



## Pediatric bipolar disorder: Treatment

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### INTRODUCTION

The mainstay of treatment for bipolar disorder in children and adolescents is pharmacotherapy [1-5]. In addition, adjunctive psychotherapy is generally regarded as essential [2-6].

In some instances, pharmacotherapy for pediatric bipolar disorder is based upon adult studies because fewer studies have been conducted in youth [7,8]. However, response to specific medications may differ between youth and adults.

More studies of pharmacotherapy for bipolar disorder have been conducted in adolescents than younger children. Nevertheless, medications can effectively treat children as well as adolescents [9-12]. Multiple randomized trials have demonstrated that medications (eg, second-generation antipsychotics) are efficacious for mania in patients as young as 10 years [13-18]. Other trials indicate that preschool and preadolescent children with bipolar disorder can respond to pharmacotherapy [17,19,20], including those age 3 to 12 years [21,22].

Although pharmacotherapy is indicated for nearly all youth with bipolar disorder, approximately one-third of patients do not receive antimanic medications, such as antipsychotics, [lithium](#), or antiseizure medications [23,24]. In addition, the wrong medication regimen is sometimes administered to children and adolescents with bipolar disorder. A retrospective study found that among 282 bipolar patients who were treated for mania with or without mixed features, antidepressant monotherapy was prescribed for 24 percent [23].

This topic reviews treatment of pediatric bipolar disorder. Other aspects of pediatric bipolar disorder are discussed separately, including the administration and side effects of second-generation antipsychotics for mania, efficacy and core elements of adjunctive psychotherapy, and the clinical features, assessment, diagnosis, and course of illness:

- (See "[Pediatric mania and second-generation antipsychotics: Administration and adverse effects](#)".)
- (See "[Pediatric bipolar disorder: Core elements and efficacy of adjunctive psychotherapy](#)".)
- (See "[Pediatric bipolar disorder: Assessment and diagnosis](#)".)
- (See "[Pediatric bipolar disorder: Clinical manifestations and course of illness](#)".)

### COMPONENTS OF TREATMENT

Pediatric bipolar disorder is typically managed with multimodal treatment [25]:

- **Pharmacotherapy** – Pharmacotherapy is the primary treatment. In addition to administering medication for mood syndromes such as mania or major depression, adjunctive medication may be indicated for symptoms such as agitation, anxiety, or insomnia, as well as comorbid conditions such as attention deficit hyperactivity disorder or anxiety disorders.
- **Duration of an adequate trial** – For acute pediatric mania, a pharmacotherapy trial generally lasts approximately three to four weeks before determining whether the regimen is beneficial [3,14,15,17-20,26]. However, further improvement can occur after week 4. As an example, a randomized trial (n = 296) found that in patients who received [aripiprazole](#) 10 mg/day, response at week 4 occurred in 45 percent, and at week 30 in 59 percent [13,16]. Among patients who received aripiprazole 30 mg/day, response at weeks 4 and 30 occurred in 64 and 65 percent.
- **Psychotherapy**
  - Psychoeducation about the disorder and its management is nearly always indicated [27]. This approach is consistent with treatment guidelines [1], including those from the National Institute for Health and Care Excellence [28], Royal Australian and New Zealand College of

Psychiatrists [29], and International Society for Bipolar Disorders Task Force [30]. (See "[Pediatric bipolar disorder: Core elements and efficacy of adjunctive psychotherapy](#)", section on 'Psychoeducation'.)

- **Family therapy** – The impact of bipolar disorder within the family is pervasive and reciprocal; the disorder usually affects the patient's family and the way in which family members respond to the patient influences the outcome of treatment and course of illness. If problems arise within the family, therapy may be indicated to alter problematic interactions between family members and improve family functioning as a unit. (See "[Pediatric bipolar disorder: Core elements and efficacy of adjunctive psychotherapy](#)", section on 'Family therapy'.)

Administration of family therapy is also discussed separately in the context of adult unipolar depression. (See "[Unipolar depression in adults: Family and couples therapy](#)".)

- **Modification of the school environment** – Children and adolescents with bipolar disorder are often best served by modifying the school environment with the following [31-33]:
  - Individual education plan
  - Excused absences for appointments with clinicians
  - Steps to minimize overstimulation in the classroom
  - More frequent breaks
  - Regular visits with the school counselor
  - Accommodation for transition to new teachers or schools
  - Specific plan for behavior problems
- **In-home services** – In-home services may also be indicated for children and adolescents with bipolar disorder, depending upon the functioning of the patient and family.
- **Communication among everyone involved** – Multimodal treatment often involves multiple clinicians. Members of the treatment team need to communicate with each other and teachers as well [25,34].

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## TREATMENT SETTING

Treatment of pediatric bipolar disorder can occur in outpatient or inpatient settings, as well as intermediate levels of care such as intensive outpatient programs, day treatment (partial hospital), and in-home services. The choice depends upon the resources that are available to ensure patient safety while maintaining the highest level of functioning within the family, at school or work, and socially.

Indications for a higher level of care include more severe symptoms (eg, suicidal behavior or psychotic features), risky or dangerous behaviors (eg, physical fights), comorbid psychopathology (eg, attention deficit hyperactivity disorder or anxiety disorder), poorer psychosocial functioning (eg, truancy), poor adherence to pharmacotherapy, and insufficient family support. 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.

For outpatient treatment of bipolar disorder, specialized mood disorder clinics may be superior to general, standard psychiatric clinics, based upon a randomized trial in adults that found readmission to the hospital occurred in fewer patients who received specialized care [35].

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## PRETREATMENT EVALUATION

As part of the pretreatment evaluation, we address the following [34]:

- **Goals** – The goals of pharmacotherapy are to reduce psychopathology, avoid adverse effects, and improve overall functioning. Optimally, patients should return to their baseline premorbid developmental trajectory. If a baseline cannot be identified, the goal is the best possible functioning achievable with the fewest adverse effects.
- **General medical pretreatment evaluation** – If more than one year has elapsed since the last examination by the primary care clinician, we suggest referral for a complete general medical history and physical examination, to rule out general medical illnesses that may account for the psychiatric symptoms, rule out contraindications for specific medications (eg, [olanzapine](#) is avoided in diabetic patients, and [lithium](#) in significant kidney or thyroid disease), and establish the absence of movement disorders at baseline.

The history includes cardiac, endocrine/metabolic, gastrointestinal, and neurologic illnesses, as well as menstrual history in children [2,34]. It is useful to assess recent somatic and cognitive symptoms (eg, headaches, stomach aches, feeling tired, sleep problems, or impaired concentration) to establish a baseline so that these symptoms are not misattributed to new medications. Clinicians should also ask about the

patient's ability to swallow pills. The family history includes cardiac conduction problems (particularly sudden cardiac death) and endocrine and metabolic illnesses.

In addition, the history should identify current medications that may interact with psychotropic medications. Specific interactions of psychotropic drugs with other medications may be determined using the [drug interactions program](#) included in UpToDate.

A baseline blood pressure, pulse, weight, and body mass index ([calculator 1](#)) should be obtained, because these are monitored during pharmacotherapy. (See '[Monitoring](#)' below.)

Focused laboratory tests are performed as indicated by the history and examination [34]. Tests are also guided by the choice of medication and are used to establish a baseline for potential adverse effects (eg, obtaining a lipid profile and glucose level before initiating an antipsychotic or obtaining kidney and thyroid function tests prior to using [lithium](#)) [36]. A pregnancy test is recommended if there is concern that a patient might be pregnant; a 12-month prospective study of female adolescents with bipolar disorder (n = 125) found that pregnancy occurred in 5 percent [37].

Assessment by other specialists, such as neurology, may be indicated [25]. If there are concerns about learning disorders or cognitive impairment, neuropsychologic testing may be indicated.

- **Discontinue potentially destabilizing antidepressants** – Children and adolescents, who are taking antidepressants and do not have an established diagnosis of bipolar disorder, may present with symptoms (eg, irritability) that appear to represent mania. We suggest initially tapering and discontinuing these potentially destabilizing medications because they may cause or exacerbate the symptoms, unless the prior history indicates that discontinuation is problematic. In addition, if the patient is not in imminent danger, initiation of antimanic pharmacotherapy is withheld to see if symptoms improve with discontinuation of the antidepressant.

There is no role for antidepressants in the treatment of current mania or hypomania, including mania or hypomania with mixed features. If these patients are taking an antidepressant, the drug should be swiftly discontinued (eg, over one to two days). However, patients with bipolar major depression can benefit from adjunctive antidepressants. (See "[Pediatric bipolar major depression: Treatment](#)".)

## TREATMENT OF MANIA

Mania is characterized by a period of mood disturbance and increased energy or activity lasting at least one week ( [table 1](#)).

**Pharmacotherapy: Stepwise approach** — We suggest that acute treatment of pediatric mania proceed according to the sequence described in the subsections below. This stepwise approach is applicable to mania with or without psychotic features, mania with or without mixed features, and patients with subsyndromal symptoms of mania [2,13,14,17,18,22,26,38-41]. Patients receive initial pharmacotherapy and progress through each step until they respond. The duration of an adequate treatment trial is discussed separately in the section above. (See '[Components of treatment](#)' above.)

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 pharmacotherapy with antipsychotic** — For children and adolescents with mania, we recommend initial treatment with a second-generation antipsychotic, such as [aripiprazole](#), [asenapine](#), [quetiapine](#), or [risperidone](#). The onset of benefit is faster with antipsychotics than [lithium](#) [42], and initial treatment with an antipsychotic is consistent with practice guidelines [29,38,43].

Multiple randomized trials have established the benefit and superiority of second-generation antipsychotics. As an example, a network meta-analysis of 18 trials in youth with acute mania or mixed mania (total n>2800) compared second-generation antipsychotics with antiseizure medications (eg, [valproate](#)), [lithium](#), and placebo [44]. The mean study duration was five weeks, and the primary results included the following:

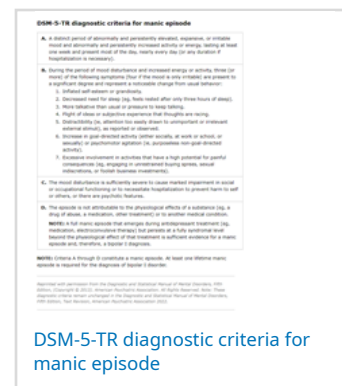


Table 1 - larger image below

- Response (eg, reduction of baseline symptoms  $\geq 50$  percent) occurred more often with second-generation antipsychotics, compared with antiseizure medications or [lithium](#) (relative risk 1.8, 95% CI 1.4-2.2).
- Six second-generation antipsychotics each improved manic symptoms more than placebo. In descending order of effect sizes (based upon indirect evidence), the drugs included [risperidone](#), [olanzapine](#), [aripiprazole](#), [quetiapine](#), [asenapine](#), and [ziprasidone](#). In addition, risperidone outperformed the other drugs, except for olanzapine.
- Discontinuation of treatment due to adverse effects was comparable for [aripiprazole](#), [asenapine](#), [olanzapine](#), [quetiapine](#), [risperidone](#), and placebo. By contrast, discontinuation was greater for [ziprasidone](#) than placebo.

In choosing a second-generation antipsychotic for children and adolescents with mania, we consider factors such as past treatment response, ease of administration, short- and long-term adverse effects ( [table 2](#)), comorbid symptoms and disorders, potential drug-drug interactions, patient preference, and cost. As an example, in patients with the following symptoms or comorbidities [\[2,38,44\]](#):

- Sleeplessness – Although each of the second-generation antipsychotics may be helpful, [quetiapine](#) may be particularly useful. Adjunctive medications can also be used. (See '[Adjunctive treatment for specific symptoms](#)' below.)
- Obesity – Patients with obesity generally do not receive [olanzapine](#) because it causes more weight gain than the other choices.
- Cardiac disease – Patients with risk factors for or a history of cardiac disease generally do not receive [ziprasidone](#) because the drug may prolong the QTc interval.

Selected adverse effects of antipsychotic medications for schizophrenia[1-3]

Table 2 - larger image below

Information about the administration and adverse effects of second-generation antipsychotics is discussed separately. (See "[Pediatric mania and second-generation antipsychotics: Administration and adverse effects](#)".)

**Subsequent trials with other antipsychotics** — For pediatric patients with mania who do not respond to treatment with one antipsychotic within four to six 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. 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, which is described immediately below.

**Antipsychotic-resistant patients** — Pediatric mania often does not respond to multiple (eg, two to three) trials of second-generation antipsychotics.

For antipsychotic-resistant mania, we begin by evaluating patients for factors other than lack of efficacy that can cause nonresponse [\[45-47\]](#). As an example, the target symptoms may be due to a different disorder, such as attention deficit hyperactivity disorder (ADHD), rather than mania. Other factors that may need to be addressed include comorbidities such as anxiety disorders, ADHD, and substance use disorders; stressors (eg, family, social, and school); and poor adherence. (See '[Adherence](#)' below.)

For patients deemed unresponsive to second-generation antipsychotics, we suggest switching to [lithium](#) for next-step treatment [\[48\]](#). Unless there are significant side effects, we typically change one drug at a time to better gauge whether a specific drug is beneficial or causing side effects [\[49\]](#). Thus, we generally maintain the same dose of antipsychotic while titrating lithium to a therapeutic serum concentration, and then taper and discontinue the antipsychotic over the next few weeks to months.

For patients who are partially responding to initial treatment with an antipsychotic, we continue the antipsychotic and add [lithium](#).

- **Prior to starting lithium** – Prior to starting [lithium](#), clinicians should obtain laboratory tests that include blood urea nitrogen, creatinine, electrolytes, and thyrotropin (thyroid stimulating hormone) [\[1,2\]](#). If there are cardiac risk factors, we also perform an electrocardiogram. These tests rule out contraindications to using lithium, and establish a baseline for monitoring lithium's long-term effects upon the kidneys, thyroid gland, and heart. The 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 [\[1,2,50\]](#). (See "[Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and neuromodulation](#)", section on 'Lithium'.)

- **Starting dose** – To minimize initial side effects, we start [lithium](#) at 300 mg/day and increase the dose every one to two days by 300 mg daily to reach the target starting dose. A reasonable alternative is to start lithium in children and adolescents at a dose of 20 to 30 mg/kg/day, in two or three divided doses [51,52].

In children and adolescents weighing <30 kg, an initial target dose of [lithium](#) is often 300 mg twice daily, and in youth weighing ≥30 kg, the initial target dose is 300 mg three times per day [2,53,54].

Doses of immediate-release preparations are initially administered in two to three divided doses. Extended-release preparations can be administered once daily. However, for patients concerned about kidney effects, the adult literature suggests that once daily dosing of immediate-release [lithium](#) may be protective for kidney functioning, particularly in the first five years of treatment [55].

- **Serum concentrations** – [Lithium](#) serum concentrations are measured after the first week at the target starting dose, and doses are titrated up by 150 to 300 mg/day every four to seven days, depending upon response, tolerability, and serum levels. The target serum concentration is 0.6 to 1.2 mEq/L (0.6 to 1.2 mmol/L) [2,50]. Serum levels at the higher end of the target range appear to provide better symptom control, but also cause more adverse effects. Thus, the lowest effective dose is preferable.

We measure [lithium](#) serum concentrations five to seven days after each dose change. 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 [2]. 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.

The serum concentration of [lithium](#) is regularly monitored because lithium has a narrow therapeutic index, meaning 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".)

- **Drug-drug interactions and serum concentrations** – [Lithium](#) levels must be closely monitored in patients taking medications that change kidney function, salt balance, or water balance; these medications can alter lithium excretion and serum lithium concentrations. In addition, nonsteroidal anti-inflammatory drugs should be avoided, because they can increase lithium levels.

Specific interactions of [lithium](#) with other medications may be determined using the [drug interactions program](#) included in UpToDate. This program also can be accessed from the UpToDate online search page or through the individual drug information topics in the section on Drug interactions.

Additional information about drug interactions with [lithium](#) is discussed separately. (See "[Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects](#)", section on 'Drug interactions with lithium'.)

- **Further monitoring** – After a stable [lithium](#) dose is achieved, we repeat the blood urea nitrogen, creatinine, electrolytes, and thyrotropin; if there are cardiac risk factors, we also repeat the electrocardiogram [1,2,50]. Subsequently, lithium serum concentrations, blood urea nitrogen, creatinine, and thyrotropin are measured every three to six months.
- **Adverse effects** – The most common side effects of [lithium](#) in children and adolescents are gastrointestinal (such as pain, diarrhea, nausea, and vomiting) [2,50,54]. Other side effects can include an acne-like rash, tremor, sedation, slowed mentation, hypothyroidism, weight gain, polyuria, polydipsia, and possible structural kidney 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 [22]. In addition, excessive thirst increased from 4 to 44 percent of patients, mean serum concentration of thyrotropin more than doubled (from 2 to 5 milliunits/L), and patients gained an average of 1.4 kg.

The weight gain incurred with [lithium](#) is generally less than that caused by second-generation antipsychotics. (See "[Pediatric mania and second-generation antipsychotics: Administration and adverse effects](#)", section on 'Weight gain'.)

It may be possible to ameliorate [lithium](#)'s adverse gastrointestinal effects by administering the drug with food, temporarily dividing the dose more frequently (eg, four doses per day), or using extended-release or liquid citrate formulations [2]. Hypothyroidism is managed by adding [levothyroxine](#) or switching from lithium to a different drug. However, if lithium is effective, we do not discontinue it due to hypothyroidism.

Children and adolescents with gastrointestinal infections can become dehydrated, which places them at risk for [lithium](#) toxicity. It is usually 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.

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".)

- **Efficacy** – Evidence supporting the use of [lithium](#) for pediatric mania includes randomized trials [48]. In a network meta-analysis that included four trials with a total of 260 youth who received lithium (mean serum concentration 1.1 mEq/L [1.1 mmol/L]), response occurred more often with lithium than placebo (relative risk 1.35, 95% CI 1.002-1.83) [44]. In addition, randomized trials in adults have demonstrated that lithium is efficacious for mania. (See "[Bipolar mania and hypomania in adults: Choosing pharmacotherapy](#)", section on 'First-line monotherapy'.)

Further, [lithium](#) is associated with fewer suicide attempts in adolescents with bipolar disorder, compared with antipsychotics and anticonvulsants [56]. In adult bipolar disorder, lithium decreases the risk of suicide compared with placebo.

**Treatment-refractory patients** — Pediatric mania often does not respond to monotherapy with second-generation antipsychotics or [lithium](#).

For these refractory patients, we suggest combining medications from different classes [2,34,48,57]. Although there are fewer studies of medication combinations than single drugs [3,34,58,59], medication combinations are frequently necessary and appear to predominate pharmacotherapy for pediatric bipolar disorder [2,28,38], such that approximately 70 to 80 percent of patients receive two or more drugs [60,61].

For children and adolescents with mania who do not respond to multiple (eg, six) trials of medication monotherapy, as well as combinations involving two drugs, regimens with three drugs (eg, a second-generation antipsychotic, [lithium](#), and divalproex) are sometimes indicated [45,62]. However, complex regimens involving more than three psychotropic drugs are generally not helpful and usually best avoided [25].

If a new drug is added to a combination of medications and no clear benefit is observed, the drug should be discontinued [1]. We also suggest changing one drug at a time to better gauge whether a specific drug is beneficial or causing side effects [49].

Specific drug combinations that we use are as follows, listed in descending order of preference:

- **Second-generation antipsychotic plus lithium** – For patients who are refractory to monotherapy trials with second-generation antipsychotics and [lithium](#), we suggest combining a second-generation antipsychotic with lithium. If monotherapy with an antipsychotic provided a partial response, we combine it with lithium. Evidence supporting this approach 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 [63]. Patients were randomly assigned to add-on treatment with one of the two remaining drugs. Response occurred in more patients who received either add-on risperidone or lithium than divalproex (53 and 27 versus 0 percent).

If none of the antipsychotics prescribed as monotherapy provided a partial response, we do not pursue combination treatment with them. Rather, we select an antipsychotic from among those that were not previously prescribed during the initial monotherapy trials.

For patients who receive an antipsychotic plus [lithium](#) and do not respond sufficiently, we suggest tapering and discontinuing the antipsychotic, and simultaneously starting and titrating up a different second-generation antipsychotic.

- **Divalproex plus a second-generation antipsychotic or lithium** – We use divalproex as an adjunctive treatment with second-generation antipsychotics or [lithium](#) for pediatric mania, based upon observational studies [2,57,64,65], as well as randomized trials in adults. (See "[Bipolar mania and hypomania in adults: Choosing pharmacotherapy](#)".)

In females of reproductive age, we nearly always avoid using divalproex because it is an established teratogen that can cause neural tube defects [2]. (See "[Risks associated with epilepsy during pregnancy and the postpartum period](#)", section on 'Valproate'.)

Baseline tests before starting divalproex include a pregnancy test, complete blood count with differential and platelets, and liver function tests [2]. 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 [2]. 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 [2,22,66]. 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. In one trial, the mean serum concentration was 114 mg/dL [67]. The maximum daily dose is 35 to 60 mg/kg/day [2,66].

[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 [2,22,66]. 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) [2]. Other common side effects, as well as rare but serious effects, are listed in the tables ( [table 3](#) and [table 4](#)), and are discussed in detail separately. (See "[Antiepileptic 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 [42,44].

- **Lamotrigine plus a second-generation antipsychotic or lithium** – Prospective observational studies suggest that [lamotrigine](#) may possibly help control manic symptoms in youth [68]. As an example, in an 18-week study of 298 patients with an active mood episode despite treatment with pharmacotherapy, improvement with add-on lamotrigine occurred in 58 percent [69]. However, randomized trials in adults with acute 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. The daily dose is taken in two divided doses once the dose titration commences [68]. In one study, the starting dose was 12.5 mg/day for week 1 [70]. The dose was then increased by 12.5 mg/week for the next three weeks and subsequently by 25 mg/week. For patients weighing  $\leq 30$  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.

Observational studies of patients with pediatric bipolar disorder have found that common side effects of [lamotrigine](#) included nausea, dyspepsia, sedation, and nonserious skin rash [68,70]. Other common side effects, as well as rare but serious effects, are listed in the tables ( [table 3](#) and [table 4](#)), and are discussed in detail separately. (See "[Antiepileptic 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'.)

- **First-generation antipsychotic plus lithium, divalproex, or lamotrigine** – First-generation antipsychotics (eg, [haloperidol](#) 2 to 5 mg/day) may possibly help pediatric mania, based upon indirect evidence in adult mania. However, first-generation antipsychotics cause extrapyramidal symptoms more often than second-generation antipsychotics [2,39,71,72]. In addition, the incidence of neuroleptic malignant syndrome, a life-threatening syndrome, is greater with first-generation antipsychotics [72]. 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'.)

**Adjunctive psychotherapy** — Psychotherapy is nearly always indicated as an adjuvant to pharmacotherapy for pediatric bipolar disorder, and prescribing psychotherapy is consistent with practice guidelines [1,4,29,38]. 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 necessitate delaying the onset of psychotherapy or suspending it.

**First line** — For pediatric bipolar disorder treated with pharmacotherapy, we suggest adjunctive psychoeducation for the patient and family, based upon its availability and efficacy in randomized trials. As an example:

- A network meta-analysis of 39 randomized trials ( $n > 3800$  adults and youths) found that favorable outcomes were more likely with psychoeducation than usual care (odds ratio 0.5, 95% CI 0.3-0.8) [73].

As an example, a trial compared three weekly sessions of adjunctive psychoeducation with 21 sessions of family psychotherapy, and followed patients for up to two years [74,75]. Despite the disparity in the number of sessions, time to recovery from either depressive symptoms or manic/hypomanic symptoms was comparable for psychoeducation and family therapy, as was time to recurrence of either depression or mania/hypomania.

- Two trials ( $n = 23$  and  $165$ , not included in the meta-analysis) compared 8 or 12 weekly sessions of adjunctive psychoeducation with usual care, and found that improvement of mood symptoms was greater with psychoeducation; the clinical benefit was moderate to large [76] and persisted for one year [77].

Administration of psychoeducation is discussed separately. (See "[Pediatric bipolar disorder: Core elements and efficacy of adjunctive psychotherapy](#)", section on 'Psychoeducation'.)

**Alternatives** — For pediatric bipolar disorder that does not respond to adjunctive psychoeducation, other psychotherapies are available, including family therapy, dialectical behavior therapy, cognitive-behavioral therapy, interpersonal and social rhythm therapy, and motivational interviewing. (See "[Pediatric bipolar disorder: Core elements and efficacy of adjunctive psychotherapy](#)".)

**Adjunctive treatment for specific symptoms** — Based upon multiple randomized trials that studied drugs such as second-generation antipsychotics as primary treatment, we suggest the following adjunctive medications to manage a variety of persistent symptoms, such as [13-15,17,19,26,67,78]:

- **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)

- **Extrapyramidal symptoms**

- [Benztropine](#) (1 to 2 mg/day in two divided doses)
- [Diphenhydramine](#)
- Benzodiazepines

- **Sleeplessness**

- Sleep hygiene
- Melatonin (eg, 0.3 to 6.0 mg)
- [Diphenhydramine](#)
- [Trazodone](#) (25 to 100 mg)
- [Mirtazapine](#) (eg, 7.5 to 15 mg)
- Benzodiazepines

**Treatment of comorbid disorders** — Comorbidity, including 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**

- **Initial therapy with an antipsychotic** – For children and adolescents with bipolar disorder and comorbid ADHD, we suggest initially prescribing a second-generation antipsychotic such as [risperidone](#), similar to patients without ADHD. Evidence supporting this approach includes randomized trials [3]:
  - An eight-week open-label trial randomly assigned [risperidone](#), [lithium](#), or divalproex to youth with mania or mixed mania [22,79]. Among the 259 patients with comorbid ADHD, response (mania much or very much improved from baseline) occurred in twice as many patients who received risperidone than lithium (relative risk 2.1, 95% CI 1.5-3.0). Presumably risperidone was also superior to divalproex, but the relative risk could not be calculated because the probability of response with divalproex was zero.
  - A four-week trial compared [aripiprazole](#) with placebo in patients with mania (n = 296), including 153 (52 percent) with comorbid ADHD. In the total sample, remission of mania occurred in more patients who received aripiprazole 10 or 30 mg than placebo (25 and 48 versus 5 percent) [13]. In addition, improvement of ADHD symptoms was greater with either dose of active drug than placebo.
- **Adjunctive stimulant if needed** – 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) [20]. 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 [3,80]. The use of stimulants in conjunction with antimanic drugs for pediatric patients with coexisting mania and ADHD is a common clinical practice [17,22,69], and is consistent with treatment guidelines [30,38,45]. 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](#)".)

In youth with bipolar disorder who are taking an antimanic drug, stimulants are generally safe and efficacious for treating comorbid ADHD [2]. However, if bipolar patients who are prescribed stimulants suffer from mania that persists despite multiple (eg, two to four) trials of antimanic drugs, we suggest tapering and discontinuing the stimulant at least temporarily (stimulant "holiday") until the manic episode resolves. When the patient achieves euthymia, the stimulant can then be restarted if it is still indicated.

We prefer once-a-day stimulant formulations. 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 [81]. Although randomized trials [82,83] and prospective observational studies [84,85] indicate that stimulants do not cause treatment emergent mania, other studies have raised persistent concerns that stimulants may possibly destabilize patients [81,84,86]. (However, mood elevated syndromes are intrinsic to bipolar disorder and frequently occur in the absence of stimulants.)

Randomized trials indicate that in juvenile patients with bipolar disorder, which is successfully managed with pharmacotherapy, add-on stimulants are efficacious for active symptoms of comorbid ADHD:

- One trial compared add-on amphetamines (5 mg twice/day) with placebo in bipolar disorder and comorbid ADHD (n = 30 patients) [82]. 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.
- A second crossover trial lasting four weeks compared add-on [methylphenidate](#) (5 to 15 mg twice/daily) with placebo in bipolar disorder plus ADHD (n = 16 patients) [83]. Improvement of ADHD was greater with adjunctive methylphenidate.

In both trials, the stimulant did not appear to exacerbate manic symptoms.

**Anxiety disorders** — Based upon randomized trials in children and adolescents with a primary diagnosis of an anxiety disorder (eg, generalized anxiety disorder or panic disorder) [87,88], we suggest cognitive-behavioral therapy as first-line treatment of comorbid anxiety disorders in youth with bipolar disorder. This approach is consistent with treatment guidelines [45]. However, no randomized trials have examined the treatment of anxiety disorders in youth with bipolar disorder.

For patients who do not have access or respond to cognitive-behavioral therapy, or who decline cognitive-behavioral therapy, we suggest other psychotherapies, such as family therapy, psychodynamic psychotherapy, solution-focused brief therapy, or mindfulness-based cognitive therapy [88]. 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 [87], as well as clinical experience with bipolar youth [81]. However, antidepressant monotherapy can destabilize patients with bipolar disorder and should thus be prescribed in conjunction with an antimanic drug [84]. (See '[Pretreatment evaluation](#)' above and '[Pediatric bipolar major depression: Treatment](#)', section on '[Add-on pharmacotherapy](#)'.)

Benzodiazepines are occasionally used to treat comorbid anxiety in pediatric bipolar disorder [45]. However, these drugs are used only for short-term management (eg, two weeks), because of their potential for abuse and adverse cognitive effects.

**Other treatment options** — Pediatric mania may be refractory to numerous (eg, 8 to 10) medication trials. For these patients, treatment options include:

- **Electroconvulsive therapy (ECT)** – ECT is used infrequently for adolescents and rarely for younger children [3,89]. Nevertheless, it may be beneficial for severe, persistent, and significantly disabling pediatric mania that is refractory to pharmacotherapy, especially episodes with psychotic features, catatonia, unrelenting suicidal behavior, fluid and food refusal that compromises the patient's health, and persistent, severe agitation or aggression [3,29,89-91]. This approach is consistent with treatment guidelines [29,45,90]. Evidence supporting the use of ECT includes retrospective studies in youth [90,92,93], as well as randomized trials in adult mania. (See '[Bipolar mania and hypomania in adults: Choosing pharmacotherapy](#)', section on '[Treatment-refractory patients](#)'.)
- **Clozapine** – [Clozapine](#) may ameliorate treatment-refractory mania in youth, but is rarely used due to concerns about side effects, including agranulocytosis, myocarditis, and seizures [1-3]. The administration and side effects of clozapine are discussed separately. (See '[Pediatric mania and second-generation antipsychotics: Administration and adverse effects](#)', section on '[Less commonly used drugs](#)'.)
- **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](#) [94]. Symptomatic improvement was greater with adjunctive celecoxib than placebo, and adverse events in the two groups were comparable.
- **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 [95]. The study was underpowered because it was prematurely terminated after multiple studies of topiramate in adult mania did not find a benefit. (See '[Bipolar mania and hypomania in adults: Choosing pharmacotherapy](#)', section on '[Other options](#)'.)
- **Carbamazepine** – We rarely use [carbamazepine](#) for pediatric mania. Evidence of efficacy in youth is limited to low-quality studies and the drug is difficult to administer because it induces hepatic enzymes that frequently cause drug-drug interactions and metabolic autoinduction [2].

In addition, adverse effects are common with [carbamazepine](#) ( [table 3](#)), especially nausea and sedation [2]. Other side effects include blurred vision, ataxia, elevated liver enzymes, transient skin rashes, and mild leukopenia and thrombocytopenia. Rare but serious adverse effects

( [table 4](#)) include aplastic anemia, agranulocytosis, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

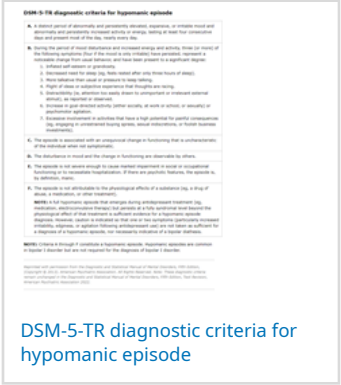
**Treatments that are not recommended** — We do not prescribe the following treatments for pediatric mania:

- **Ketamine** – [Ketamine](#) is an investigational drug for adults with bipolar disorder [96]. We do not use it for juvenile bipolar disorder because the purported benefits are based upon low-quality evidence [97]. More so, ketamine has psychotomimetic effects and acts as a transient intoxicant/euphoriant/hallucinogenic that renders it liable to abuse, addiction, and diversion as an illicit recreational drug. (See "[Ketamine and esketamine for treating unipolar depression in adults: Administration, efficacy, and adverse effects](#)", section on 'Adverse effects'.)
- **Omega-3 fatty acids** – Multiple randomized trials that examined omega-3 fatty acids for pediatric mania failed to find a beneficial effect [76,98,99].
- **Oxcarbazepine** – A seven-week randomized trial in 110 youth with mania found that improvement with [oxcarbazepine](#) (mean dose 1515 mg/day) and placebo was comparable [100].
- **Transcranial magnetic stimulation** – A randomized trial of 26 adolescents with mania found that the benefit of add-on active or sham transcranial magnetic stimulation was comparable [101].

TREATMENT OF OTHER SYNDROMES

**Hypomania** — Hypomanic episodes ( [table 5](#)) warrant treatment if they cause distress, poor judgment, impulsivity, and disregard for risks (eg, spending sprees), and functional impairment. However, we do not treat hypomania characterized by a pleasurable elevated mood, increased productivity, and the absence of negative consequences.

Hypomania that requires treatment is managed with the same medications that are used for mania. 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 [51]. 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) [102]. Treating pediatric hypomania and pediatric mania with the same medications is consistent with treatment guidelines [4,38].



DSM-5-TR diagnostic criteria for hypomanic episode

Table 5 - larger image below

Pharmacotherapy for mania is described elsewhere in this topic. (See '[Treatment of mania](#)' above.)

**Rapid cycling** — For pediatric bipolar disorder with rapid cycling, we use second-generation antipsychotics (eg, [risperidone](#)) as first-line therapy, which is similar to treatment for patients without rapid cycling. This approach is consistent with treatment guidelines [4]. (See '[Pharmacotherapy: Stepwise approach](#)' above.)

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 [13]:

- One trial found that [risperidone](#) was superior to [divalproex](#) in 65 patients, and rapid cycling was present at baseline in 81 percent [19].
- In a trial (n = 144 youth) that found [olanzapine](#) was superior to placebo, rapid cycling at baseline was present in 21 percent [15].

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 '[Initial pharmacotherapy with antipsychotic](#)' above.)

**Major depression** — Bipolar depression in children and adolescents is discussed elsewhere. (See "[Pediatric bipolar major depression: Treatment](#)".)

FOLLOW-UP AND MAINTENANCE TREATMENT

**Adherence** — Clinicians prescribing pharmacotherapy should monitor patients for adherence, because nonadherence is common [28]. Observational studies of youth with manic or mixed episodes indicate that problematic adherence ranges from approximately 33 to 66 percent [103,104]. In those with bipolar depression, discontinuation of all pharmacotherapy occurs in 14 to 30 percent, depending upon the specific medication regimen prescribed [60].

- Risk factors for nonadherence – Among adolescents with bipolar disorder, multiple factors are associated with poor adherence to treatment, including cognitive difficulties, greater illness severity, denial of one's illness, impaired family functioning, as well as treatment regimens that involve multiple drugs, frequent (eg, three or four) daily doses, and adverse effects [25,105,106]. Resistance to taking medication may also stem from difficulties accepting bipolar disorder as part of one's identity and concerns about fitting in with peer groups. Another factor is the youth's developmental stage; concrete thinking may prevent younger adolescents from understanding the consequences of not taking their medications [106].

Conversely, factors that are associated with favorable adherence include good family support and functioning, parents who believe the medical disorder is serious and that the treatment is effective, having close friends, an internal locus of control, and perceived empathy from one's clinician [106].

- Assessment – Prior to initiating treatment, we assess factors that can interfere with pharmacotherapy [3]. These include prior nonadherence to medications and fears, prejudices, and false beliefs regarding medication on the part of patients and parents.

During treatment, adherence in adolescents is typically assessed by initially asking open-ended questions (eg, "When do you take your pills" and "What do you dislike about the medicine") [106]. This is followed by more direct questions about remembering to take the medication and asking patients to rate their own adherence using a Likert scale anchored at one end by never taking the medication and the other end by always taking the medication. We suggest asking patients about adherence without the parent/caregiver present, because patients may be more likely to disclose times when they received medication from the parent but did not take it. In discussions with adolescents about adherence to pharmacotherapy, clinicians should monitor their own responses for negative attitudes and judgmental evaluations.

However, prospective studies suggest that subjective reports from patients, parents, and prescribing clinicians overestimate adherence [105]. Other means of assessing adherence include serum concentrations for relevant medications, pill counts, electronic monitoring of pill bottles or boxes, and checking prescription refills. Counting pills may be inaccurate because they can be discarded rather than ingested. In a 20-week, prospective observational study of youth treated with lithium (n = 107), pill counts suggested that adherence to lithium was 100 percent [103]. By contrast, the proportion of serum concentrations greater than the minimal therapeutic level (<0.6 mEq/L/0.6 mmol/L) was 66 percent.

- Promoting good adherence – To facilitate adherence to medication regimens in pediatric bipolar disorder, we suggest the following approach:
  - Family involvement – Clinicians must involve the patient's parents/caregivers in treatment; treatment is unlikely to succeed without the family's co-operation [3,25,28]. School personnel may also need to assist patients in taking their medication [25].
  - Preparing the patient – Informing the patient and family about potential adverse effects without creating negative expectations (nocebo effects), and preparing everyone involved for the possibility that multiple treatment trials may be necessary to optimize efficacy and adverse effects.
  - Patient preferences – Adherence may also be improved by taking a flexible approach to accommodate patient preferences to the extent that they are feasible. One option when selecting a medication is to provide a list of comparable possibilities and allow patients to make the final choice. In addition, patients are more likely to adhere to treatment if they choose the drug formulation (eg, extended-release pills, sublingual tablets, transdermal patches, and liquid) and timing of administration.
  - Pillboxes – Weekly pillboxes can help everyone involved track whether doses are taken, while allowing trustworthy adolescents to take primary responsibility [25]. Parents/caregivers do not remind the adolescent about taking the medication unless the dose is still in the box after the dose time.
  - Reducing the frequency of doses (eg, twice per day rather than three times per day).
  - Motivational interviewing – Adjunctive motivational interviewing can be used to focus primarily upon adherence. As an example, a three-session, motivational interviewing intervention addresses adherence by educating patients about bipolar disorder and medications, eliciting thoughts and feelings about pharmacotherapy, assessing to what extent patients are ready to change their behavior regarding adherence, collaborating with patients to create an action plan for improving adherence, and evaluating the utility of the plan and need for modifications [107].

General information about motivational interviewing is discussed separately, as are other adjunctive psychotherapies administered for pediatric bipolar disorder that address medication adherence among other elements. (See "[Overview of psychotherapies](#)", section on '[Motivational interviewing](#)' and "[Pediatric bipolar disorder: Core elements and efficacy of adjunctive psychotherapy](#)", section on '[Motivational interviewing](#)'.)

Additional information about adherence, including interventions such as psychoeducation, cognitive-behavioral therapy, family therapy, and motivational interviewing, is discussed separately in the context of adult bipolar disorder. (See "[Bipolar disorder in adults: Managing poor adherence to maintenance pharmacotherapy](#)".)

**Maintenance pharmacotherapy** — Maintenance pharmacotherapy is indicated for children and adolescents with bipolar disorder who recover from acute mood episodes, because bipolar disorder is highly recurrent. (See "[Pediatric bipolar disorder: Clinical manifestations and course of illness](#)", [section on 'Course of illness'](#).)

For nearly all patients with an acute bipolar mood episode that responds to pharmacotherapy, we suggest continuing the same treatment, unless the regimen is poorly tolerated. This approach is consistent with treatment guidelines and reviews [1-3,5,45,50], and is standard practice for adults. (See "[Bipolar disorder in adults: Choosing maintenance treatment](#)".)

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

- A 72-week randomized trial compared maintenance [aripiprazole](#) with placebo in children with bipolar disorder who initially responded to acute phase treatment with aripiprazole (n = 60) [108]. Time to recurrence of a mood episode was greater with aripiprazole than placebo (26 versus 3 weeks). However, weight gain was greater with aripiprazole (2.6 versus 0.4 kg), as was the incidence of stomach and musculoskeletal pain.
- A study enrolled youth with an acute mood episode unresponsive to pharmacotherapy and treated them with add-on [lamotrigine](#) [69]. Those who responded (n = 173) were randomly assigned to continue lamotrigine or to taper lamotrigine and substitute placebo for 36 weeks. After controlling for potentially confounding variables (eg, use of antipsychotics), time to intervention for a mood episode was longer with add-on lamotrigine than placebo (hazard ratio 0.5, 95% CI 0.3-0.9).

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 maintenance [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) [109]. The median time to recurrence in the two groups was comparable.

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: Treatment](#)", [section on 'Add-on pharmacotherapy'](#).)

**Duration** — Following recovery from acute bipolar mood episodes, we suggest that children and adolescents continue treatment for at least one to two years, and preferably longer, especially for patients with a history of multiple severe lifetime mood episodes (eg, marked by psychosis and suicide attempts). This approach is consistent with practice guidelines and reviews [1,5,45].

- **Mania without psychotic features** – For mania without psychotic features, the duration of maintenance treatment varies among patients; some patients require maintenance treatment for many years, and others require it their entire lives [1,45]. Maintenance treatment should last longer for patients with a more severe course of illness. 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. 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 re-evaluated 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 lifetime pharmacotherapy.

- **Mania with psychotic features** – For mania with psychotic features that remits with combination treatment, such as a second-generation antipsychotic plus [lithium](#), we suggest continuing both drugs for at least two to six months [39]. 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 either [lithium](#) or the second-generation antipsychotic. The choice should be made in conjunction with the patient and family, and depends upon the relative benefit versus side-effects for each medication. Following discontinuation of the one drug, treatment with the other drug is maintained.

**Discontinuation of pharmacotherapy** — Despite the benefits of maintenance treatment, patients with pediatric bipolar disorder may insist upon stopping it because of side effects, 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 leads to a new mood episode in more than 50 percent. (See "[Bipolar disorder in adults: Choosing maintenance treatment](#)", [section on 'Discontinuation'](#).)

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

If patients and families 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 [34]. 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 eventually 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 recur.

**Monitoring** — For patients with pediatric bipolar disorder, we suggest systematically monitoring symptoms, medication adverse effects (eg, extrapyramidal symptoms and metabolic dysregulation), adherence, and functioning [2]. In addition, monitoring typically includes blood pressure, pulse, weight, waist size, body mass index ([calculator 1](#)), and metabolic laboratory tests.

Parents/caregivers must be involved in assessments of clinical response. Although some children and adolescents have good insight into the nature of their symptoms, others do not, and lack of insight is a common feature of mania or hypomania. One four-week randomized trial (n = 296 patients) found that parent and clinician ratings of mania severity agreed with each other, whereas patient ratings were substantially lower [110]. Teachers can also provide information when symptoms or medications affect school behavior or performance.

- **Symptoms** – We generally assess changes in symptoms by interviewing patients and their parents. Some clinicians augment the interview with standardized caregiver questionnaires such as the parent-rated Young Mania Rating Scale (YMRS), General Behavioral Inventory, or Child Mania Rating Scale ( [form 1](#)) [111-114]. More systematic monitoring involves clinician-administered rating scales, such as the YMRS, Kiddie-Schedule for Affective Disorders and Schizophrenia Mania Rating Scale, and the Children's Depression Rating Scale, Revised, but these scales are time intensive and usually reserved for research settings [115-119].
- **Adverse effects** – Adverse effects are also monitored by interviewing patients and their parents. The adverse effects of specific medications are discussed elsewhere, including:
  - Second-generation antipsychotics (see "[Pediatric mania and second-generation antipsychotics: Administration and adverse effects](#)", [section on 'Class-wide adverse effects'](#))
  - [Lithium](#) (see '[Antipsychotic-resistant patients](#)' above)
  - Divalproex and [lamotrigine](#) (see '[Treatment-refractory patients](#)' above)
- **Frequency** – The frequency of monitoring clinical progress and side effects generally ranges from daily to monthly, depending upon the severity of persistent mood symptoms. Hospitalized patients are seen daily, and patients with suicidal ideation, a specific plan, and intent to kill themselves may require constant observation. Acutely ill outpatients are generally seen weekly or every other week, until they achieve substantial improvement in the number, intensity, and frequency of symptoms; at that point, outpatients are seen every two to four weeks until they remit.

Patients with bipolar disorder who remit can initially be seen every month. For those patients who remain stable, the schedule of visits can be tapered down to a few (eg, four) times per year [34].

For stable patients who discontinue pharmacotherapy, we suggest that clinicians continue monitoring for signs of recurrence [34]. The schedule is initially more frequent (eg, monthly) when the risk of recurrence is greatest, and can be tapered down to a lower frequency (eg, two to four times per year) over multiple years (eg, two to four years), at which point it may be reasonable to discontinue monitoring.

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## 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](#)".)

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## INFORMATION FOR PATIENTS AND FAMILIES

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

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

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

These educational materials can be used as part of psychoeducational psychotherapy. (See ['First line'](#) above.)

The United States National Institute of Mental Health also has educational material explaining the symptoms, course of illness, and treatment of pediatric bipolar disorder in a booklet entitled "[Bipolar Disorder in Children and Teens](#)" which is freely available for downloading and printing.

The United Kingdom National Institute for Health and Care Excellence has information explaining the symptoms, assessment, diagnosis, and treatment of pediatric bipolar disorder in a document entitled [Information for the public](#). The document also suggests questions about bipolar disorder, which patients and families can ask their clinicians.

The [Depression and Bipolar Support Alliance](#) (800-826-3632) is a national organization that educates members about bipolar disorder and how to cope with it. Other functions include increasing public awareness of the illness and advocating for more research and services. The organization is administered and maintained by patients and family members, and has local chapters.

The [National Alliance on Mental Illness](#) (800-950-6264) is a similarly structured organization devoted to education, support, and advocacy for patients with any mental illness, including bipolar disorder.

## SUMMARY AND RECOMMENDATIONS

- **Components of treatment** – The mainstay of treatment for pediatric bipolar disorder is pharmacotherapy. In addition, adjunctive psychotherapy is generally regarded as essential, and the school environment is often modified as well. (See ['Components of treatment'](#) 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 ['Treatment 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 2C**). The most widely studied and used options include [aripiprazole](#), [asenapine](#), [olanzapine](#), [quetiapine](#), and [risperidone](#); the specific choice depends upon factors such as past response to medications, side effect profiles, and comorbidities. 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 pharmacotherapy with antipsychotic'](#) above.)
  - **Antipsychotic-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 2C**). (See ['Antipsychotic-resistant patients'](#) above.)
  - **Treatment-refractory patients** – Pediatric mania that does not respond to monotherapy with second-generation antipsychotics or [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](#); lithium plus divalproex or lamotrigine; or a first-generation antipsychotic plus lithium, divalproex or lamotrigine. (See ['Treatment-refractory patients'](#) above.)
- **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 other options (**Grade 2B**). (See ['Adjunctive psychotherapy'](#) above.)
- **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 monotherapy with a second-generation antipsychotic rather than combination therapy (**Grade 2C**). (See ['Attention deficit hyperactivity disorder'](#) above.)

If bipolar symptoms respond to a second-generation antipsychotic, and comorbid ADHD persists, we add an additional treatment for ADHD. (See ["Attention deficit hyperactivity disorder in children and adolescents: Overview of treatment and prognosis"](#).)

- **Bipolar depression** – Bipolar depression in children and adolescents is typically treated with pharmacotherapy plus psychotherapy. (See "[Pediatric bipolar major depression: Treatment](#)".)
- **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 "[Follow-up and maintenance treatment](#)" above.)

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## GRAPHICS

Table 1: DSM-5-TR diagnostic criteria for manic episode

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>A.</b> A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least one week and present most of the day, nearly every day (or any duration if hospitalization is necessary).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <p><b>B.</b> During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:</p> <ol style="list-style-type: none"> <li>1. Inflated self-esteem or grandiosity.</li> <li>2. Decreased need for sleep (eg, feels rested after only three hours of sleep).</li> <li>3. More talkative than usual or pressure to keep talking.</li> <li>4. Flight of ideas or subjective experience that thoughts are racing.</li> <li>5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.</li> <li>6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (ie, purposeless non-goal-directed activity).</li> <li>7. Excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).</li> </ol> |
| <p><b>C.</b> The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <p><b>D.</b> The episode is not attributable to the physiological effects of a substance (eg, a drug of abuse, a medication, other treatment) or to another medical condition.</p> <p><b>NOTE:</b> A full manic episode that emerges during antidepressant treatment (eg, medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

**NOTE:** Criteria A through D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

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Table 2: Selected adverse effects of antipsychotic medications for schizophrenia

|                                        | Weight gain | Glucose abnormalities | Hyperlipidemia | Akathisia | Parkinsonism | Dystonia | Tardive dyskinesia | Prolactin elevation | Sedation |
|----------------------------------------|-------------|-----------------------|----------------|-----------|--------------|----------|--------------------|---------------------|----------|
| <b>Second-generation agents</b>        |             |                       |                |           |              |          |                    |                     |          |
| Aripiprazole                           | +           | +                     | +              | ++        | +            | +        | +                  | 0                   | +        |
| Asenapine                              | ++          | ++                    | ++             | ++        | +            | ++       | ++                 | ++                  | ++       |
| Brexipiprazole <sup>¶</sup>            | +           | +                     | ++             | ++        | +            | +        | +                  | 0                   | ++       |
| Cariprazine <sup>¶</sup>               | ++          | +                     | +              | ++        | +            | +        | +                  | +                   | ++       |
| Clozapine <sup>Δ</sup>                 | +++         | +++                   | +++            | +         | +            | +        | +                  | +                   | +++      |
| Iloperidone                            | ++          | ++                    | +              | +         | +            | +        | +                  | ++                  | ++       |
| Lumateperone <sup>¶</sup>              | +           | +                     | +              | +         | +            | +        | +                  | 0                   | +        |
| Lurasidone                             | +           | ++                    | ++             | ++        | ++           | ++       | ++                 | ++                  | ++       |
| Olanzapine                             | +++         | +++                   | +++            | ++        | ++           | +        | +                  | ++                  | +++      |
| Paliperidone                           | ++          | +                     | ++             | ++        | ++           | ++       | ++                 | +++                 | ++       |
| Pimavanserin                           | –           | +                     | +              | +         | +            | +        | +                  | +                   | +        |
| Quetiapine                             | ++          | ++                    | +++            | +         | +            | +        | +                  | +                   | +++      |
| Risperidone                            | ++          | ++                    | +              | +++       | +++          | ++       | ++                 | +++                 | ++       |
| Ziprasidone                            | +           | +                     | +              | ++        | +            | +        | +                  | ++                  | ++       |
| <b>Other antipsychotic medications</b> |             |                       |                |           |              |          |                    |                     |          |
| Xanomeline-trospium <sup>¶</sup>       | 0           | 0                     | 0              | 0         | 0            | 0        | 0                  | 0                   | +        |
| <b>First-generation agents</b>         |             |                       |                |           |              |          |                    |                     |          |
| Chlorpromazine                         | ++          | ++                    | +              | ++        | ++           | ++       | +++                | +                   | +++      |
| Fluphenazine                           | ++          | +                     | +              | +++       | +++          | +++      | +++                | +++                 | +        |
| Haloperidol                            | ++          | +                     | +              | +++       | +++          | +++      | +++                | +++                 | +        |
| Loxapine                               | +           | +                     | +              | ++        | ++           | ++       | ++                 | ++                  | ++       |
| Molindone                              | +           | +                     | +              | ++        | ++           | ++       | ++                 | ++                  | ++       |
| Perphenazine                           | ++          | +                     | +              | ++        | ++           | ++       | ++                 | ++                  | ++       |
| Pimozide                               | +           | +                     | +              | +++       | +++          | ++       | +++                | +++                 | +        |
| Thioridazine <sup>§</sup>              | ++          | +                     | +              | +         | +            | +        | +                  | ++                  | +++      |
| Thiothixene                            | +           | +                     | +              | +++       | +++          | +++      | +++                | +++                 | +        |
| Trifluoperazine                        | ++          | +                     | +              | ++        | ++           | ++       | ++                 | ++                  | +        |

Adverse effect rankings, with the exception of the QTc classifications, are consistent with American Psychiatric Association practice guidelines for the treatment of schizophrenia.<sup>[1]</sup> The QTc classifications are determined by UpToDate Lexidrug according to US Food & Drug Administration guidance.<sup>[2,4]</sup> Other sources may use different classification systems resulting in some agents being classified differently.

ECG: electrocardiogram; IV: intravenous.

\* Clinically significant QTc prolongation was not detected in preliminary studies or reported in the manufacturer's labeling.

¶ Based upon limited experience.

Δ Clozapine also causes granulocytopenia or agranulocytosis in approximately 1% of patients requiring regular blood cell count monitoring. Clozapine has been associated with excess risk of myocarditis and venous thromboembolic events including fatal pulmonary embolism. These issues are addressed in the UpToDate topic review of guidelines for prescribing clozapine section on adverse effects.

◇ Available data suggest that iloperidone QTc risk is relatively low (+) at usual therapeutic doses. However, moderate QTc prolongation may occur at high doses and with interacting medications; caution (eg, regular ECG monitoring or avoidance) is warranted, particularly in high-risk patients.

§ Thioridazine is also associated with dose-dependent retinitis pigmentosa. Refer to UpToDate text.

#### References:

1. Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association 2020. Available at: <https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines> (Accessed on March 24, 2020).
2. UpToDate Lexidrug. More information available at <https://online.lexi.com/>.

3. Lin X, Siafis S, Tian J et al. Antipsychotic-Related Prolactin Changes: A Systematic Review and Dose-Response Meta-analysis. *CNS Drugs*. 2025 Oct;39:937.
  4. Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs – Questions and Answers; Guidance for Industry US Food and Drug Administration, June 2017 (revision 2). Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073161.pdf>.
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Graphic 82533 Version 47.0

Table 3: Common side effects of antiseizure medications

| Antiseizure medication | Systemic side effects                                                                                                           | Neurologic side effects                                                                                                                                                                                         |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Brivaracetam *         | Nausea, vomiting, constipation, fatigue                                                                                         | Headache, somnolence, dizziness, ataxia, abnormal coordination, nystagmus                                                                                                                                       |
| Cannabidiol            | Anemia, decreased appetite, diarrhea, infection, dose-related elevations of liver transaminases (ALT and/or AST), rash, fatigue | CNS depression (eg, drowsiness, lethargy, sedation), malaise, insomnia, sleep disturbance                                                                                                                       |
| Carbamazepine          | Nausea, vomiting, diarrhea, hyponatremia, rash, pruritus                                                                        | Drowsiness, dizziness, blurred or double vision, lethargy, headache                                                                                                                                             |
| Cenobamate             | Fatigue                                                                                                                         | Somnolence, dizziness, headache, diplopia                                                                                                                                                                       |
| Clobazam               | Increased salivation, nausea, vomiting, constipation                                                                            | Somnolence, aggression, irritability, ataxia, insomnia                                                                                                                                                          |
| Eslicarbazepine        | Nausea, vomiting, diarrhea, fatigue, hyponatremia, rash                                                                         | Dizziness, drowsiness, headache, diplopia, vertigo, ataxia, attention disturbance, blurred vision, tremor<br>(NOTE: Dizziness, diplopia, and ataxia reported more frequently in combination with carbamazepine) |
| Ethosuximide           | Nausea, vomiting                                                                                                                | Sleep disturbance, drowsiness, hyperactivity                                                                                                                                                                    |
| Felbamate              | Nausea, vomiting, anorexia, weight loss                                                                                         | Insomnia, dizziness, headache, ataxia                                                                                                                                                                           |
| Fenfluramine           | Diarrhea, vomiting, decreased appetite                                                                                          | Asthenia, drooling, drowsiness, fatigue, lethargy, malaise, sedated state                                                                                                                                       |
| Gabapentin             | Infrequent                                                                                                                      | Somnolence, dizziness, ataxia                                                                                                                                                                                   |
| Lacosamide             | Nausea, vomiting, fatigue                                                                                                       | Ataxia, dizziness, headache, diplopia                                                                                                                                                                           |
| Lamotrigine            | Rash, nausea                                                                                                                    | Dizziness, tremor, diplopia                                                                                                                                                                                     |
| Levetiracetam          | Fatigue, infection                                                                                                              | Somnolence, dizziness, agitation, anxiety, irritability, depression                                                                                                                                             |
| Oxcarbazepine          | Nausea, rash, hyponatremia                                                                                                      | Sedation, headache, dizziness, vertigo, ataxia, diplopia                                                                                                                                                        |
| Perampanel             | Weight gain, fatigue, nausea                                                                                                    | Dizziness, somnolence, irritability, gait disturbance, falls, aggression, mood alteration                                                                                                                       |
| Phenobarbital          | Nausea, rash                                                                                                                    | Alteration of sleep cycles, sedation, lethargy, behavioral changes, hyperactivity, ataxia, tolerance, dependence                                                                                                |
| Phenytoin              | Gingival hypertrophy, rash                                                                                                      | Confusion, slurred speech, double vision, ataxia                                                                                                                                                                |
| Pregabalin             | Weight gain, peripheral edema, dry mouth                                                                                        | Dizziness, somnolence, ataxia, tremor                                                                                                                                                                           |
| Primidone              | Nausea, rash                                                                                                                    | Alteration of sleep cycles, sedation, lethargy, behavioral changes, hyperactivity, ataxia, tolerance, dependence                                                                                                |
| Rufinamide             | Nausea, vomiting, fatigue                                                                                                       | Dizziness, somnolence, headache                                                                                                                                                                                 |
| Stiripentol            | Nausea, decreased appetite, weight loss                                                                                         | Somnolence, agitation, ataxia, hypotonia, tremor, dysarthria, insomnia                                                                                                                                          |
| Tiagabine              | Abdominal pain, nausea, lack of energy                                                                                          | Dizziness, somnolence, nervousness, tremor, difficulty concentrating                                                                                                                                            |
| Topiramate             | Weight loss, paresthesia, fatigue                                                                                               | Nervousness, difficulty concentrating, confusion, depression, anorexia, language problems, anxiety, mood problems, tremor                                                                                       |
| Valproate              | Weight gain, nausea, vomiting, hair loss, easy bruising                                                                         | Tremor, dizziness                                                                                                                                                                                               |
| Vigabatrin             | Vision loss, fatigue                                                                                                            | Drowsiness, dizziness                                                                                                                                                                                           |
| Zonisamide             | Nausea, anorexia                                                                                                                | Somnolence, dizziness, ataxia, confusion, difficulty concentrating, depression                                                                                                                                  |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CNS: central nervous system.

\* Based upon limited experience from preapproval clinical trials.

Table 4: Rare but serious side effects of antiseizure medications

| Drug                      | Side effects*                                                                                                                                                                                        |
|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Brivaracetam <sup>¶</sup> | Hypersensitivity reactions (including bronchospasm and angioedema), leukopenia, neutropenia, psychosis, SJS/TEN                                                                                      |
| Cannabidiol               | Hypersensitivity reactions (including angioedema, erythema, and pruritus), suicidal ideation                                                                                                         |
| Carbamazepine             | Agranulocytosis, aplastic anemia, SJS/TEN, hepatic failure, DRESS, dermatitis/rash, serum sickness, pancreatitis, lupus syndrome, hypogammaglobulinemia                                              |
| Cenobamate                | QT interval shortening, DRESS/multiorgan hypersensitivity                                                                                                                                            |
| Clobazam                  | Respiratory depression, SJS/TEN, DRESS                                                                                                                                                               |
| Eslicarbazepine           | Prolonged PR interval, atrioventricular block, hyponatremia (rarely severe), SJS/TEN                                                                                                                 |
| Ethosuximide              | Agranulocytosis, SJS/TEN, aplastic anemia, hepatic failure, dermatitis/rash, serum sickness, drug-induced immune thrombocytopenia                                                                    |
| Felbamate                 | Aplastic anemia, liver failure                                                                                                                                                                       |
| Fenfluramine              | Cardiac valve injury, pulmonary hypertension, serotonin syndrome                                                                                                                                     |
| Gabapentin                | Multiorgan hypersensitivity, respiratory depression                                                                                                                                                  |
| Lacosamide                | Prolonged PR interval, atrioventricular block, multiorgan hypersensitivity, neutropenia                                                                                                              |
| Lamotrigine               | SJS/TEN, DRESS/multiorgan hypersensitivity, aseptic meningitis, hypogammaglobulinemia, cardiac rhythm and conduction abnormalities                                                                   |
| Levetiracetam             | SJS/TEN, anaphylaxis and angioedema, pancytopenia, psychosis, hypogammaglobulinemia                                                                                                                  |
| Oxcarbazepine             | SJS/TEN, DRESS/multiorgan hypersensitivity, agranulocytosis, pancytopenia, leukopenia                                                                                                                |
| Perampanel                | Severe neuropsychiatric effects (eg, hostility, aggression)                                                                                                                                          |
| Phenobarbital             | Agranulocytosis, SJS/TEN, hepatic failure, dermatitis/rash, serum sickness, connective tissue contractures (eg, Dupuytren), complex regional pain syndrome                                           |
| Phenytoin                 | Agranulocytosis, SJS/TEN, DRESS, aplastic anemia, hepatic failure, dermatitis/rash, serum sickness, adenopathy, pseudolymphoma, neuropathy, ataxia, lupus syndrome, hirsutism                        |
| Pregabalin                | Angioedema, hypersensitivity reactions, rhabdomyolysis, respiratory depression                                                                                                                       |
| Primidone                 | Acute toxic reaction (sedation, dizziness, ataxia, nausea, and vomiting), agranulocytosis, SJS/TEN, hepatic failure, dermatitis/rash, serum sickness, connective tissue contractures (eg, Dupuytren) |
| Rufinamide                | SJS/TEN, DRESS, dermatitis/rash, shortened QT interval                                                                                                                                               |
| Stiripentol               | Limited information: severe somnolence, marked weight loss, neutropenia and thrombocytopenia, suicidal ideation and behavior                                                                         |
| Tiagabine                 | SJS/TEN, nonconvulsive status epilepticus                                                                                                                                                            |
| Topiramate                | Acute myopia and glaucoma, kidney stones, oligohidrosis and hyperthermia (which primarily occur in children)                                                                                         |
| Valproate                 | Agranulocytosis, SJS/TEN, aplastic anemia, hepatic failure, dermatitis/rash, serum sickness, pancreatitis, polycystic ovary syndrome, hypogammaglobulinemia                                          |
| Vigabatrin                | MRI abnormalities, depression, weight gain                                                                                                                                                           |
| Zonisamide                | Rash, SJS/TEN, aplastic anemia, agranulocytosis, nephrolithiasis; acute myopia and secondary angle closure glaucoma, hyperammonemia and encephalopathy; in children, oligohidrosis and hyperthermia  |

DRESS: drug reaction with eosinophilia and systemic symptoms; MRI: magnetic resonance imaging; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.

\* As a class, antiseizure medications have been associated with an increased risk of suicidal ideation and suicidal behavior.

<sup>¶</sup> Based upon limited experience from preapproval clinical trials.

Table 5: DSM-5-TR diagnostic criteria for hypomanic episode

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>A.</b> A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least four consecutive days and present most of the day, nearly every day.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>B.</b> During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree: <ol style="list-style-type: none"> <li>1. Inflated self-esteem or grandiosity.</li> <li>2. Decreased need for sleep (eg, feels rested after only three hours of sleep).</li> <li>3. More talkative than usual or pressure to keep talking.</li> <li>4. Flight of ideas or subjective experience that thoughts are racing.</li> <li>5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.</li> <li>6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.</li> <li>7. Excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).</li> </ol> |
| <b>C.</b> The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>D.</b> The disturbance in mood and the change in functioning are observable by others.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>E.</b> The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>F.</b> The episode is not attributable to the physiological effects of a substance (eg, a drug of abuse, a medication, or other treatment). <p><b>NOTE:</b> A full hypomanic episode that emerges during antidepressant treatment (eg, medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for a diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.</p>                                                                                                                                                                                                                                                                                                                                                                              |

**NOTE:** Criteria A through F constitute a hypomanic episode. Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

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**Form 1: Child Mania Rating Scale (CMRS), Parent Version**

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 Child's name

---

 Date of Birth (mm/dd/yy)

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 Case # / ID #
**Instructions**

The following questions concern your child's mood and behavior in the **past month**. Please place a checkmark or an 'X' in a box for each item. Please consider it a problem if it is **causing trouble** and is beyond what is normal for your child's age. Otherwise, check 'rare or never' if the behavior is not causing trouble.

| Does your child . . .                                                                                                                                                                                | Never/<br>rarely               | Sometimes                      | Often                          | Very<br>often                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| 1. Have periods of feeling super happy for hours or days at a time, extremely wound up and excited, such as feeling "on top of the world"                                                            | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 2. Feel irritable, cranky, or mad for hours or days at a time                                                                                                                                        | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 3. Think that they can be anything or do anything (eg, leader, best basketball player, rap singer, millionaire, princess) beyond what is usual for that age                                          | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 4. Believe that they have unrealistic abilities or powers that are unusual, and may try to act upon them, which causes trouble                                                                       | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 5. Need less sleep than usual; yet does not feel tired the next day                                                                                                                                  | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 6. Have periods of too much energy                                                                                                                                                                   | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 7. Have periods when they talk too much or too loud or talks a mile-a-minute                                                                                                                         | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 8. Have periods of racing thoughts that their mind cannot slow down, and it seems that your child's mouth cannot keep up with their mind                                                             | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 9. Talk so fast that they jump from topic to topic                                                                                                                                                   | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 10. Rush around doing things nonstop                                                                                                                                                                 | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 11. Have trouble staying on track and is easily drawn to what is happening around them                                                                                                               | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 12. Do many more things than usual, or is unusually productive or highly creative                                                                                                                    | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 13. Behave in a sexually inappropriate way (eg, talk dirty, exposing, playing with private parts, masturbating, making sex phone calls, humping on dogs, playing sex games, touches others sexually) | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 14. Go and talk to strangers inappropriately, is more socially outgoing than usual                                                                                                                   | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 15. Do things that are unusual for them that are foolish or risky (eg, jumping off heights, ordering CDs with your credit cards, giving things away)                                                 | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 16. Have rage attacks, intense and prolonged temper tantrums                                                                                                                                         | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |
| 17. Crack jokes or pun more than usual, laugh loud, or act silly in a way that is out of the ordinary                                                                                                | <input type="text" value="0"/> | <input type="text" value="1"/> | <input type="text" value="2"/> | <input type="text" value="3"/> |

|                                             |              |              |              |              |
|---------------------------------------------|--------------|--------------|--------------|--------------|
| 18. Experience rapid mood swings            | <div>0</div> | <div>1</div> | <div>2</div> | <div>3</div> |
| 19. Have any suspicious or strange thoughts | <div>0</div> | <div>1</div> | <div>2</div> | <div>3</div> |
| 20. Hear voices that nobody else can hear   | <div>0</div> | <div>1</div> | <div>2</div> | <div>3</div> |
| 21. See things that nobody else can see     | <div>0</div> | <div>1</div> | <div>2</div> | <div>3</div> |

Total score \_\_\_\_\_

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