Pediatric bipolar disorder and pharmacotherapy: General principles

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INTRODUCTION

The mainstay of treatment for bipolar disorder in children and adolescents is pharmacotherapy [1-3]. There are several general principles for prescribing medications, and following these best practices may improve outcomes [4].

This topic reviews the general principles for using pharmacotherapy to treat pediatric bipolar disorder. Other aspects of pediatric bipolar disorder are discussed separately, including an overview of choosing treatment; choosing treatment for bipolar major depression; the efficacy, administration, and side effects of second-generation antipsychotics for mania; the efficacy and core elements of adjunctive psychotherapy; assessment and diagnosis of pediatric bipolar disorder; and the epidemiology, clinical features, and course of illness:

- (See "Pediatric bipolar disorder: Overview of choosing treatment".)
- (See "Pediatric bipolar major depression: Choosing treatment".)
- (See "Pediatric mania and second-generation antipsychotics: Efficacy, administration, and side effects".)
- (See "Pediatric bipolar disorder: Efficacy and core elements of adjunctive psychotherapy".)
- (See "Pediatric bipolar disorder: Assessment and diagnosis".)
- (See "Pediatric bipolar disorder: Clinical manifestations and course of illness".)

ROLE OF THE PEDIATRICIAN

Although some pediatricians have the requisite training and experience to diagnose and manage juvenile bipolar disorder, the large majority of patients are referred to psychiatrists and other mental health clinicians if these specialists are available [2,5,6]. Common indications for referral include:

- Diagnostic uncertainty
- Suicidal ideation and behavior (see "Suicidal ideation and behavior in adults")
- Psychotic features (eg, auditory hallucinations commanding patients to kill themselves) (see "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation", section on 'Clinical manifestations')
- Catatonia – Prominent psychomotor disturbances, such as immobility, mutism, and posturing, which occur during most of the mood episode (see "Catatonia in adults: Epidemiology, clinical features, assessment, and diagnosis" and "Catatonia: Treatment and prognosis")
- Impulsive and dangerous behavior (eg, running away from home or significant aggression)
- Fluctuating symptoms
- Pregnancy
- Functional impairment (eg, not attending school)
- Comorbid psychopathology (eg, attention deficit hyperactivity disorder, anxiety disorders, and substance-related and addictive disorders)
- Use of potentially destabilizing medications (see 'Potentially destabilizing drugs' below)
- Multiple (eg, two) failed medication trials due to poor response or lack of tolerability
- Administering adjunctive psychotherapy
- Recurrent mood episodes
- Poor adherence
- Discontinuing treatment following a period of stability

Primary care clinicians who refer patients to specialists are encouraged to remain involved in management [5]. Pediatricians can help educate patients and families about the benefits and risks of pharmacotherapy and reinforce the need for adherence, and typically collaborate in evaluating patients prior to treatment by obtaining a general medical history and performing a physical examination, and monitoring vital signs, weight, height, waist size, and metabolic laboratory tests during treatment.

PRETREATMENT EVALUATION

Prior to commencing pharmacotherapy for pediatric bipolar disorder, clinicians should evaluate patients to establish the diagnosis and determine the treatment plan. Interviews should include the patient and parents, and reports from the school may be helpful as well [7]. The assessment may take several hours and multiple visits [8,9].

However, children and adolescents may present with severe symptoms that require clinicians to initiate pharmacotherapy after an expedited evaluation, but before the diagnosis of bipolar disorder is certain. In these situations, family psychiatric history, prior treatment history (including response and adverse effects), comorbidities, and burden of current manic or depressive symptoms can guide decisions about potential risks and benefits of specific pharmacologic treatments. As an example, if a patient without a family history of bipolar disorder clearly has attention deficit hyperactivity disorder (ADHD) and possibly has manic symptoms, but has never had a trial of stimulants, the risk/benefit ratio might favor an initial trial of stimulants rather than an antimanic drug. By contrast, if a patient with ADHD symptoms also has recurrent, distinct one- to two-day episodes of elated mood, decreased need for sleep, grandiosity, and increased goal-directed activity, along with a family history of mania, and has become agitated and aggressive during trials of two different stimulants, the risk-benefit ratio favors treatment with an antimanic drug.

The evaluation identifies target symptoms for pharmacotherapy, including symptoms of mania, hypomania, and major depression (table 1 and table 2 and table 3), as well as anxiety, psychosis, inattention, and hyperactivity [9]. As an example, chronic distractibility and impulsivity in a child with bipolar disorder and comorbid ADHD often do not improve substantially with antimanic drugs; however, euphoria, irritability, grandiosity, and decreased need for sleep should improve. Identifying the target symptoms often requires probing. A patient with episodes of rage may reveal that the episodes stem from an inability to complete homework, which in turn is due to anxiety and poor attention [5]. Target symptoms may need to be modified over time as patients undergo developmental changes [10]. A comprehensive

assessment of symptoms enables clinicians to subsequently distinguish psychiatric adverse effects secondary to pharmacotherapy from the baseline disorder [9].

Pretreatment assessments also address factors that can interfere with pharmacotherapy [9]. These include prior nonadherence to medications as well as fears, prejudices, and false beliefs regarding medication on the part of patients and parents. Treatment is unlikely to succeed without the family's cooperation [7,9]. (See 'Adherence' below.)

If many (eg, three or more) months have 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 renal or thyroid disease), and establish the absence of movement disorders at baseline. The history includes cardiac illnesses, endocrine or metabolic problems, gastrointestinal difficulties, and neurologic symptoms, as well as menstrual history in girls [4]. It is useful to ask about 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. Family history of cardiac conduction problems (particularly sudden cardiac death) and endocrine and metabolic illnesses is important.

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 Lexicomp drug interactions tool (Lexi-Interact Online) 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). Laboratory tests are performed as indicated by the history and examination [4]. 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 before initiating an antipsychotic or obtaining renal function tests prior to using lithium) [11]. A pregnancy test is recommended for all postmenarchal females; a 12-month prospective study of female adolescents with bipolar disorder (n = 125) found that pregnancy occurred in 5 percent [12].

Assessment by other specialists may indicated, such as neurology [7]. If there are concerns about learning disorders or cognitive impairment, neuropsychological testing may be indicated.

Additional information about assessing youth for bipolar disorder and making the diagnosis is discussed separately. (See "Pediatric bipolar disorder: Assessment and diagnosis", section on

'Assessment'.)

Patients with pediatric bipolar disorder may have parents with psychopathology (eg, bipolar or unipolar depressive disorders) that can affect treatment outcomes in the offspring. We suggest referring parents for evaluation if they are not receiving psychiatric treatment and appear to have a mental illness or difficulty coping with their child's illness.

PATIENT AGE

More studies of pharmacologic treatment for bipolar disorder have been conducted in adolescents than in younger children. Nevertheless, pharmacotherapy can effectively treat children as well as adolescents. Multiple randomized trials have demonstrated that medications (eg, second-generation antipsychotics) are efficacious for mania in patients aged 10 to 17 years [13-18]. Randomized trials also indicate that preadolescent and preschool children with bipolar disorder, as well as adolescents, respond to pharmacotherapy [17,19,20]. As an example:

- A small, six-week trial compared risperidone with placebo for mania in children aged three to seven years (n = 25) and found that improvement was greater with risperidone [21].
- An eight-week trial found that risperidone was efficacious for treating mania in 279 youth and that the rate of response (symptoms improved much or very much from baseline) appeared to be comparable for children age 6 to 12 years and adolescents age 13 to 15 years (65 and 75 percent) [22].

In addition, multiple observational studies suggest that medications can successfully treat mania in children as young as age four years [23-26].

INDICATIONS

Nearly all children and adolescents with bipolar disorder are treated with pharmacotherapy. However, electroconvulsive therapy (ECT) is indicated for severely and persistently ill patients who are refractory to many (eg, four to five) medication trials.

Pharmacotherapy — Pharmacotherapy is indicated for treatment of bipolar youth with [1,27-30]:

- Mania (table 1) or hypomania (table 2)

- Subsyndromal symptoms that do not meet diagnostic criteria for mania or hypomania, but nevertheless impair functioning; these syndromes are diagnosed as “other specified bipolar and related disorder”

- Comorbid attention-deficit hyperactivity disorder or anxiety disorders that impair functioning

- Moderate to severe major depression (table 3) (eg, substantial impairment, psychotic features, or suicidal ideation with a plan for self-harm)

Medications are also indicated for treatment of major depression of mild severity if psychotherapy is not available or effective.

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'.)

The goals of pharmacotherapy are to reduce mood symptoms and symptoms of comorbid disorders, and to improve the overall functioning of the child or adolescent. Optimally, the child or adolescent should return to their baseline “premorbid” position on the developmental trajectory, prior to the onset of mood symptoms. In many youth with bipolar disorder, it can be difficult to identify a premorbid baseline, in which case the goal is the best possible functioning achievable with the fewest adverse effects.

Practice guidelines from the United Kingdom National Institute for Health and Care Excellence recommend judicious use of pharmacotherapy in treating pediatric bipolar disorder [2,6]. As an example, ongoing treatment with antipsychotics should be periodically re-evaluated (eg, every three months). In addition, valproate is avoided in females of childbearing age unless alternatives are not available and contraception is used, due to the risk of teratogenesis and developmental abnormalities.

The clinical features and diagnosis of mania, hypomania, major depression, psychosis, and other specified bipolar and related disorder in children and adolescents with bipolar disorder are discussed separately. (See "Pediatric bipolar disorder: Clinical manifestations and course of illness", section on 'Clinical presentation' and "Pediatric bipolar disorder: Assessment and diagnosis", section on 'Diagnosis'.)

Electroconvulsive therapy — The indications for ECT in bipolar disorder are similar for youth and adults. Indications include [9,31,32]:

- Severe mood episodes, such as those with psychotic features, that do not respond to multiple (eg, five or more) trials of pharmacotherapy.
- Catatonia that does not respond to pharmacotherapy.
- Acute safety concerns that are caused by mood episodes and cannot be mitigated by environmental interventions or pharmacotherapy; safety concerns include recurrent suicide attempts, fluid and food refusal that compromises the patient's health, and persistent, severe agitation or aggression.

ECT is used infrequently for adolescents and rarely for younger children.

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 and day treatment or partial hospital. The choice is based 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 behaviors or psychotic features), risky or dangerous behaviors (eg, physical fights), comorbid psychopathology (eg, substance-related disorder or anxiety disorder), poorer psychosocial functioning (eg, truancy), problematic adherence to pharmacotherapy, and insufficient family support.

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 [33].

CHOOSING TREATMENT

Choosing a specific medication regimen is discussed separately. (See "Pediatric bipolar disorder: Overview of choosing treatment" and "Pediatric bipolar major depression: Choosing treatment".)

Informed consent — Part of choosing treatment is obtaining informed consent from the parents; in addition, clinicians should try to obtain assent from the patient [7]. The discussion includes the intended purpose of pharmacotherapy, available options (including no treatment),

and the demonstrated efficacy and potential adverse effects for each option. Printed and online information can facilitate the discussion. (See 'Information for patients and families' below.)

MONOTHERAPY

For children and adolescents with bipolar disorder, we generally initiate pharmacotherapy with monotherapy to facilitate adherence, avoid drug-drug interactions, and minimize adverse effects and costs [7]. Nevertheless, many patients require medication combinations. (See 'Medication combinations' below.)

Successfully achieving monotherapy is more likely if one takes a “start low, go slow, but keep moving up” approach, particularly in outpatient settings [7] (see 'Dose' below). Metabolism and tolerability of antimanic medications vary widely in children, so using low starting doses and cautious titration schedules can reduce the risk of substantial side effects that lead to medication discontinuation. However, the correct dose of medication is the one that provides optimal response with an acceptable level of side effects, so continued titration upward is required if there are persistent symptoms and the drug is tolerated. Undertreatment can lead to prematurely discontinuing a potentially efficacious medication and categorizing it as ineffective [29].

Nonresponse — Medications are often not beneficial for children and adolescents diagnosed with bipolar disorder. However, factors other than lack of efficacy can cause nonresponse, including [27,29,34]:

- Misdiagnosis.
- Poor adherence. (See 'Adherence' below and "Bipolar disorder in adults: Managing poor adherence to maintenance pharmacotherapy".)
- Comorbidities (eg, anxiety disorders, attention deficit hyperactivity disorder [ADHD], and substance use disorders) – As an example, a meta-analysis of five observational studies of children and adolescents with bipolar disorder (total n = 273) found that response was less likely in youth with comorbid ADHD than youth without ADHD (relative risk 0.82, 95% CI 0.69-0.97) [35].
- Stressors (eg, family, social, and school).

If a monotherapy trial provides minimal benefit in the absence of factors that can lead to nonresponse, then it is best to switch to another medication and cross-taper the drugs, removing one agent while simultaneously adding the other. However, if a partial response

occurs and tolerability prevents a dose increase, then adding another drug from a different class may be indicated [27,29].

MEDICATION COMBINATIONS

Medication combinations are frequently necessary and appear to predominate pharmacotherapy for pediatric bipolar disorder [2,29,36], such that approximately 70 to 80 percent of patients receive at least two drugs. As an example, a retrospective study of youth with bipolar disorder who were treated in a specialty clinic (n = 53) found that monotherapy was used in only 23 percent and that the mean number of medications was three [37]. In addition, a study of administrative claims data for the first month of treatment in children and adolescents with bipolar depression (n >5400) found that monotherapy was used in 31 percent, two medications in 49 percent, and three medications in 20 percent [38].

Adding a second medication can be especially useful for patients with [4,9,29]:

- Partial response to monotherapy
- Severe symptoms (eg, psychosis)
- Severe mood episodes (eg, inpatients)
- Comorbid illnesses such as attention deficit hyperactivity disorder or anxiety disorders
- Side effects from an otherwise efficacious drug (eg, extrapyramidal symptoms due to antipsychotics)

However, there are fewer studies of medication combinations than single drugs [4,9,30,39].

Medication combinations should generally involve drugs from different classes, such as [4,29,40-42]:

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

Combining two second-generation antipsychotics is typically not indicated and the evidence supporting this approach is limited.

Children and adolescents with poorly controlled bipolar disorder may present with a treatment regimen that consists of multiple medications. In such cases, we suggest discontinuing at least one medication before adding another [43].

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 [5].

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 consisting of three drugs (eg, a second-generation antipsychotic, lithium, and divalproex) are sometimes indicated [27,44]. However, complex regimens involving more than five psychotropic drugs are rarely helpful and almost always best avoided [7].

POTENTIALLY DESTABILIZING DRUGS

Children and adolescents who are taking antidepressants and/or stimulants, and do not have an established diagnosis of bipolar disorder, may present with symptoms (eg, irritability) that appear to represent mania. We suggest tapering and discontinuing these potentially destabilizing medications because they may cause or exacerbate the symptoms, unless prior history indicates that discontinuation is problematic [29]. 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 antidepressants and/or stimulants.

Antidepressants and stimulants are potentially destabilizing in patients with an established diagnosis of bipolar disorder, especially those who are suffering an episode of mania [22,43,45,46]:

- **Antidepressants** – 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: Choosing treatment".)

- **Stimulants** – In youth with bipolar disorder who are taking an antimanic drug, stimulants are generally safe and efficacious for treating comorbid attention deficit hyperactivity disorder [29]. This approach is consistent with the International Society for Bipolar Disorders Task Force report on pediatric bipolar disorder [47]. 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. (See "Pediatric bipolar disorder: Overview of choosing treatment", section on 'Attention deficit hyperactivity disorder'.)

DOSE

We suggest starting medications at a low dose and titrating upward [7]. Metabolism and tolerability of antimanic medications vary widely in children, so using low starting doses and cautious titration schedules can reduce the risk of substantial side effects that lead to medication discontinuation. However, the correct dose of medication is the one that provides optimal response with an acceptable level of side effects, so continued titration upward is required if there are persistent symptoms and the drug is tolerated. Undertreatment can lead to prematurely discontinuing a potentially efficacious medication and categorizing it as ineffective [29].

Weight-adjusted doses are typically higher in youth (especially larger adolescents) than adults, to achieve the same serum concentrations and therapeutic benefits [7]. This is due in part to differences in pharmacokinetics between youth and adults. As an example, hepatic metabolic activity is greater in childhood than adulthood because the liver is proportionally larger in youth. In addition, the volume of distribution for water soluble drugs is greater in younger children because they have a greater volume of extracellular water.

COMPREHENSIVE TREATMENT

Pediatric bipolar disorder is typically managed with multimodal treatment [7]. Although pharmacotherapy is the primary treatment, psychotherapy, such as psychoeducation about the disorder and its management, is nearly always indicated as well. This approach is consistent with treatment guidelines [1], including those from the National Institute for Health and Care Excellence [2], Royal Australian and New Zealand College of Psychiatrists [48], and International Society for Bipolar Disorders Task Force [47]. (See "Pediatric bipolar disorder: Efficacy and core elements of adjunctive psychotherapy".)

In addition, 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 interactions between family members and improve family functioning as a unit. Detailed information about family therapy is discussed separately in the context of adult unipolar depression. (See "Unipolar depression in adults: Family and couples therapy".)

Furthermore, children and adolescents with bipolar disorder are often best served by modifications of the school environment [49,50]:

- Individual education plan
- Excused absences for appointments with clinicians
- Steps to minimize overstimulation in the classroom
- More frequent breaks
- Regular visits with school counselor
- Accommodation for transition to new teachers or schools
- Specific plan for behavior problems

Multimodal treatment often involves multiple clinicians. Communication among the members of the treatment team is necessary and may need to include teachers [4,7].

In-home services may also be indicated for children and adolescents with bipolar disorder.

MONITORING

Monitoring of patients prescribed medications includes symptoms, adverse effects (including extrapyramidal symptoms and movement disorders), adherence, and functioning, and typically includes blood pressure, pulse, weight, waist size, body mass index (calculator 1), and metabolic laboratory tests.

Changes in symptoms can be monitored with clinician administered rating scales, such as the Young Mania Rating Scale (YMRS), Kiddie-Schedule for Affective Disorders and Schizophrenia Mania Rating Scale, and the Children's Depression Rating Scale – Revised, as well as caregiver questionnaires such as the parent-rated YMRS, Global Behavioral Inventory, or Child Mania Rating Scale [51-59]. 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 than parent and clinician ratings [60]. Teachers can also provide information when symptoms or medications affect school behavior or performance.

Clinicians can use the Abnormal Involuntary Movement Scale (form 1) to monitor patients for extrapyramidal symptoms and movement disorders.

Monitoring for specific medications (eg, weight and lipid profile in patients treated with risperidone) is discussed separately. (See "Pediatric mania and second-generation antipsychotics: Efficacy, administration, and side effects" and "Pediatric bipolar disorder: Overview of choosing treatment", section on 'Treatment-resistant patients' and "Pediatric bipolar disorder: Overview of choosing treatment", section on 'Treatment-refractory patients'.)

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 [4].

For stable patients who discontinue pharmacotherapy, clinicians are advised to continue monitoring for signs of recurrence [4]. 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) until the patient reaches adulthood, at which point it may be reasonable to discontinue monitoring.

Adherence — Clinicians prescribing pharmacotherapy to youth with bipolar disorder should monitor adherence, because noncompliance is common [2].

Multiple prospective observational studies of patients with manic or mixed episodes indicate that problematic adherence ranges from approximately 33 to 66 percent:

- A 20-week study of children and adolescents who were treated with lithium (n = 107) found that the proportion of serum concentrations less than the minimal therapeutic level (<0.6 mEq/L/0.6 mmol/L) was 34 percent [61].
- A study of bipolar adolescents (n = 71) who were hospitalized and then followed for up to 12 months found that full medication adherence (medication taken as prescribed >75 percent of the time) was reported by only 35 percent of the patients [62].

In addition, adherence is often poor in pediatric bipolar depression. A six-month study of administrative claims data found that among children and adolescents with bipolar depression (n >5400), discontinuation of all pharmacotherapy occurred in 14 to 30 percent, depending upon the specific medication regimen prescribed [38].

Among adolescents with bipolar disorder, multiple factors are associated with poor adherence to treatment, including greater illness severity, denial of one's illness, impaired family functioning, complex medication regimens, frequent (eg, three or four) daily doses, cognitive difficulties, and adverse effects [7,63,64]. Resistance to taking medication may also stem from difficulties accepting bipolar disorder as part of one's identity (feeling different from peers), and concerns about fitting in with peer groups. Conversely, factors that are associated with good adherence include good family 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 [64].

Another factor involved in adherence is the youth's developmental stage. Concrete thinking may prevent younger adolescents from understanding the consequences of not taking their medications [64].

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") [64]. 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.

Other means of assessing adherence include serum concentrations for relevant medications (eg, lithium), pill counts, electronic monitoring of pill bottles or boxes, and checking prescription refills. Counting pills may yield higher estimates of adherence than serum concentrations. In a 20-week, prospective observational study of children and adolescents who were treated with lithium (n = 107), pill counts suggested that adherence to lithium was 100 percent [61]. By contrast, the proportion of serum concentrations greater than the minimal therapeutic level (<0.6 mEq/L/0.6 mmol/L) was 66 percent. Other prospective studies suggest that subjective reports from patients, parents, and prescribing clinicians overestimate adherence [63].

Parents/caregivers must be involved in treatment to facilitate adherence to medication regimens [2,7,9]. School personnel may also need to assist patients taking their medication [7].

Use of weekly pillboxes can help everyone involved monitor whether doses are taken, while allowing trustworthy adolescents to take primary responsibility [7]. Parents/caregivers do not remind the adolescent about taking the medication unless the dose is still in the box after the dose time.

Other steps for enhancing adherence include informing the patient and family about potential adverse effects without creating negative expectations (nocebo effects), reducing the frequency of doses (eg, twice per day rather than three times per day), and preparing everyone involved for the possibility that multiple treatment trials may be necessary to optimize efficacy and adverse effects.

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.

Different adjunctive psychotherapies administered for pediatric bipolar disorder often address medication adherence, and adjunctive motivational interviewing can be used to focus primarily upon adherence. As an example, one specialty clinic developed a three-session, motivational interviewing intervention that targeted 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 [65]. Adjunctive psychotherapies for bipolar disorder in children and adolescents are discussed separately. (See "Pediatric bipolar disorder: Efficacy and core elements of adjunctive psychotherapy".)

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".)

DURATION OF AN ADEQUATE TRIAL

An acute pharmacotherapy trial for mania generally lasts approximately four to eight weeks before determining whether the regimen is beneficial [9,14,15,17-20,66]. Although treatment for longer periods has been studied, response rates do not appear to increase much beyond those achieved after four to eight weeks. As an example, a 30-week randomized trial (n = 296) compared aripiprazole (target dose either 10 or 30 mg/day) with placebo [13,16]. Among patients who received aripiprazole 10 mg/day, response (reduction of baseline symptoms ≥50 percent) at week 4 occurred in 45 percent, and response at week 30 occurred in 59 percent of patients. Among patients who received aripiprazole 30 mg/day, response at weeks 4 and 30 occurred in 64 and 65 percent.

The duration of an adequate trial for judging the benefit of medication regimens for pediatric bipolar major depression is approximately eight weeks, based upon one randomized trial. This is comparable to the length of antidepressant trials in juvenile unipolar major depression. (See "Pediatric bipolar major depression: Choosing treatment", section on 'Initial drugs' and "Pediatric unipolar depression and pharmacotherapy: General principles", section on 'Duration of an adequate trial'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Bipolar disorder".)

INFORMATION FOR PATIENTS AND FAMILIES

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

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

- Basics topics (see "Patient education: Bipolar disorder (The Basics)" and "Patient education: Coping with high drug prices (The Basics)")

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

These educational materials can be used as part of psychoeducational psychotherapy. (See "Pediatric bipolar disorder: Overview of choosing treatment", section on 'First line'.)

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. Bipolar disorder is one of their priorities.

SUMMARY AND RECOMMENDATIONS

- **Role of the pediatrician** – Although some pediatricians can manage pediatric bipolar disorder, nearly all patients are referred to psychiatrists. Nevertheless, the referring pediatrician is encouraged to remain involved in management. (See 'Role of the pediatrician' above.)

- **Pretreatment evaluation** – Prior to commencing pharmacotherapy for pediatric bipolar disorder, clinicians should evaluate patients to establish the diagnosis and identify target symptoms (table 1 and table 2 and table 3) and factors that can interfere with

pharmacotherapy. However, some patients may present with severe symptoms that require clinicians to initiate pharmacotherapy after an expedited evaluation. (See 'Pretreatment evaluation' above and "Pediatric bipolar disorder: Assessment and diagnosis", section on 'Assessment'.)

- **Treatment setting** – Treatment of pediatric bipolar disorder can occur in outpatient or inpatient settings, and intermediate levels of care. Indications for a higher level of care include more severe symptoms, comorbid psychopathology, poorer psychosocial functioning, problematic adherence to pharmacotherapy, and insufficient family support. (See 'Treatment setting' above.)

- **Pharmacotherapy**

  - Multiple medications are available to treat pediatric bipolar disorder. (See "Pediatric bipolar disorder: Overview of choosing treatment" and "Pediatric bipolar major depression: Choosing treatment".)

  - For most children and adolescents with bipolar disorder, we suggest initiating pharmacotherapy with monotherapy rather than medication combinations, to facilitate adherence, avoid drug-drug interactions, and minimize adverse effects and costs (**Grade 2C**). (See 'Monotherapy' above.)

  - Medication combinations involving drugs from different classes are used in bipolar patients who respond incompletely to monotherapy, and patients with severe mood episodes, comorbidities, or side effects from an otherwise efficacious drug. (See 'Medication combinations' above.)

  - Antidepressants and/or stimulants may possibly destabilize children and adolescents with bipolar disorder. (See 'Potentially destabilizing drugs' above.)

  - Medications are generally started at low doses and slowly titrated upward. Weight-adjusted doses are typically higher in youth than adults, to achieve the same serum concentrations and therapeutic benefits. (See 'Dose' above.)

- **Comprehensive treatment** – Pediatric bipolar disorder is typically managed with multimodal treatment that includes pharmacotherapy and psychotherapy. (See 'Comprehensive treatment' above.)

- **Monitoring** – Patient monitoring ’includes symptoms, adverse effects, adherence, and functioning, as well as blood pressure, pulse, weight, waist size, body mass index (calculator 1), and metabolic laboratory tests. (See 'Monitoring' above.)

- **Adherence** – Adherence to pharmacotherapy requires involvement of parents and may be enhanced by using weekly pillboxes, reducing the complexity of medication regimens and the frequency of doses, and informing patients and families about potential adverse effects without creating negative expectations. (See 'Adherence' above.)

- **Acute pharmacotherapy trials** – An acute pharmacotherapy trial for pediatric mania generally lasts approximately four to eight weeks before determining whether the regimen is beneficial, and approximately eight weeks for bipolar major depression. (See 'Duration of an adequate trial' above.)

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