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Pediatric bipolar major depression: Choosing treatment

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INTRODUCTION

Pediatric bipolar disorder often includes episodes of major depression. As an example, a four-year, prospective observational study of children and adolescents with bipolar disorder (n = 413) found that they were ill with major depression for 6 percent of the follow-up time and ill with subsyndromal depressive symptoms for another 12 percent of the time [1].

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

- (See "Pediatric bipolar disorder: Overview of choosing treatment".)
- (See "Pediatric bipolar disorder and pharmacotherapy: General principles".)
- (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".)

GENERAL PRINCIPLES

A separate topic discusses the general principles for treating pediatric bipolar disorder with pharmacotherapy, including the role of the pediatrician; assessing patients prior to treatment;

prescribing medications to age-appropriate patients; indications for pharmacotherapy (and electroconvulsive therapy); using monotherapy, medication combinations, and drugs that may destabilize patients; administering medications as part of comprehensive treatment; monitoring patient progress; the duration of an adequate drug trial; and information for patients and families. (See "Pediatric bipolar disorder and pharmacotherapy: General principles".)

APPROACH TO TREATMENT

We suggest that acute treatment of pediatric bipolar major depression proceed according to the sequence described in the subsections below, which is summarized in the algorithm (algorithm 1). Patients receive initial pharmacotherapy and progress through each step until they respond. The duration of an adequate treatment trial is discussed separately. (See "Pediatric bipolar disorder and pharmacotherapy: General principles", section on 'Duration of an adequate trial'.)

In addition, psychotherapy is nearly always indicated as an adjuvant to pharmacotherapy for pediatric bipolar disorder. (See "Pediatric bipolar disorder: Overview of choosing treatment", section on 'Adjunctive psychotherapy'.)

Following response to acute treatment, patients receive maintenance treatment to prevent recurrences. (See 'Using antidepressants' below and "Pediatric bipolar disorder: Overview of choosing treatment", section on 'Maintenance pharmacotherapy'.)

Initial drugs — Based upon randomized trials, first-line treatment for children and adolescents with bipolar major depression is either lurasidone monotherapy or an alternative second-generation antipsychotic plus a selective serotonin reuptake inhibitor (SSRI).

Lurasidone monotherapy is started at a dose of 20 mg/day for one week; the drug is administered once daily in the evening with food [2]. Depending upon efficacy and tolerability, lurasidone is titrated up (eg, 20 mg/day each week) until the patient responds or reaches the maximum dose of 80 mg/day.

When combining a second-generation antipsychotic and an antidepressant, the two drugs are typically started simultaneously. However, for patients who are moderately ill, a reasonable alternative is to initially start only an antipsychotic; patients who respond within one to two weeks continue with antipsychotic monotherapy, whereas patients who do not respond satisfactorily receive add-on treatment with an SSRI. The second-generation antipsychotics that we use include aripiprazole, olanzapine, quetiapine, and risperidone. SSRIs typically used

include escitalopram, fluoxetine, and sertraline. Citalopram is generally avoided, given the concerns about cardiac conduction problems at doses higher than 40 mg/day; paroxetine is also not recommended given problems with withdrawal symptoms and drug interactions.

For pediatric bipolar major depression that does not respond to lurasidone monotherapy, we suggest that clinicians continue the antipsychotic and add an SSRI.

For pediatric bipolar major depression that does not respond to a second-generation antipsychotic plus an SSRI within six to eight weeks, we suggest that clinicians continue the antipsychotic and switch to another antidepressant. We generally switch to a different SSRI by cross-tapering the two drugs over a few days to one week. If patients do not respond to the antipsychotic plus a different SSRI within six to eight weeks, we usually continue the antipsychotic and switch to another antidepressant, such as a serotonin-norepinephrine reuptake inhibitor (SNRI; eg, venlafaxine) or bupropion. The antidepressants are cross-tapered over one to two weeks. However, a reasonable alternative is to continue the SSRI and switch antipsychotics by cross-tapering them over one to two weeks. Additional information about switching antidepressants is discussed separately in the context of adults. (See "Switching antidepressant medications in adults".)

A network meta-analysis and randomized trials support treatment of pediatric bipolar major depression with lurasidone monotherapy or an alternative second-generation antipsychotic plus an SSRI:

- A network meta-analysis (four trials, 797 youths ages 10 to 18) compared second-generation antipsychotics, lurasidone, quetiapine, and olanzapine plus fluoxetine in the treatment of bipolar I major depression [3]. Treatment with either lurasidone (-5.7; 95% CI -8.66 to -2.76) or olanzapine plus fluoxetine (-5.01; 95% CI -8.63 to 1.38) resulted in improvements in the Children's Depression Rating Scale-Revised versus placebo. Furthermore, lurasidone was associated with smaller change in weight, cholesterol, and triglycerides from baseline versus olanzapine plus fluoxetine or quetiapine.

- A six-week trial compared lurasidone (mean dose 33 mg/day) with placebo in youth with bipolar I major depression (n = 347) [2]. Adjunctive pharmacotherapy was allowed for agitation, anxiety, extrapyramidal symptoms, and insomnia; stimulants were permitted for comorbid attention deficit hyperactivity disorder. Response (reduction of baseline depressive symptoms ≥50 percent) occurred in more patients treated with lurasidone than placebo (60 versus 37 percent). Improvement of anxiety and functioning was also greater with lurasidone. Discontinuation of treatment due to adverse effects was identical with

lurasidone and placebo (2 percent). The most frequent adverse events with lurasidone were nausea (16 percent of patients) and somnolence (11 percent).

- An eight-week trial compared placebo with olanzapine plus fluoxetine in children and adolescents with bipolar major depression (n = 255) [4]. Olanzapine was initiated at 3 mg/day and the final mean dose was 8 mg/day; fluoxetine was started at 25 mg/day and the final mean dose was 38 mg/day. Remission occurred in more patients treated with olanzapine/fluoxetine than placebo (59 versus 43 percent), and the median time to remission with active drug was approximately seven weeks. In addition, switching to mania was comparable for active drug and placebo (1 and 0 percent). However, discontinuation of treatment due to adverse effects was more than twice as high in patients receiving olanzapine/fluoxetine than placebo (14 and 6 percent). Mean weight gain was greater with olanzapine/fluoxetine than placebo (4.4 versus 0.5 kg), and the incidence of sedation, tremor, hyperlipidemia, or hyperprolactinemia was greater with olanzapine/fluoxetine. Increases in heart rate and corrected QT interval were also greater with olanzapine/fluoxetine.

The efficacy of lurasidone monotherapy and of olanzapine plus fluoxetine for short-term treatment of bipolar major depression in youth is consistent with results from randomized trials in adults with bipolar major depression. (See "Bipolar major depression in adults: Efficacy and adverse effects of second-generation antipsychotics", section on 'Lurasidone' and "Bipolar major depression in adults: Efficacy and adverse effects of antidepressants", section on 'Olanzapine plus fluoxetine'.)

Indirect evidence supporting the use of quetiapine and risperidone for bipolar major depression includes randomized trials in adults. (See "Bipolar major depression in adults: Efficacy and adverse effects of second-generation antipsychotics", section on 'Efficacy'.)

Multiple randomized trials that compared quetiapine monotherapy with placebo for eight weeks in youth with bipolar major depression have found that quetiapine was not superior; however, placebo response rates were high in these trials, calling into question the apparent lack of benefit [5]. One trial found that response (reduction of baseline symptoms ≥50 percent) to placebo (n = 100 patients) occurred in 55 percent [6], and a second trial found that response to placebo (n = 15) occurred in 10 patients (67 percent) [7].

Aripiprazole has been studied in prospective observational studies of pediatric bipolar major depression [8], and the drug is generally not sedating and has a favorable metabolic profile relative to some other antipsychotics used for pediatric bipolar disorder. (See "Pediatric mania

and second-generation antipsychotics: Efficacy, administration, and side effects", section on 'Weight gain'.)

In patients with pediatric bipolar major depression who do not respond to initial treatment with a second-generation antipsychotic plus an SSRI, indirect evidence that supports switching the SSRI to a second SSRI or to venlafaxine includes randomized trials in youth and in adults with unipolar major depression. (See "Pediatric unipolar depression and pharmacotherapy: Choosing a medication", section on 'Second-line' and "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Antidepressants'.)

Using antidepressants — It is reasonable to prescribe antidepressants for pediatric bipolar major depression, provided that antimanic drugs such as a second-generation antipsychotics or lithium are also used [9]. However, antidepressants should not be used in bipolar major depression with mixed features (symptoms of mania/hypomania).

Patients treated with antidepressants are monitored for symptoms of mania (eg, irritability, mood lability, agitation, or other mood symptoms). Although a randomized trial [4] and a prospective observational study [10] both indicate that antidepressants do not increase the risk of treatment emergent mania, other observational studies have raised persistent concerns that antidepressants may destabilize children and adolescents with bipolar disorder [11-15].

For patients with bipolar depression who are successfully treated with adjunctive antidepressants and remain stable for several (eg, three to six) months, we suggest slowly tapering the antidepressant (eg, over two to four months) and discontinuing the antidepressant, unless this has precipitated relapse in the past.

Additional information about the use of adjunctive antidepressants in bipolar major depression, including the role and efficacy of antidepressants and the risk of switching to mania, is discussed separately in the context of adults. (See "Bipolar major depression in adults: Efficacy and adverse effects of antidepressants".)

Treatment-resistant patients — Pediatric bipolar major depression often does not respond sufficiently to multiple (eg, two to three) trials of a second-generation antipsychotic plus an antidepressant. For these treatment-resistant patients, we suggest lamotrigine, lithium, or omega-3 fatty acids (n-3 polyunsaturated fatty acids). If patients partially responded to a second-generation antipsychotic plus an antidepressant, we add lamotrigine, lithium, or omega-3 fatty acids to the existing regimen. If there was little to no response to the antipsychotic plus antidepressant, we discontinue the antidepressant and add lamotrigine, lithium, or omega-3 fatty acids to the antipsychotic; however, a reasonable alternative is to

discontinue both the antipsychotic and antidepressant, and to start lamotrigine or lithium monotherapy. Omega-3 fatty acids are rarely used as monotherapy.

Patients unresponsive to either lamotrigine or lithium (as add-on treatment or monotherapy) are switched to the other drug by cross-tapering them over one to two weeks. Omega-3 fatty acids can be added at any point during treatment because they are well tolerated.

Administration of lamotrigine and lithium are discussed separately. (See "Pediatric bipolar disorder: Overview of choosing treatment", section on 'Treatment-refractory patients' and "Pediatric bipolar disorder: Overview of choosing treatment", section on 'Treatment-resistant patients'.)

In using omega-3 fatty acids, we prefer formulations with a ratio of eicosapentaenoic acid to docosahexaenoic acid of approximately two to one. The dose is typically 500 to 1000 mg twice per day.

Antidepressants should generally be tapered before discontinuation. A taper of approximately 25 to 50 percent per week provides a gradual decrease that allows the body time to adjust to the lower dose. As an example, sertraline 200 mg per day can be decreased to 150 mg per day for week 1, 100 mg per day for week 2, 50 mg per day for week 3, and 25 mg per day for week 4, after which the medication is stopped. However, the half-life of fluoxetine is long enough such that abrupt discontinuation generally does not cause problems. Additional information about discontinuing antidepressants is discussed separately. (See "Discontinuing antidepressant medications in adults".)

Second-generation antipsychotics that are discontinued are generally tapered over one to two weeks before the drug is stopped.

Using lamotrigine to treat pediatric bipolar major depression is supported by small observational studies [16-18]. As an example, an eight-week prospective study included 19 adolescents who were treated with lamotrigine (typically as monotherapy), which was started at 10 to 25 mg/day and slowly increased over several weeks to a mean final dose of 132 mg/day [8]. Remission occurred in 11 patients (58 percent). The most frequent side effects were headache, fatigue, nausea, and diaphoresis.

Small observational studies also suggest that lithium may help pediatric bipolar major depression. A six-week prospective study included 27 hospitalized adolescents with bipolar major depression (including patients with psychotic features), who were treated with lithium monotherapy that was prescribed to achieve a target serum concentration of 1 to 1.2 mEq/L (1 to 1.2 mmol/L) [19]. Remission occurred in eight patients (30 percent). Mean weight gain was

1.7 kg; other adverse effects included headache, gastrointestinal distress, polyuria, and polydipsia.

Indirect evidence supporting the use of omega-3 fatty acids includes two small randomized trials:

- A 12-week trial enrolled children 5 to 12 years of age with manic, hypomanic, or mixed (mood elevated plus depressive) symptoms; the study included a treatment arm (n = 7 patients) with omega-3 fatty acid monotherapy (3000 mg/day) [20]. Improvement of baseline depressive symptoms ≥50 percent occurred in three patients (43 percent).

- Another 12-week trial randomly assigned youth 7 to 14 years of age with subsyndromal bipolar disorder to one of four treatments: omega-3 fatty acids (2000 mg/day) plus individual family psychoeducational psychotherapy (n = 5), omega-3 plus active monitoring (n = 5), placebo plus individual family psychoeducational psychotherapy (n = 7), or placebo plus active monitoring (n = 6) [21]. Improvement on one of the depression rating scales was superior with omega-3 plus individual family psychoeducational psychotherapy, compared with placebo plus active monitoring. However, omega-3 plus active monitoring provided no advantage over placebo plus active monitoring.

In addition, randomized trials in adults with bipolar major depression suggest omega-3 fatty acids may be beneficial. (See "Bipolar major depression in adults: Choosing treatment".)

Treatment-refractory patients — For children and adolescents with bipolar major depression who do not respond to initial and subsequent treatment, we suggest other medication combinations, such as lamotrigine plus lithium. However, a reasonable alternative is to add an antidepressant (eg, SSRI, SNRI, or bupropion) to lithium, based upon observational studies [22,23]. As an example, a retrospective study of youth with bipolar disorder (n = 42) found that improvement of depressive symptoms was seven times more likely to occur in patients who received an SSRI as part of treatment than patients who did not [11].

Other options — Other treatment options for pediatric bipolar major depression that does not respond to pharmacotherapy include adjunctive bright light therapy and electroconvulsive therapy (ECT).

- **Adjunctive bright light therapy** – Adjunctive bright light therapy is an option for patients who respond insufficiently to their treatment regimen but do not want to add a medication or switch medications. Light therapy is added to treatment regimens that include medications that can prevent episodes of mania and hypomania, such as second-generation antipsychotics, lamotrigine, or lithium. However, many children and

adolescents decline light therapy because it necessitates sitting in front of a light box for a minimum of 30 minutes every day. The administration, safety, and side effects of bright light therapy are discussed in the context of seasonal affective disorder. (See "Seasonal affective disorder: Treatment", section on 'Bright light therapy'.)

Indirect evidence supports the use of add-on bright light therapy for nonseasonal pediatric bipolar major depression. As an example, randomized trials in adults with nonseasonal, unipolar depression suggest that adjunctive light therapy may be efficacious. (See "Unipolar depression in adults: Investigational and nonstandard treatment", section on 'Bright light therapy'.)

In addition, an observational study in adults with nonseasonal bipolar depression (n = 9) [24] and a randomized trial in youth with seasonal affective disorder (n = 28) [25] suggest that bright light therapy may be helpful. However, an eight-week randomized trial that compared adjunctive light therapy with a placebo condition in adults with bipolar depression (n = 44) found that active treatment was not beneficial [26].

- **Electroconvulsive therapy** – For children and adolescents with severe, persistent, and disabling bipolar major depression that is unresponsive to multiple (eg, four or five) pharmacotherapy trials, we suggest ECT. This approach is consistent with treatment guidelines [9,27]. In particular, indications for ECT include suicidal plans plus intent, suicidal behavior, catatonia, or psychotic features. ECT is used infrequently for adolescents and rarely for younger children [28]. Evidence supporting the use of ECT includes retrospective studies in youth [27,29-31], as well as randomized trials in adult bipolar major depression. (See "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy", section on 'Bipolar major depression'.)

COMORBID DISORDERS

Treatment of pediatric bipolar disorder that is comorbid with attention deficit hyperactivity disorder or anxiety disorders is discussed separately. (See "Pediatric bipolar disorder: Overview of choosing treatment", section on 'Comorbid disorders'.)

MAINTENANCE TREATMENT

Children and adolescents with an acute bipolar major depressive episode who respond to acute pharmacotherapy usually receive the same regimen as maintenance treatment unless the regimen is poorly tolerated. Maintenance treatment for pediatric bipolar disorder is discussed

separately. (See "Pediatric bipolar disorder: Overview of choosing treatment", section on 'Maintenance pharmacotherapy'.)

Pediatric bipolar major depression may respond to an acute regimen that includes an antidepressant. The use of antidepressants in maintenance treatment is discussed elsewhere in this topic. (See 'Using antidepressants' above.)

ADJUNCTIVE PSYCHOTHERAPY

Psychotherapy is nearly always indicated as an adjuvant to pharmacotherapy for pediatric bipolar disorder. If symptoms are not responding adequately to psychotherapy, the frequency and/or intensity is increased (through multiple visits per week, intensive outpatient program, or partial hospitalization program). The use of psychotherapy for bipolar depression in youth is consistent with practice guidelines [32].

Choosing adjunctive psychotherapy for patients with bipolar major depression is discussed separately. (See "Pediatric bipolar disorder: Overview of choosing treatment", section on 'Adjunctive psychotherapy'.)

SOCIETY GUIDELINE LINKS

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

INFORMATION FOR PATIENTS

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: Depression in children and teens (The Basics)" and "Patient education: Depression in adults (The Basics)" and "Patient education: Medicines for depression (The Basics)" and "Patient education: Bipolar disorder (The Basics)" and "Patient education: When you have depression and another health problem (The Basics)")

- Beyond the Basics topics (see "Patient education: Depression in children and adolescents (Beyond the Basics)" and "Patient education: Depression treatment options for children and adolescents (Beyond the Basics)" and "Patient education: Bipolar disorder (Beyond the Basics)" and "Patient education: Depression in adults (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- For initial treatment of pediatric bipolar major depression, we suggest either lurasidone monotherapy or a different second-generation antipsychotic plus a selective serotonin reuptake inhibitor (SSRI), rather than other medication regimens (algorithm 1) (**Grade 2C**). If patients do not respond to lurasidone monotherapy, we typically continue the drug and add an SSRI. If patients do not respond to an antipsychotic and SSRI combination, we typically continue the antipsychotic and switch antidepressants. However, a reasonable alternative is to continue the initial antidepressant and switch to a different second-generation antipsychotic. (See 'Initial drugs' above.)

- Pediatric bipolar major depression that does not respond to a second-generation antipsychotic plus an antidepressant can be treated with lamotrigine, lithium, or omega-3 fatty acids:

  - If patients partially responded to a second-generation antipsychotic plus an antidepressant, we add lamotrigine, lithium, or omega-3 fatty acids to the existing regimen.

  - If there was little to no response to the antipsychotic plus antidepressant, we discontinue the antidepressant and add lamotrigine, lithium, or omega-3 fatty acids to the antipsychotic; however, a reasonable alternative is to discontinue both the antipsychotic and antidepressant, and to start lamotrigine or lithium monotherapy. Omega-3 fatty acids are rarely used as monotherapy. (See 'Treatment-resistant patients' above.)

- Other treatment options for bipolar major depression include medication combinations such as lamotrigine plus lithium or lithium plus an antidepressant, as well as adjunctive bright light therapy. We use electroconvulsive therapy (ECT) for severe, persistent, and disabling bipolar major depression that is unresponsive to several (eg, four to five) pharmacotherapy trials. (See 'Treatment-refractory patients' above and 'Other options' above.)

- For severe bipolar depression with catatonia, we suggest ECT rather than other treatment regimens (**Grade 2C**). (See 'Other options' above.)

- Children and adolescents with an acute bipolar major depressive episode who respond to acute pharmacotherapy usually receive maintenance treatment unless the regimen is poorly tolerated. (See 'Maintenance treatment' above and "Pediatric bipolar disorder: Overview of choosing treatment", section on 'Maintenance pharmacotherapy'.)

- Psychotherapy is nearly always indicated as an adjuvant to pharmacotherapy for pediatric bipolar disorder. (See "Pediatric bipolar disorder: Overview of choosing treatment", section on 'Adjunctive psychotherapy'.)

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