Pediatric bipolar disorder: Overview of choosing treatment

AUTHOR: David Axelson, MD
SECTION EDITOR: David Brent, MD
DEPUTY EDITOR: David Solomon, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Oct 2023.**
This topic last updated: **Aug 30, 2022.**

INTRODUCTION

The mainstay of treatment for bipolar disorder in children and adolescents is pharmacotherapy [1]. In addition, adjunctive psychotherapy is generally regarded as essential [2].

Fewer studies have been conducted in pediatric bipolar patients than adult patients; thus, treatment is often based upon adult studies [3,4]. However, response to specific medications may differ between youth and adults.

Although pharmacotherapy is indicated for nearly all youth with bipolar disorder, approximately one-third of patients do not receive medications [5]. As an example, an eight-year prospective observational study enrolled youth with mania who were treated in the community (n = 115), and found that antimanic medications (antipsychotics, lithium, or anticonvulsants) were never prescribed to 37 percent [6].

In addition, the wrong medication regimen is frequently administered to children and adolescents with bipolar disorder. A retrospective study found that among bipolar patients who were treated for mania with or without mixed features (n = 282), antidepressant monotherapy was prescribed for 24 percent [5].

This topic reviews the choice of treatment for pediatric bipolar disorder. Other aspects of pediatric bipolar disorder are discussed separately, including the general principles of using

pharmacotherapy; efficacy, administration, and side effects of second-generation antipsychotics for mania; efficacy and core elements of adjunctive psychotherapy; assessment and diagnosis; and the epidemiology, clinical features, and course of illness:

- (See "Pediatric bipolar disorder and pharmacotherapy: General principles".)
- (See "Pediatric mania and second-generation antipsychotics: Efficacy, administration, and side effects".)
- (See "Pediatric bipolar disorder: Efficacy and core elements of adjunctive psychotherapy".)
- (See "Pediatric bipolar disorder: Assessment and diagnosis".)
- (See "Pediatric bipolar disorder: Clinical manifestations and course of illness".)

SETTING

The appropriate level of care (setting) for treating youth with bipolar disorder varies. During periods of significant impairment or elevated risk of suicidal or dangerous behavior, inpatient, intermediate levels of care (eg, partial hospitalization, intensive outpatient programs, or in-home services), or frequent outpatient visits and phone/electronic contact may be required. When indicated, higher levels of care can provide a safer treatment environment, closer monitoring of symptoms and side effects, more frequent adjustments of pharmacotherapy, and/or more intensive psychotherapy.

GENERAL PRINCIPLES OF PHARMACOTHERAPY

A separate topic discusses the general principles for treating pediatric bipolar disorder with pharmacotherapy, including the role of the pediatrician; assessing patients prior to treatment; prescribing medications to age appropriate patients; indications for pharmacotherapy (and electroconvulsive therapy); using monotherapy, medication combinations, and drugs that may destabilize patients; administering medications as part of comprehensive treatment; monitoring patient progress; the duration of an adequate drug trial; and information for patients and families. (See "Pediatric bipolar disorder and pharmacotherapy: General principles".)

MANIA

Approach to treatment — We suggest that acute treatment of pediatric mania proceed according to the sequence described in the subsections below. Patients receive initial pharmacotherapy and progress through each step until they respond. The duration of an

adequate treatment trial is discussed separately. (See "Pediatric bipolar disorder and pharmacotherapy: General principles", section on 'Duration of an adequate trial'.)

The primary treatments that are suggested for pediatric mania, either as monotherapy or combination therapy, include:

- Second-generation antipsychotics
- Lithium

In addition, psychotherapy is nearly always indicated as an adjuvant to pharmacotherapy for pediatric bipolar disorder. (See 'Adjunctive psychotherapy' below.)

Following response to acute treatment, patients receive maintenance treatment to prevent recurrences. (See 'Maintenance pharmacotherapy' below.)

Initial drugs — Initial pharmacotherapy for pediatric mania is a second-generation antipsychotic, such as aripiprazole, asenapine, olanzapine, quetiapine, risperidone, or ziprasidone. The efficacy and tolerability of these drugs has been established in many studies, including 10 randomized trials [7-16]. As an example, an eight-week open-label trial in youth with mania or mixed mania (n = 279) found that improvement was greater with risperidone, compared with either lithium or divalproex [7]. Based upon randomized trials, clinicians can expect that remission with second-generation antipsychotics will occur in approximately 25 to 70 percent of patients, and response (eg, reduction of baseline symptoms ≥50 percent) in 50 to 90 percent [7-16]. The use of second-generation antipsychotics for mania is consistent with multiple treatment guidelines [1,17-19] as well as common clinical practice [20].

No head-to-head randomized trials have compared different second-generation antipsychotics in children and adolescents with mania; across separate trials, the clinical effect of these drugs appears to be comparable [21]. The specific choice thus depends on factors such as past response to medications, side effect profiles, comorbidities, potential drug-drug interactions, patient preference, and cost. As an example [19,22]:

- Extrapyramidal symptoms may occur less often with quetiapine or olanzapine than other atypical antipsychotics, such as risperidone.
- Hyperprolactinemia may occur more often with risperidone than other second-generation antipsychotics.
- Metabolic side effects, such as weight gain and hyperlipidemia, appear to be more pronounced with olanzapine than other atypical antipsychotics, and least likely to occur in ziprasidone.

- Patients with risk factors for or a history of cardiac disease generally do not receive ziprasidone because the drug may prolong the QTc interval.

The efficacy, administration, monitoring, and side effects of second-generation antipsychotics in pediatric mania are discussed separately. (See "Pediatric mania and second-generation antipsychotics: Efficacy, administration, and side effects".)

For pediatric patients with mania who do not respond to treatment with one antipsychotic within four to eight weeks of starting treatment, or do not tolerate the drug, we suggest tapering and discontinuing the failed medication over one to two weeks, and simultaneously starting and titrating up another second-generation antipsychotic. (Response is defined as substantial improvement in the number, intensity, and frequency of symptoms.) The failed medication is generally tapered by the same amount for each dose decrease. As an example, quetiapine 300 mg per day is decreased by 50 mg per day, every one to three days. We generally attempt two or three trials of antipsychotics before proceeding to next-step treatment.

Treatment-resistant patients — Pediatric mania often does not respond to multiple (eg, two to three) trials of second-generation antipsychotics. For these treatment-resistant patients, we suggest lithium. For patients who responded partially to initial treatment with an antipsychotic, we add lithium to the antipsychotic. For patients who demonstrate little or no response to antipsychotics, we taper and discontinue the antipsychotic over one to two weeks, and at the same time start lithium and titrate the dose up.

Prior to starting lithium, clinicians should obtain laboratory tests that include blood urea nitrogen, creatinine, electrolytes, thyrotropin (thyroid stimulating hormone), and an electrocardiogram [1,22]. These tests establish a baseline for monitoring lithium's long-term effects upon the kidneys, thyroid gland, and heart, and ruling out contraindications to using lithium. These long-term side effects and contraindications are discussed separately. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects".)

Females of childbearing potential should be informed of lithium's teratogenic effects, and a urine pregnancy test should be obtained prior to initiating lithium and whenever there is a possibility that a patient is pregnant [1,23]. (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Lithium'.)

Lithium is often started in children and adolescents at a dose of 30 mg/kg/day, in two or three divided doses [24,25]. However, a reasonable alternative is to initiate treatment at 15 to 25

mg/kg/day in patients who are concerned about side effects. Another alternative in youth weighing <30 kg is to initiate lithium at a dose of 300 mg twice daily, and in youth weighing ≥30 kg to start treatment at a dose of 300 mg three times per day [26,27].

Lithium serum concentrations are measured after the first week of treatment, and doses are titrated up by 300 mg/day every four to seven days, depending upon response and tolerability, as well as serum levels. The target serum concentration is 0.6 to 1.4 mEq/L (0.6 to 1.4 mmol/L) [22,23]. Serum levels at the higher end of the target range appear to provide better symptom control, but also cause more adverse effects. Doses of immediate release preparations ≥900 mg/day are administered in three divided doses, and doses <900 mg/day in two divided doses; clinicians should attempt to avoid prescribing more than 900 mg at any one time because the tolerability of high single doses is frequently poor. Extended-release preparations are usually given twice per day, but can be administered once daily.

Lithium serum concentrations are measured four to seven days after each dose change [22]. Lithium levels are drawn approximately 12 hours after the last dose (12-hour serum trough level), and generally collected in the morning before the first dose of the day. However, levels drawn 11 to 13 hours after the last dose, or even 10 to 14 hours, provide meaningful information. By contrast, serum levels drawn a few hours after lithium ingestion provide less meaningful information.

After a stable lithium dose is achieved, we repeat the blood urea nitrogen, creatinine, electrolytes, thyrotropin, and electrocardiogram [1,22,23]. Subsequently, lithium serum concentrations, blood urea nitrogen, creatinine, and thyrotropin are measured every three to six months.

The most common side effects of lithium in children and adolescents are gastrointestinal (such as pain, diarrhea, nausea, and vomiting) [22,23,27]. Other side effects can include an acne-like rash, tremor, sedation, slowed mentation, hypothyroidism, weight gain, polyuria, polydipsia, and possible structural renal changes from long-term use. As an example, a randomized trial found that between baseline and week 8, the prevalence of abdominal pain in patients treated with lithium (n = 84) increased from 6 to 41 percent of patients [7]. In addition, excessive thirst increased from 4 to 44 percent of patients, mean serum concentration of thyrotropin more than doubled (from 2 to 5 mU/L), and patients gained an average of 1.4 kg. (However, another eight-week trial found that weight gain with lithium and placebo was comparable [27].) It may be possible to ameliorate adverse gastrointestinal effects by administering the drug with food, dividing the dose more frequently (eg, four doses per day), or using extended-release or liquid citrate formulations [22]. Hypothyroidism is managed by adding levothyroxine or switching from lithium to a different drug. Additional information about adverse effects is discussed

separately in the context of adults. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Managing lithium adverse effects' and "Renal toxicity of lithium" and "Lithium and the thyroid".)

The serum concentration of lithium is regularly monitored because lithium has a narrow therapeutic index, which means that the dose at which it is clinically effective is only slightly lower than the dose at which it becomes toxic. The symptoms and management of lithium toxicity are discussed separately. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Lithium toxicity' and "Lithium poisoning".)

In addition, lithium levels must be closely monitored in patients taking medications that change renal function, salt balance, or water balance; these medications can alter lithium excretion and serum lithium concentrations. Drug interactions with lithium are discussed separately. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Drug interactions with lithium'.)

Children and adolescents with gastrointestinal infections can get dehydrated, which places them at risk for lithium toxicity. It usually is best to hold lithium until patients can retain fluids. In addition, youth taking lithium should be encouraged to maintain adequate fluid intake during hot weather or heavy exercise.

Evidence supporting the use of lithium includes randomized trials [28]:

- An eight-week trial compared lithium with placebo in youth (ages 7 to 17 years) with a manic or mixed episode (n = 81) [27]. The mean lithium serum concentration at study endpoint was 0.98 mEq/L (0.98 mmol/L). Response (much or very much improved) occurred in more patients treated with lithium than placebo (47 versus 21 percent).

- A six-week trial compared lithium (target serum concentration 0.9 to 1.3 mEq/L [0.9 to 1.3 mmol/L]) with placebo in adolescents with either bipolar disorder (n = 17) or unipolar major depression (n = 8) [29]. All patients had comorbid substance use disorders (eg, alcohol and cannabis) and received psychotherapy. Response (partial or complete resolution of mood and substance use disorder symptoms) occurred in more patients treated with lithium than placebo (6 in 13 versus 1 in 12 [46 versus 8 percent]). However, the results are limited by the small sample size and diagnostic heterogeneity, and the study did not specify whether bipolar patients were manic or depressed.

- A six-week, open-label trial randomly assigned children and adolescents with hypomania or mania (n = 41) to lithium (target serum concentration 0.8 to 1.2 mEq/L [0.8 to 1.2

mmol/L]), carbamazepine (target serum concentration 7 to 10 mcg/L), or divalproex (target serum concentration 85 to 110 mcg/L) [24]. Response (reduction of baseline symptoms ≥50 percent) was comparable in patients treated with lithium (5 in 13, 38 percent), carbamazepine (5 in 13, 38 percent), or divalproex (8 in 15, 53 percent). The lack of a placebo arm makes it difficult to interpret the results, as does the small sample size and lack of blinding.

Indirect evidence of lithium's efficacy for pediatric mania includes randomized trials in adults with mania. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'First-line monotherapy'.)

Treatment-refractory patients — Pediatric mania often does not respond to second-generation antipsychotics and lithium. For these refractory patients, we suggest medication combinations. For patients who are refractory to monotherapy trials with second-generation antipsychotics and lithium, we suggest combining a second-generation antipsychotic with lithium. The antipsychotic is selected from amongst those that were not previously prescribed during the initial monotherapy trials. For patients who received an antipsychotic plus lithium and did not respond sufficiently, we suggest tapering and discontinuing the antipsychotic, and simultaneously starting and titrating up a different second-generation antipsychotic.

Evidence supporting the use of medication combinations includes an eight-week, open-label randomized trial in youth with mania (n = 65) who had partially responded to monotherapy with risperidone, lithium, or divalproex [30]. Patients were randomly assigned to add-on treatment with one of the two remaining drugs. Response (much or very much improved from baseline) occurred in more patients who received either adjunctive risperidone or lithium than divalproex (53 and 27 versus 0 percent). Although the difference between risperidone and lithium was not statistically significant, a difference of this magnitude, if real, would be clinically meaningful.

Other evidence supporting the use of medication combinations includes prospective observational studies that have examined several different medication combinations in youth with mania [31-33]. Indirect evidence for the efficacy of medication combinations, such as antipsychotics plus lithium, includes multiple randomized trials in adults with mania. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Initial treatment'.)

Medication combinations should generally involve drugs from different classes [22,33-36]. Aside from second-generation antipsychotics plus lithium, other combinations that may be useful include second-generation antipsychotics plus an antiepileptic (eg, divalproex or lamotrigine),

lithium plus an antiepileptic (eg, divalproex, lamotrigine, or carbamazepine), and first-generation antipsychotics plus lithium or an antiepileptic (eg, divalproex or lamotrigine).

The efficacy, administration, and side effects of divalproex, lamotrigine, carbamazepine, and first-generation antipsychotics for pediatric mania are as follows:

- **Divalproex** – We use divalproex as an adjunctive treatment with second-generation antipsychotics or lithium [22,33,35,37]. Evidence supporting the use of add-on divalproex includes a six-week randomized trial that compared quetiapine (mean daily dose 432 mg) plus divalproex (mean serum concentration 114 mg/dL) with placebo plus divalproex in 30 adolescents [34]. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients treated with combination therapy than monotherapy (13 in 15 versus 8 in 13 [87 versus 53 percent]). However, it is not clear that quetiapine plus divalproex is any more beneficial than quetiapine alone, because quetiapine alone is superior to divalproex alone for treating pediatric mania. (See "Pediatric mania and second-generation antipsychotics: Efficacy, administration, and side effects", section on 'Quetiapine'.)

  Baseline tests before starting divalproex include a complete blood count with differential and platelets, and liver function tests [22]. Weight should also be assessed.

  Divalproex is an enteric coated formulation of valproic acid that is generally preferred because it causes fewer gastrointestinal side effects (eg, dyspepsia and abdominal pain) than preparations lacking the enteric coating [22]. The starting dose is approximately 10 to 15 mg/kg/day in two divided doses; the dose is then titrated up by 125, 250, or 500 mg/day every one to seven days, depending upon response, tolerability, and serum concentrations [7,22,38]. The serum concentration is checked approximately one week after initiating treatment and after every one or two dose increases. The target serum concentration is 50 to 125 mcg/mL. The maximum daily dose is 35 to 60 mg/day [22,38].

  Valproate levels are drawn approximately 12 hours after the last dose (12-hour serum trough level), and generally collected in the morning before the first dose of the day. However, levels drawn 11 to 13 hours after the last dose, or even 10 to 14 hours, provide meaningful information.

  Adverse effects in randomized trials of divalproex in patients with pediatric bipolar disorder included abdominal pain, drowsiness, nausea, excessive thirst, and weight gain, as well as decreased platelet count and increased serum ammonia concentration [7,38]. It may be possible to ameliorate adverse gastrointestinal effects by administering the drug with food or dividing the dose more frequently (eg, three or four doses per day) [22]. Other common side effects, as well as rare but serious effects, are listed in the tables

(table 1 and table 2), and are discussed in detail separately. (See "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Valproate'.)

Monitoring of youth treated with divalproex is discussed in the context of epilepsy. (See "Seizures and epilepsy in children: Initial treatment and monitoring", section on 'Follow-up and monitoring'.)

We generally do not use divalproex as monotherapy for pediatric mania because several randomized trials indicate that divalproex alone is not efficacious. As an example, a four-week trial compared divalproex (target serum concentration 80 to 125 mcg/mL) with placebo in 144 youth with mania, and found that improvement was comparable for the two groups [38]. In addition, multiple trials have found that second-generation antipsychotics (eg, quetiapine and risperidone) are superior to divalproex. (See "Pediatric mania and second-generation antipsychotics: Efficacy, administration, and side effects", section on 'Specific drugs'.)

- **Lamotrigine** – Prospective observational studies suggest that lamotrigine may possibly help control manic symptoms in youth [39,40]. As an example, one study enrolled patients (n = 298) who were moderately to markedly ill with an active mood episode despite treatment with pharmacotherapy, such as second-generation antipsychotics, lithium, divalproex, and/or carbamazepine; patients with comorbid attention deficit hyperactivity disorder were also receiving stimulants [41]. Patients were treated with adjunctive open-label lamotrigine for up to 18 weeks, and improvement occurred in 58 percent. However, randomized trials in adults with mania indicate that lamotrigine is not effective. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Other options'.)

  Lamotrigine is started at a low dose and titrated up slowly to reduce the risk of serious and life-threatening skin rash. In one study, the starting dose was 12.5 mg/day for week 1 [40]. The dose was then increased by 12.5 mg/week for the next three weeks and subsequently by 25 mg/week. For patients weighing ≤30 kg, the target dose was 150 mg/day, and for patients >30 kg the target dose was 200 mg/day; the dose titration occurred over eight weeks. The daily dose is taken in two divided doses once the dose titration commences [39].

  Observational studies of patients with pediatric bipolar disorder have found that common side effects of lamotrigine included nausea, dyspepsia, sedation, and nonserious skin rash [39,40]. Other common side effects, as well as rare but serious effects, are listed in the

tables (table 1 and table 2), and are discussed in detail separately. (See "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Lamotrigine'.)

Monitoring of youth treated with lamotrigine is discussed in the context of epilepsy. (See "Seizures and epilepsy in children: Initial treatment and monitoring", section on 'Follow-up and monitoring'.)

- **Carbamazepine** – Evidence for the efficacy of carbamazepine in pediatric mania includes a six-week, open-label trial that randomly assigned children and adolescents with hypomania or mania (n = 41) to carbamazepine (target serum concentration 7 to 10 mcg/L), lithium (target serum concentration 0.8 to 1.2 mEq/L [0.8 to 1.2 mmol/L]), or divalproex (target serum concentration 85 to 110 mcg/L) [24]. Response was comparable with each drug. Additional evidence comes from observational studies in children and adolescents [42-44], as well as randomized trials in adults. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'First-line monotherapy'.)

  Carbamazepine is often not combined with antipsychotics, based upon randomized trials in adults that found this combination is no more efficacious than carbamazepine alone [45,46]. Carbamazepine induces hepatic enzymes that metabolize antipsychotics [22], and in one trial lowered the antipsychotic serum concentration by 40 percent [46].

  Before starting carbamazepine, baseline tests include a complete blood count with differential and platelets, blood urea nitrogen, creatinine, electrolytes, liver enzymes, and a urine pregnancy test [22]. The starting dose of carbamazepine is approximately 15 mg/kg/day, in three divided doses. Serum concentrations are measured after one week, and the dose is adjusted to achieve a serum concentration of 4 to 12 mcg/mL [22].

  Common side effects with carbamazepine (table 1) include nausea and sedation [22]. Other side effects include blurred vision, ataxia, elevated liver enzymes, mild leukopenia, and thrombocytopenia. Rare but serious adverse effects (table 2) include aplastic anemia and agranulocytosis. (See "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Carbamazepine'.)

  In addition, carbamazepine may induce hypersensitivity reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis; these reactions are increased in patients with specific alleles (eg, HLA-B*1502 allele). Additional information about the association of carbamazepine induced hypersensitivity reactions with specific alleles and the role of genotyping is discussed separately in the context of pediatric epilepsy. (See

"Seizures and epilepsy in children: Initial treatment and monitoring", section on 'Role of pretreatment HLA testing'.)

Monitoring of youth treated with carbamazepine is also discussed in the context of epilepsy. (See "Seizures and epilepsy in children: Initial treatment and monitoring", section on 'Follow-up and monitoring'.)

- **First-generation antipsychotics** – First-generation antipsychotics (eg, haloperidol 2 to 5 mg/day) may possibly help pediatric mania, but also cause extrapyramidal symptoms, based upon indirect evidence from randomized trials of youth with psychotic disorders [47,48] and adults with mania, as well as observational studies in juvenile psychotic mania [49]. First-generation antipsychotics are generally not combined with second-generation antipsychotics.

  The efficacy of first-generation antipsychotics for mania in adults is discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'First-line monotherapy'.)

Additional information about medication combinations is discussed separately. (See "Pediatric bipolar disorder and pharmacotherapy: General principles", section on 'Medication combinations'.)

Other options — Pediatric mania may be refractory to numerous (eg, 8 to 10) medication trials. Treatment options include:

- **Clozapine** – Pediatric mania may respond to clozapine, but it is typically not used due to concerns about side effects, including agranulocytosis, myocarditis, and seizures [1]. The efficacy, administration, and side effects of clozapine are discussed separately. (See "Pediatric mania and second-generation antipsychotics: Efficacy, administration, and side effects", section on 'Clozapine'.)

- **Electroconvulsive therapy** – Electroconvulsive therapy (ECT) may be beneficial for severe, persistent, and significantly disabling pediatric mania that is refractory to pharmacotherapy, especially episodes with psychosis or catatonia. This approach is consistent with treatment guidelines [50,51]. ECT is used infrequently for adolescents and rarely for younger children [52]. Evidence supporting the use of ECT includes retrospective studies in youth [51,53-55], as well as randomized trials in adult mania. (See "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy", section on 'Mania'.)

Agitation, anxiety, extrapyramidal symptoms, or sleeplessness — In multiple randomized trials that studied drugs such as second-generation antipsychotics, adjunctive medications were used to manage a variety of persistent problems, such as [8-12,14,34]:

- **Agitation**
  - Benzodiazepines (eg, lorazepam 1 to 4 mg/day in two to four divided doses)
  - Diphenhydramine 25 to 50 mg two to three times per day
  - Hydroxyzine 50 to 100 mg per day in four divided doses
- **Anxiety** – The symptom of anxiety is treated with:
  - Benzodiazepines
  - Hydroxyzine

  Treatment of comorbid anxiety disorders is discussed elsewhere in this topic. (See 'Anxiety disorders' below.)
- **Extrapyramidal symptoms**
  - Benztropine 1 to 2 mg/day in two divided doses
  - Diphenhydramine
  - Benzodiazepines
- **Sleeplessness**
  - Melatonin
  - Diphenhydramine
  - Benzodiazepines

Nonstandard drugs that are possibly beneficial — Drugs that are possibly helpful for mania, but lack conclusive evidence due to small samples and/or mixed results, include the following:

- **Omega-3 fatty acids**
  - A 16-week randomized trial compared linolenic acid (an omega-3 fatty acid, target dose 6.6 grams/day) with placebo as adjunctive pharmacotherapy or monotherapy in 51

youth with symptomatic bipolar disorder (primarily mania with mixed features) [56]. Improvement was comparable for both groups.

- A trial randomly assigned children with bipolar spectrum disorders, aged 5 to 12 years, to one of three treatments: omega-3 fatty acids plus placebo, inositol plus placebo, or omega-3 fatty acids plus inositol [57]. Improvement (much or very much) of manic and depressive symptoms was greater with combination treatment than either monotherapy; the benefit of omega-3 fatty acids alone and inositol alone was comparable.

- A 12-week randomized trial compared omega-3 fatty acids plus active monitoring with placebo plus active monitoring in 11 youth with subsyndromal bipolar disorder [58]. Two rating scales were used to assess mania and each showed that improvement did not differ statistically between the two groups; nevertheless, one of the scales showed that manic symptoms decreased more with omega-3 fatty acids than placebo and the clinical benefit was large.

- **Celecoxib** – An eight-week randomized trial compared celecoxib (100 mg twice per day) with placebo as adjunctive treatment in adolescents (n = 40) hospitalized for mania and treated with lithium plus risperidone [59]. Improvement was greater with adjunctive celecoxib than placebo, but remission was comparable (85 and 60 percent). Adverse events in the two groups were comparable.

- **Ketamine** – A retrospective study included 39 youth with bipolar disorder, who did not respond to standard medications such as lithium and second-generation antipsychotics, and were treated with adjunctive intranasal ketamine (mean dose 165 mg, once every two to five days) for a mean of 1.7 years [60]. Improvement (much or very much) occurred in 87 percent. Most patients experienced dizziness, impaired gait, and/or nasal discomfort, which lasted less than one hour. Persistent adverse effects included pain on urination in five patients (12 percent).

- **Topiramate** – In a four-week randomized trial that compared topiramate (mean daily dose 278 mg) with placebo in 56 children and adolescents with mania, improvement did not differ statistically between the two groups; nevertheless, manic symptoms decreased more in the topiramate group and the clinical benefit was moderate [61]. The study was underpowered because it was prematurely terminated after multiple studies of topiramate in adult mania found negative results. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Other options'.)

Drugs with little to no benefit — A seven-week randomized trial that compared oxcarbazepine (mean dose 1515 mg/day) with placebo in 110 youth with mania found that improvement was comparable for both groups [62].

MANIA WITH MIXED FEATURES

For pediatric mania with mixed features (depressive symptoms), we suggest second-generation antipsychotics as first-line therapy. Evidence for the efficacy of this approach includes a randomized trial that compared quetiapine (600 mg/day) with placebo in 184 youth with mania; improvement of depressive symptoms was greater with active drug [14]. In addition, many of the randomized trials that established the efficacy of second-generation antipsychotics for pediatric mania included a substantial number of patients with mixed features at baseline [9,10]. As an example:

- In an eight-week trial (n = 279 youth with mania) that found risperidone was superior to lithium or divalproex, mixed features were present in 98 percent [7]. Depressive symptoms improved more quickly with risperidone and depressive symptoms were much or very much improved in more patients taking risperidone than lithium or divalproex (61 versus 42 and 35 percent) [63].

- A four-week trial found that ziprasidone was superior to placebo for treating mania in 237 children and adolescents [15]. Mixed features were present in 62 percent.

- One trial compared aripiprazole with placebo in 296 manic pediatric patients; mixed features were present in 42 percent [8].

Treatment studies of mania with and without mixed features have generally not found differences in response based upon episode subtype (although differences may not have been examined or there was insufficient power to adequately evaluate subtype effects). A review that examined the benefit of second-generation antipsychotics for pediatric mania with mixed features in prospective observational studies found that improvement of depressive symptoms occurred in 36 to 60 percent of patients [64].

For pediatric mania with mixed features that does not respond to monotherapy with one second-generation antipsychotic, we suggest switching to another atypical antipsychotic by tapering and discontinuing the failed antipsychotic over one to two weeks and simultaneously starting and titrating up a different antipsychotic. For patients unresponsive to multiple (eg, two to three) trials of a second-generation antipsychotic, subsequent treatment is similar to mania without mixed features. (See 'Treatment-resistant patients' above.)

Electroconvulsive therapy (ECT) may be beneficial for severe, persistent, and significantly disabling pediatric mania with mixed features that is refractory to multiple (eg, at least five) pharmacotherapy trials. This approach is consistent with treatment guidelines [50,51]. ECT is used infrequently for adolescents and rarely for younger children [52]. We use ECT prior to a trial of clozapine for mania with mixed features. Evidence supporting the use of ECT includes retrospective studies in youth [51,53-55], as well as randomized trials in adult mania. (See "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy", section on 'Mania'.)

MANIA WITH PSYCHOTIC FEATURES

For pediatric patients with mania with psychotic features (eg, delusions, hallucinations, or grossly disorganized behavior or thinking), we suggest second-generation antipsychotics. We generally select risperidone or quetiapine, but reasonable alternatives include aripiprazole, olanzapine, or ziprasidone. Evidence for the efficacy of this approach includes the following:

- In an eight-week study, 215 youth with psychotic mania were randomly assigned to receive risperidone (mean dose 2.6 mg/day), lithium (mean serum concentration 1.1 mEq/L [1.1 mmol/L]), or divalproex (mean serum concentration 114 mcg/mL) [7]. Response (much or very much improved from baseline) occurred in more patients who received risperidone than lithium or divalproex (69 versus 33 and 25 percent); lithium and divalproex were comparable.

- A four-week randomized trial compared quetiapine (400 to 600 mg/day) with divalproex (serum concentration 80 to 120 mcg/mL) for mania with psychotic features in 23 patients, and found that response (much or very much improved) occurred in more patients treated with quetiapine than divalproex (6 in 11 versus 1 in 12 [55 versus 8 percent]) [9].

For patients with psychotic mania who do not respond to monotherapy with one second-generation antipsychotic, we suggest switching to another atypical antipsychotic by tapering and discontinuing the failed antipsychotic over one to two weeks and simultaneously starting and titrating up a different antipsychotic.

For patients unresponsive to multiple (eg, two to three) trials of second-generation antipsychotic monotherapy, we suggest adding lithium [22]. A prospective observational study found that in adolescents with mania with psychotic features (n = 35) who received an antipsychotic plus lithium, improvement (much or very much) occurred in 18 patients (51

percent) [49]. Reasonable alternatives to lithium include adjunctive divalproex or lamotrigine. (See 'Treatment-refractory patients' above.)

Additional information about medication combinations is discussed separately. (See "Pediatric bipolar disorder and pharmacotherapy: General principles", section on 'Medication combinations'.)

Electroconvulsive therapy (ECT) may be beneficial for severe, persistent, and significantly disabling pediatric mania with psychotic features that is refractory to multiple (eg, at least five) pharmacotherapy trials. This approach is consistent with treatment guidelines [50,51]. ECT is used infrequently for adolescents and rarely for younger children [52]. We use ECT prior to a trial of clozapine for mania with psychotic features. Evidence supporting the use of ECT includes retrospective studies in youth [51,53-55], as well as randomized trials in adult mania. (See "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy", section on 'Mania'.)

An investigational drug for psychosis in patients with bipolar disorder is ketamine. In a retrospective study of pediatric mania with psychotic features (n = 12), which was refractory to antipsychotics, lithium, and anticonvulsants, intranasal ketamine appeared to be helpful [65].

HYPOMANIA

Despite clinical differences between hypomania and mania, for the purpose of treatment they are considered to be similar and thus treated with the same medications (see 'Mania' above). As an example, in a six-week randomized trial that assigned carbamazepine, divalproex, or lithium to children and adolescents with bipolar disorder (n = 42), 52 percent presented with hypomania [24]. In addition, a 12-week prospective observational study of patients diagnosed with other specified bipolar and related disorder or cyclothymic disorder found that hypomanic symptoms responded to quetiapine (mean dose approximately 450 mg/day) [66]. Treating pediatric hypomania and pediatric mania with the same medications is consistent with treatment guidelines [17,18].

SUBSYNDROMAL SYMPTOMS

Subsyndromal symptoms that do not meet diagnostic criteria for mania or hypomania, but nevertheless impair functioning, are treated with the same medications that are used to treat mania. (See 'Mania' above.)

RAPID CYCLING

We suggest second-generation antipsychotics (eg, risperidone) for treating children and adolescents with rapid cycling mood episodes, which is consistent with treatment guidelines [18]. Evidence supporting this approach includes randomized trials that established the efficacy of second-generation antipsychotics for mania, and included patients whose mood episode occurred in the context of a rapid cycling course. As an example [8]:

- One trial found that risperidone was superior to divalproex in 65 patients, and rapid cycling was present at baseline in 81 percent [11].
- In a trial (n = 144 youth) that found olanzapine was superior to placebo, rapid cycling at baseline was present in 21 percent [12].

However, neither trial examined the efficacy of the antipsychotic specifically in the subgroup with rapid cycling.

The efficacy of second-generation antipsychotics for pediatric mania is discussed separately. (See "Pediatric mania and second-generation antipsychotics: Efficacy, administration, and side effects", section on 'Specific drugs'.)

MAJOR DEPRESSION

Bipolar major depression in children and adolescents is typically treated with pharmacotherapy and psychotherapy. (See "Pediatric bipolar major depression: Choosing treatment".)

COMORBID DISORDERS

Comorbidity, including attention deficit hyperactivity disorder (ADHD) or anxiety disorders, is common in pediatric bipolar disorder. (See "Pediatric bipolar disorder: Clinical manifestations and course of illness", section on 'Comorbidity'.)

Attention deficit hyperactivity disorder — For children and adolescents with bipolar disorder and comorbid ADHD, we suggest initially prescribing a second-generation antipsychotic, based upon randomized trials:

- An eight-week open-label trial randomly assigned risperidone (mean dose 2.6 mg/day), lithium (mean serum concentration 1.1 mEq/L [1.1 mmol/L]), or divalproex (mean serum

concentration 114 mcg/mL) to youth with mania or mixed mania; among the 279 study patients, comorbid ADHD was present in 93 percent [7]. Response (mania much or very much improved from baseline) occurred in more patients who received risperidone than lithium or divalproex (69 versus 36 and 24 percent).

- A four-week trial compared aripiprazole (target dose either 10 mg/day or 30 mg/day) with placebo in patients with mania (n = 296), including 153 (52 percent) with comorbid ADHD. Remission of mania occurred in more patients who received aripiprazole 10 mg or 30 mg than placebo (25 and 48 versus 5 percent) [8]. In addition, improvement of ADHD symptoms was greater with either dose of active drug than placebo.

However, second-generation antipsychotic monotherapy that is beneficial for pediatric mania may not help comorbid ADHD. As an example, a six-week trial compared aripiprazole with placebo in manic patients with comorbid ADHD (n = 43) [13]. Although remission of mania occurred in more patients treated with aripiprazole than placebo (72 versus 32 percent), improvement of ADHD was comparable for the two groups.

For patients with pediatric mania that responds to a second-generation antipsychotic, and comorbid ADHD that does not, we suggest a stimulant as add-on treatment [22]. We prefer once a day stimulant formulations. The use of stimulants in conjunction with antimanic drugs for pediatric patients with coexisting mania and ADHD is consistent with treatment guidelines [50], as well as common clinical practice [7,14,41]. In addition, stimulants are first-line treatment for children and adolescents with a primary diagnosis of ADHD. (See "Attention deficit hyperactivity disorder in children and adolescents: Treatment with medications".)

Stimulants should be started at a low dose and titrated up slowly in youth with bipolar disorder, and patients or families should contact their clinicians if irritability, mood lability, agitation, or other mood symptoms ensue [67]. Although randomized trials [68,69] and prospective observational studies [70,71] indicate that stimulants do not cause treatment emergent mania, other studies have raised persistent concerns that stimulants may possibly destabilize patients [67,70,72]. (However, it is important to note that mood elevated syndromes are intrinsic to bipolar disorder and frequently occur in the absence of stimulants.)

Evidence for the efficacy of adjunctive stimulants in euthymic patients with active symptoms of comorbid ADHD includes the following:

- A study compared amphetamines (5 mg twice/day) plus divalproex with placebo plus divalproex in youth with bipolar disorder and comorbid ADHD (n = 30) [68]. The patients' manic symptoms had initially responded to open-label divalproex, but the ADHD symptoms had not. Patients were randomly assigned to adjunctive amphetamines or

placebo for two weeks, and then crossed over to the other adjunctive treatment for another two weeks. Improvement of ADHD was greater during treatment with adjunctive amphetamines, and the stimulant did not appear to exacerbate manic symptoms.

- A second randomized crossover trial lasting four weeks compared add-on methylphenidate (5 to 15 mg twice/daily) with placebo in children and adolescents with bipolar disorder plus ADHD (n = 16); the patients were taking either lithium or divalproex and were euthymic, but continued to have symptoms of ADHD [69]. Improvement of ADHD was greater with adjunctive methylphenidate, and the stimulant did not appear to worsen mood symptoms.

However, a third crossover trial lasting four weeks compared adjunctive methylphenidate with placebo in youth with bipolar disorder and ADHD (n = 14), whose mood symptoms were stable on aripiprazole [73]. Improvement of ADHD was comparable for both groups.

Anxiety disorders — Based upon randomized trials in patients with a primary diagnosis of an anxiety disorder [74,75], we suggest cognitive-behavioral therapy (CBT) as first-line treatment of comorbid anxiety disorders in youth with bipolar disorder. This approach is consistent with treatment guidelines [50]. However, no randomized trials have examined the treatment of anxiety disorders (eg, generalized anxiety disorder or panic disorder) in youth with bipolar disorder.

For patients who do not have access to CBT, do not respond to CBT, or who decline CBT, we suggest other psychotherapies, such family therapy or psychodynamic psychotherapy [74]. If psychotherapy is not beneficial, we suggest adjunctive treatment with a selective serotonin reuptake inhibitor, based upon randomized trials of patients with a primary diagnosis of an anxiety disorder [75], as well as clinical experience with bipolar youth [67]. Antidepressants as monotherapy may destabilize patients with bipolar disorder and should thus be prescribed in conjunction with an antimanic drug [70]. (See "Pediatric bipolar major depression: Choosing treatment", section on 'Using antidepressants'.)

Benzodiazepines are occasionally used to treat comorbid anxiety in pediatric bipolar disorder [50]. However, these drugs are used only for short-term (eg, two weeks) management, because of their potential for abuse and adverse cognitive effects.

MAINTENANCE PHARMACOTHERAPY

For children and adolescents with an acute bipolar mood episode that responds to pharmacotherapy, we suggest continuing the same treatment to prevent recurrences, unless

the regimen is poorly tolerated. This approach is consistent with treatment guidelines and reviews [1,23,50].

Evidence for the efficacy of maintenance treatment in pediatric bipolar disorder includes randomized trials:

- A 72-week randomized trial compared aripiprazole (mean daily dose 0.26 mg/kg) with placebo in children with bipolar disorder who initially responded to acute phase treatment with aripiprazole (n = 60) [76]. Time to recurrence of a mood episode was greater with active drug than placebo (26 versus 3 weeks). However, weight gain was greater with aripiprazole than placebo (2.6 versus 0.4 kg), as was the incidence of stomach pain and musculoskeletal pain.

- A study initially recruited patients with an active mood episode despite treatment with pharmacotherapy, such as second-generation antipsychotics, lithium, divalproex, and/or carbamazepine; patients with comorbid ADHD were also receiving stimulants [41]. Patients were treated with adjunctive open-label lamotrigine, and those who stabilized (n = 173) were randomly assigned to continue lamotrigine or to taper lamotrigine and substitute placebo. Patients were followed for up to 36 weeks. After controlling for patient age and sex, type of index mood episode, and use of antipsychotics and stimulants, time to recurrence of a mood episode was longer with adjunctive lamotrigine than placebo (hazard ratio 0.63).

There is no indication from head-to-head trials that any drug is superior for maintenance treatment. As an example, a 76-week randomized trial compared lithium monotherapy with divalproex monotherapy in children and adolescents who initially responded to acute phase treatment with the combination of lithium plus divalproex (n = 60) [77]. The median time to recurrence with lithium monotherapy and divalproex monotherapy was comparable (approximately 16 weeks).

We suggest that patients with psychotic features who respond to combination treatment, such as a second-generation antipsychotic plus lithium, continue both drugs for at least two to six months [49]; combination treatment longer than six months is suggested for patients who were severely ill (eg, attempted suicide) during the index episode or patients whose prior history indicates the need for maintenance treatment with multiple medications. Patients who remain stable on combination treatment can eventually attempt to gradually taper and discontinue lithium (see 'Discontinuation' below). Patients should subsequently maintain treatment with the second-generation antipsychotic.

Pediatric bipolar major depression may respond to an acute regimen that includes an antidepressant. The use of antidepressants in maintenance treatment is discussed separately. (See "Pediatric bipolar major depression: Choosing treatment", section on 'Using antidepressants'.)

Duration — Following recovery from acute bipolar mood episodes, we suggest that children and adolescents continue treatment for at least one to two years. This approach is consistent with practice guidelines [1,50].

Although the duration of maintenance treatment varies among patients, some patients require maintenance treatment for many years, and some patients require it their entire lives [1,50]. Factors to consider include prior response to medication discontinuation, how many years the patient has had bipolar disorder, and the lifetime number and severity of mood episodes. Maintenance treatment should last longer for patients with a more severe course of illness. Although intolerable side effects may truncate maintenance treatment altogether, clinicians should first try to find better tolerated alternatives.

Some patients are discouraged by the prospect of taking their medication "forever." In such cases, it is important to emphasize the long-term nature of the relationship between the clinician and patient, and that the need for maintenance treatment will periodically be reevaluated in light of the patient's progress in maintaining symptomatic and functional stability. It may also help to point out that other chronic illnesses such as diabetes mellitus and asthma often require life-time medications.

Discontinuation — Patients with pediatric bipolar disorder may want to stop maintenance medications because of side effects, inadequate benefits, general medical illnesses, pregnancy, or a wish to be medication-free after a prolonged period of euthymia. However, studies of adult patients suggest that discontinuing stable treatment usually leads to a new mood episode. (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Discontinuation'.)

Other risks of stopping maintenance treatment include hospitalization, persistent subsyndromal symptoms, family and economic losses, and suicide. Psychoeducation may help discourage patients from discontinuing effective maintenance treatment. (See "Pediatric bipolar disorder: Efficacy and core elements of adjunctive psychotherapy", section on 'Psychoeducation' and "Bipolar disorder in adults: Managing poor adherence to maintenance pharmacotherapy", section on 'Consequences'.)

If patients insist on stopping treatment, we suggest slowly tapering the medication; based upon clinical experience, the drug is tapered over a period of several months (at least four to six months) unless negative effects dictate a more rapid taper. For patients who are taking multiple

medications, we slowly taper and discontinue one drug at a time [36]. The first drug to be removed is generally the adjuvant; if both drugs are considered essential, the first drug to be stopped is the one most likely to cause side effects with long-term use.

During the process of tapering and discontinuing pharmacotherapy, clinicians should monitor patients regularly (eg, every two to four weeks) for prodromal symptoms of recurrence [1]. Prospective observational studies in adults show that tapering maintenance medication more slowly is associated with lower rates of recurrence, but that most patients suffer a recurrence despite the slower taper. Patients and families should be educated about the symptoms of relapse and counseled to quickly seek clinical attention if they occur.

ADJUNCTIVE PSYCHOTHERAPY

Psychotherapy is nearly always indicated as an adjuvant to pharmacotherapy for pediatric bipolar disorder, and prescribing psychotherapy is consistent with practice guidelines [1,17,18]. If symptoms are not responding adequately to treatment, the frequency and/or intensity of psychotherapy is increased (multiple visits per week, intensive outpatient program, or partial hospitalization program). However, severe symptoms (eg, agitation, psychosis, or psychomotor retardation) may delay onset of psychotherapy.

First line — For pediatric bipolar disorder, we suggest psychoeducation as adjunctive psychotherapy with pharmacotherapy, based upon a randomized trial that found mood symptoms improved more with psychoeducation plus usual care than usual care alone [78]. In addition, another trial compared 3 sessions of psychoeducation with 21 sessions of family psychotherapy in adolescents with bipolar disorder who were treated with pharmacotherapy and followed for up to two years after study entry (n = 145) [79]. Both time to recovery from a mood episode and time to recurrence were comparable for the two groups, despite the disparity in number of sessions. (See "Pediatric bipolar disorder: Efficacy and core elements of adjunctive psychotherapy", section on 'Psychoeducation'.)

Second line — For pediatric bipolar disorder that does not respond to adjunctive psychoeducation, we suggest adjunctive family therapy, based upon randomized trials. As an example, a trial compared family psychotherapy with psychotherapy as usual (control) in 69 acutely symptomatic children receiving pharmacotherapy [80]. Both groups received 12 weekly sessions. Reduction of manic and depressive symptoms was greater with family therapy. (See "Pediatric bipolar disorder: Efficacy and core elements of adjunctive psychotherapy", section on 'Family therapy'.)

Other options — Family therapy as add-on treatment with pharmacotherapy may not be effective or available, or may be declined by patients and/or families. Other psychotherapy options include dialectical behavior therapy, cognitive-behavioral therapy, interpersonal and social rhythm therapy, and motivational interviewing. (See "Pediatric bipolar disorder: Efficacy and core elements of adjunctive psychotherapy".)

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 AND FAMILIES

Information for patients and families that can be printed and given to patients and families is discussed separately. (See "Pediatric bipolar disorder and pharmacotherapy: General principles", section on 'Information for patients and families'.)

SUMMARY AND RECOMMENDATIONS

- **Overview** – The mainstay of treatment for bipolar disorder in children and adolescents is pharmacotherapy. In addition, adjunctive psychotherapy is generally regarded as essential. (See 'Introduction' above.)
- **Setting** – Level of care and frequency of visits and monitoring are increased during periods of symptom exacerbation or elevated risk for suicidal or dangerous behavior. (See 'Setting' above.)
- **Mania**
  - **Initial drugs** – For pediatric patients with mania, we recommend a second-generation antipsychotic as first line pharmacotherapy, rather than other drugs (**Grade 1B**). Aripiprazole, asenapine, olanzapine, quetiapine, risperidone, and ziprasidone are the best studied options; the specific choice depends on factors such as past response to medications and side effect profiles. If patients do not respond to one antipsychotic or do not tolerate the drug, we taper and discontinue the failed medication over one to two weeks, and simultaneously start and titrate up another antipsychotic. (See 'Initial drugs' above.)

- **Treatment-resistant patients** – Pediatric mania often does not respond to treatment with multiple (eg, two to three) trials of second-generation antipsychotics. For these treatment-resistant patients, we suggest lithium rather than other drugs (**Grade 2B**). (See 'Treatment-resistant patients' above.)

- **Treatment-refractory patients** – Pediatric mania that does not respond to second-generation antipsychotics and lithium is typically managed with medication combinations that involve drugs from different classes, such as a second-generation antipsychotic plus lithium. Other potentially useful combinations include a second-generation antipsychotic plus divalproex or lamotrigine; or lithium plus divalproex, lamotrigine, or carbamazepine. (See 'Treatment-refractory patients' above.)

- **Bipolar major depression** – Bipolar major depression in children and adolescents is typically treated with pharmacotherapy and psychotherapy. (See "Pediatric bipolar major depression: Choosing treatment".)

- **Mania plus comorbid attention deficit hyperactivity disorder (ADHD)** – Pediatric bipolar disorder is often comorbid with ADHD. For children and adolescents with mania and comorbid ADHD, we suggest initially prescribing a second-generation antipsychotic, rather than other medication regimens (**Grade 2B**). If bipolar symptoms respond to a second-generation antipsychotic, and comorbid ADHD remains impairing, we suggest adding a stimulant, rather than other drugs (**Grade 2B**). (See 'Attention deficit hyperactivity disorder' above.)

- **Maintenance pharmacotherapy** – After the acute bipolar mood episode has resolved, we recommend maintenance pharmacotherapy to prevent recurrences (**Grade 1A**). We generally use the same regimen that was effective for acute treatment, provided the regimen is well tolerated. The minimum duration of maintenance treatment is generally one to two years. (See 'Maintenance pharmacotherapy' above.)

- **Choosing adjunctive psychotherapy** – Psychotherapy is nearly always indicated as an adjuvant to pharmacotherapy for pediatric bipolar disorder. For children and adolescents with bipolar disorder, we suggest psychoeducation as adjunctive psychotherapy, rather than family therapy (**Grade 2B**). Patients unresponsive to psychoeducation may benefit from family therapy. (See 'Adjunctive psychotherapy' above.)

Topic 15925 Version 8.0