patients with dementia-related psychosis and for increased risk of suicidal thoughts and behaviors in patients under age 25 years.

**Dosing and monitoring**

Recommended dosing is 15 to 30 mg daily in adults but many patients may better tolerate aripiprazole if started at a lower dose and slowly titrated up to a minimum effective dose. Dosing in children is 2 to 10 mg daily. Aripiprazole LAI is administered at 300 to 400 mg IM every 4 weeks, though clinically some patients have been found to require more frequent dosing. Aripiprazole lauroxil can be administered every 6 weeks to 2 months but has not been studied in bipolar disorder.

**Cost**

Aripiprazole is available as a very inexpensive generic. The oral disintegrating formulation is expensive, and both of the long-acting injection formulations are very expensive as well. Pricing for the tablet containing a sensor to track ingestion has not yet been made available.

**Ziprasidone**

Ziprasidone is FDA-approved for adult bipolar mania based on multiple DBPC trials and was found to be effective for maintenance in open-label extensions of the mania trials; it was also found in a placebo-controlled withdrawal study to delay symptomatic relapse when administered adjunctively to lithium or valproate [89–91]. A network analysis of anti-manic agents, however, found it to be the least effective SGA for mania [62]. Ziprasidone was also well-tolerated and effective for manic symptoms in a DBPC trial involving 10–17-year-olds (NNT 3) [92] and two open-label trials including patients 10–17 and 6–
17 years of age [93, 94]. Ziprasidone was not found to be effective for bipolar depression, with a particularly poor NNT of 77.4 [64].

Side effects and contraindications

Ziprasidone has a very good adverse effect profile, especially with regard to weight and metabolic effects. It may be associated with sedation and elevated prolactin, and may be contraindicated in individuals at risk for prolonged QTc. There is a black box warning for increased risk of death in elderly patients with dementia-related psychosis.

Dosing and monitoring

Dosing in adults is 80 to 160 mg daily, usually administered twice daily. Children appear to tolerate a similar dose range.

Cost

Ziprasidone is available in a fairly inexpensive generic formulation.

Lurasidone

Lurasidone is FDA-approved in adults with bipolar disorder only for episodes of depression, as monotherapy or in combination with lithium or valproate [95]. With an NNT of 5.24, based on multiple DBPC trials, lurasidone is second only to the combination of olanzapine and fluoxetine in efficacy [64]. In addition, the results from a large DBPC clinical trial enrolling children and adolescents 10–17 years old have led to lurasidone recently receiving supplemental FDA approval for bipolar depression in this population as well [96]. There is little data for the use of lurasidone in bipolar mania or for maintenance treatment, but one post hoc study did observe improvement in hypomanic symptoms associated with major depression [97].

Side effects and contraindications

Lurasidone has been found to be particularly well tolerated, with little weight gain and a low incidence of metabolic adverse effects. However, lurasidone treatment can be associated with increased prolactin levels and other potential consequences of its relatively high dopamine receptor occupancy. There are black box warnings for increased risk of death in elderly patients with dementia-related psychosis and for increased risk of suicidal thoughts and behaviors in children, adolescents, and young adults.
Dosing and monitoring

Dosing in adults ranges from 20 to 120 mg daily; in children, dosing ranges from 20 to 80 mg daily.

Cost

Lurasidone is not available as a generic and is very expensive.

Cariprazine

The use of cariprazine in both bipolar mania and depression is supported by DBPC trials, though only the former is FDA-approved [98, 99]. Efficacy in mania has been favorably compared to lithium, while in the single published DBPC bipolar depression trial, the effect size of cariprazine response was slightly lower than that of FDA-approved SGAs [62, 98]. There remains little data for the use of cariprazine as a maintenance medication in bipolar disorder or for its use in children and adolescents.

Side effects and contraindications

Cariprazine is reported to be relatively well tolerated, with a favorable metabolic profile. There is a black box warning for increased risk of death in elderly patients with dementia-related psychosis.

Dosing and monitoring

Dosing ranges from 3 to 6 mg daily in adults.

Cost

Cariprazine is not available as a generic and is very expensive.

Asenapine

Based on multiple DBPC studies, asenapine is FDA-approved for bipolar mania as monotherapy for age 10 years through adulthood and as an adjunct to lithium or valproate in adults [100–102]. Moreover, while not FDA-approved for bipolar maintenance, asenapine has been found to be safe and effective in several double-blind extension trials [103, 104]. There is limited data for its use in bipolar depression but in a post hoc analysis of adult patients with mixed symptoms, it appeared to be helpful for depressive symptomatology [105].
### Side effects and contraindications

In addition to potential metabolic adverse effects, asenapine is particularly sedating. In addition, many patients complain of dysgeusia, particularly with the original, non-flavored formulation. There is a black box warning for increased risk of death in elderly patients with dementia-related psychosis.

### Dosing and monitoring

Asenapine is available only in an orally dissolving formulation. Dosing starts at 5 and 10 mg for children and adults, respectively. Doses range up to 20 mg in split dosing, though asenapine is often administered as a single bedtime dose due to its strong sedating effects.

### Cost

Asenapine is not available as a generic and is expensive.

## Iloperidone

Iloperidone has not been studied for use in bipolar disorder with the exception of single open-label study showing efficacy in bipolar patients with mixed manic and depressive symptoms [106].

### Side effects and contraindications

The medication can be associated with sedation, weight gain, and metabolic adverse effects. Iloperidone is particularly associated with hypotension and was associated with an almost 40% dropout rate in the open-label bipolar trial; common adverse effects in the study included tachycardia, palpitations, and urinary effects. There is a black box warning for increased risk of death in elderly patients with dementia-related psychosis.

### Dosing and monitoring

Dosing is typically from 6 to 12 mg daily.

### Cost

Iloperidone is not available as a generic and is expensive.

## Clozapine

Clozapine is typically reserved for treatment-resistant manic patients due to the significant adverse effects associated with this medication. Its use
is supported by multiple open-label clinical trials and case series, some of them in explicitly treatment-resistant populations [107]. There is limited data for maintenance but longer-term open-label trials suggest continued efficacy [108, 109]. Clozapine has not been studied in patients with bipolar depression and there is little data for its use in children with bipolar disorder.

Side effects and contraindications

As noted, clozapine is associated with a panoply of potentially significant adverse effects including QTc prolongation, hypotension, weight gain, metabolic effects, a dose-dependent increased risk of seizures, myocarditis, and sialorrhea. Orthostatic hypotension with clozapine administration has been associated with respiratory and cardiac arrest. In addition, the risk of agranulocytosis mandates weekly blood tests for at least 6 months, fortnightly blood tests for the next 6 months, and monthly lab tests for the duration of use—prescribers should be careful to consult the testing guidelines approved by the FDA. There are multiple black box warnings for clozapine reflecting these adverse effects, as well as a warning about increased risk of death in elderly patients with psychosis.

Dosing and monitoring

Dosing for bipolar disorders may vary widely but should not exceed 900 mg per day except under unusual circumstances.

Cost

Clozapine is moderately expensive and patients will need to pay for frequent blood tests as well as the medication.

Conclusion

Initiation of treatment for bipolar disorder with evidence-based regimens have the best chance of reducing the significant decline in function and subsequent morbidity and mortality that is currently associated with this disorder. While many patients with bipolar disorder may eventually need subspecialty care, primary care providers are in a critical position to change the outcomes for these patients by assisting with early intervention. Future areas of research include exploring models of integrated and collaborative care so that the professionals in the front lines of healthcare continue to have access to expertise so that up-to-date evidence approaches are used in the service of patients with mental illness.
Compliance with Ethical Standards

Conflict of Interest
Caleb Adler declares that he has no conflict of interest. L. Rodrigo Patino Duran declares that he has no conflict of interest. Hilja Ruegg declares that she has no conflict of interest. Suzanne Watson declares that she has no conflict of interest. Melissa DelBello declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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