Pediatric mania and second-generation antipsychotics: Efficacy, administration, and side effects

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INTRODUCTION

For children and adolescents with mania, second-generation antipsychotics are often efficacious and thus frequently prescribed. As an example, a nationally representative survey of outpatient visits for bipolar disorder in the United States between 2005 and 2009 found that in adolescents, antipsychotics were prescribed in 29 percent of the visits [1]. In younger children, antipsychotics were prescribed in 12 percent of the visits.

This topic reviews the efficacy, administration, and side effects of second-generation antipsychotics in youth with mania. 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".)

SPECIFIC DRUGS

Randomized trials have demonstrated the efficacy of aripiprazole, asenapine, olanzapine, quetiapine, risperidone, and ziprasidone for children and adolescents with mania. No head-to-head trials have compared these drugs; nevertheless, there appear to be differences in some adverse effects.

Aripiprazole — Evidence for the efficacy of aripiprazole in treating pediatric mania, mixed mania, and subsyndromal manic symptoms includes three randomized trials:

- A four-week trial (n = 296) that compared aripiprazole (target dose either 10 mg/day or 30 mg/day) with placebo found that remission occurred in more patients who received aripiprazole 10 mg or 30 mg than placebo (25 and 48 versus 5 percent) [2].
- A six-week trial compared aripiprazole (mean dose 14 mg/day) with placebo in manic patients with comorbid attention deficit hyperactivity disorder (ADHD) (n = 43) [3]. Remission of mania occurred in more patients treated with aripiprazole than placebo (72 versus 32 percent). However, improvement of ADHD was comparable for the two groups, as was improvement of mixed (depressive) features.
- A 12-week trial compared aripiprazole (mean dose 7 mg) with placebo in youth aged 5 to 17 years (n = 59), who were diagnosed with cyclothymic disorder or bipolar disorder not otherwise specified, and had a family history of bipolar disorder [4]. Improvement of manic symptoms and functioning was greater with aripiprazole than placebo, and the clinical difference was large. However, emesis was greater with active drug, as was weight gain (2.3 versus 0.7 kg).

In children and adolescents, oral aripiprazole is routinely administered once daily at bedtime, and the starting dose frequently depends upon the child's weight [2,3]. Based upon one study, we suggest that patients weighing <25 kg receive 1 mg/day at treatment onset, patients weighing 25 to 50 kg receive 2 mg/day, and those weighing >50 kg start at 5 mg/day [5]. The dose is then titrated up by 1 to 5 mg every two to seven days depending upon response and tolerability, to a target dose ranging from 5 to 30 mg/day.

Common side effects include akathisia, sedation, nausea, vomiting, and weight gain [6]. As an example, a randomized trial (n = 296) found that akathisia occurred in more patients treated with aripiprazole 10 mg/day and 30 mg/day than placebo (8 and 11 versus 2 percent), as did sedation (19 and 26 versus 3 percent) [2,7]. In addition, mean weight gain over 30 weeks was greater with aripiprazole 10 mg/day and 30 mg/day than placebo (7 and 7 versus 3 kg) [8].

Asenapine — Evidence for the efficacy of asenapine in treating pediatric mania or mixed mania includes a three-week randomized trial (n = 395) that compared asenapine at three different

doses (2.5, 5, or 10 mg twice per day) with placebo [9]. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received asenapine 2.5, 5, or 10 mg than placebo (42, 54, and 52 versus 28 percent). Discontinuation of treatment due to adverse effects was comparable for all doses of asenapine (5 to 7 percent of patients) and placebo (4 percent).

Common side effects of asenapine in the randomized trial included sedation, increased appetite, and oral hypo/paresthesia [9]. (Asenapine is administered sublingually, and the oral hypo/paresthesia is due to local anesthetic effects.) In addition, weight gain ≥7 percent from baseline occurred in more patients treated with asenapine 2.5, 5, or 10 mg twice per day, compared with placebo (12, 9, and 8 versus 1 percent). Increases in fasting glucose, insulin, cholesterol, low density lipoprotein, and triglycerides were each greater with all asenapine doses than placebo; although the difference between asenapine and placebo for each of these metabolic factors was not statistically different in this three-week study, the findings nevertheless suggest the potential for metabolic problems with long-term treatment.

Olanzapine — Evidence for the efficacy of olanzapine for juvenile mania and mixed mania includes a three-week randomized trial (n = 161) that compared olanzapine (2.5 to 20 mg/day, mean daily dose 9 mg) with placebo [10]. Remission occurred in more patients treated with olanzapine than placebo (35 versus 11 percent). In addition, psychosocial functioning improved more with active drug [11].

Another important benefit of olanzapine is that if mania gives way to major depression, it is reasonable to continue olanzapine and add fluoxetine. (See "Pediatric bipolar disorder: Overview of choosing treatment", section on 'Major depression'.)

Olanzapine is typically administered once daily at bedtime, and started at a dose of 1 to 5 mg; doses at the lower end of this range are used for children (eg, age 4 to 6 years) and doses at the higher end of the range for adolescents (eg, age 15 to 18 years) [6]. The dose is then titrated up by increments of 1 to 5 mg/day every one to seven days, depending upon response and tolerability. The target dose is 10 mg/day, but efficacious doses range from 2.5 to 20 mg/day [12].

Weight gain with olanzapine is problematic:

- A three-week randomized (n = 161 manic adolescents) demonstrated that weight gain was greater with olanzapine than placebo (3.7 versus 0.3 kg) [10].
- An eight-week observational study (n = 17 children and adolescents with mania or hypomania) found that mean weight gain exceeded 5 kg [13].

- A pooled analysis of observational and randomized trial data from 179 adolescents with a variety of diagnoses, who were exposed to olanzapine for at least 24 weeks, found that mean weight gain was >11 kg [14].

Adjunctive topiramate (eg, 25 to 100 mg/day) may partially forestall olanzapine induced weight gain [13].

One randomized trial showed that sedation is more common with olanzapine than placebo [10]. In addition, olanzapine caused greater increases in systolic blood pressure and pulse, as well as total cholesterol, triglycerides, glucose, hepatic enzymes, prolactin, and uric acid.

Paliperidone — An eight-week prospective observational study found that among youth with mania, mixed mania, or hypomania who were treated with paliperidone (n = 15), remission occurred in seven (47 percent) [15]. The drug was started at 3 mg per day, once per day. In patients 12 years and older who weighed >45 kg, did not respond sufficiently after two weeks, and tolerated the drug, the dose was increased to 6 mg/day. Common side effects included decreased energy, headache, and insomnia; mean weight gain was 1.9 kg. Patients receiving paliperidone should be monitored for side effects that are common with second-generation antipsychotics. (See 'Class-wide side effects' below.)

Quetiapine — Evidence for the efficacy of quetiapine in treating pediatric mania and mixed mania includes three randomized trials:

- A three-week trial (n = 277 youth) found that remission occurred in more patients who received quetiapine 400 mg or 600 mg, compared with placebo (45 and 52 versus 23 percent) [16].

- A four-week trial compared quetiapine (400 to 600 mg/day) with divalproex (serum concentration 80 to 120 mcg/mL) in 50 patients, and found that remission occurred in more patients treated with quetiapine than divalproex (60 versus 28 percent) [17].

- A six-week trial in 109 youth compared quetiapine (400 to 600 mg/day) with lithium (serum concentration 1.0 to 1.2 mEq/L); response occurred more frequently with quetiapine (72 versus 49 percent) [18].

Quetiapine is started at 25 mg at bedtime or 25 mg twice daily. In children (eg, age 4 to 12 years), the dose is usually increased every day by 25 to 50 mg/day, and in adolescents (eg, age 13 to 18 years) by 50 to 100 mg/day [6]. The drug is generally administered in two divided doses; however, once daily dosing may suffice [17]. Although the target dose is 400 to 600

mg/day, clinical experience suggests that some youth respond to 200 to 300 mg/day, and others may require doses >600 mg/day (eg, 800 mg/day).

Rapid oral loading of quetiapine is feasible, generally well tolerated, and may be useful for severely ill patients (eg, inpatients), but is not standard treatment. A randomized trial (n = 25, mean age 15 years) [17] and a retrospective study (n = 75, mean age 10 years) [19] administered quetiapine 100 mg on day one and titrated the drug up to 400 mg/day within four to seven days.

Common adverse effects with quetiapine include dizziness, sedation, tachycardia, and weight gain [6]. In a three-week randomized trial (n = 188) that compared quetiapine (400 mg/day) with placebo, the incidence of dizziness was 19 and 2 percent, sedation was 23 and 4 percent, and tachycardia was 5 and 0 percent; and mean weight gain was 1.7 and 0.4 kg [16]. It may be possible to ameliorate sedation by administering the drug in three divided doses, and/or giving a larger dose at bedtime and a smaller dose during the day.

Risperidone — Several randomized trials indicate that risperidone can ameliorate pediatric mania and mixed mania:

- A three-week trial compared risperidone (target dose either 0.25 to 2.5 mg/day or 3 to 6 mg/day) with placebo in 169 patients [20]. Remission was greater in both groups that received risperidone than placebo (43 and 43 versus 16 percent of patients).

- A six-week trial that compared risperidone (0.5 to 2.0 mg/day) with divalproex (target serum concentration 80 to 120 mcg/mL) in 65 patients found that remission occurred more often with risperidone (63 versus 33 percent of patients) [21].

- An eight-week, open-label trial randomly assigned patients (n = 279) to receive risperidone (mean dose 2.6 mg/day), lithium (mean serum concentration 1.1 mEq/L [1.1 mmol/L]), or divalproex (mean serum concentration 114 mcg/mL) [22]. Response (much or very much improved from baseline) occurred in more patients who received risperidone than lithium or divalproex (69 versus 36 and 24 percent); lithium and divalproex were comparable. Suicidal ideation was present at baseline in 45 percent of the patients treated with risperidone; by week eight, suicidal ideation was observed in 6 percent; comparable reductions occurred with lithium and divalproex. In addition, depressive symptoms during the manic/mixed episode improved more with risperidone than either lithium or divalproex [23].

  Patients (n = 25) who did not respond to their randomly assigned treatment were included in a second eight-week, open-label randomized trial, along with other patients (n = 64)

who were evaluated for the initial trial, but did not participate because they were treated at baseline with one of the three study drugs and were not responding [24]. The 89 patients were randomly assigned to switch to one of the two remaining drugs. Response occurred in more patients who switched to risperidone than lithium or divalproex (48 versus 13 and 17 percent).

Risperidone can be administered orally once daily, or given twice daily to minimize adverse effects [6]. The typical starting dose for children weighing ≤40 kg is 0.25 mg/day, and the dose is increased every one to three days by 0.25 mg/day, depending upon efficacy and tolerability. The maximum generally does not exceed 4 mg/day. For children and adolescents who weigh more than 40 kg, the initial dose is generally 0.5 mg/day, and is increased by 0.25 to 0.5 mg/day every two to three days, with a maximum of 6 mg/day. Although doses up to 6 mg/day have been studied (eg, in youth weighing >50 kg) [22], the efficacy data indicate that many youth respond to lower doses (eg, 0.5 to 2 mg/day).

In addition, a case series described three patients who initially responded to oral risperidone and were subsequently treated with risperidone long-acting injection [25].

Common side effects of risperidone in children and adolescents include extrapyramidal symptoms (EPS), headache, sedation, and weigh gain [6]. As an example, an eight-week randomized trial (n = 279) found that mean weight gain was greater with risperidone than either lithium or divalproex (3.3 versus 1.4 or 1.7 kg), and among patients treated with risperidone, sedation from baseline to week 8 increased from 18 to 51 percent [22]. EPS may be reduced by titrating the dose more slowly (eg, increasing the dose every four to five days) and prescribing smaller total daily doses (eg, 1 to 2 mg/day).

Although hyperprolactinemia may be greater with risperidone than other second-generation antipsychotics, we do not monitor serum prolactin concentrations during treatment with risperidone because side effects attributable to prolactin (eg, irregular menses, galactorrhea, breast enlargement, and decreased bone density) typically do not occur [6,26]. Nevertheless, we suggest obtaining a baseline level prior to starting risperidone; if side effects that may be attributable to hyperprolactinemia emerge, the baseline level can be compared with subsequent levels. The clinical manifestations and evaluation of hyperprolactinemia are discussed separately. (See "Clinical manifestations and evaluation of hyperprolactinemia".)

Ziprasidone — Randomized trials indicate that ziprasidone is efficacious for youth with mania and mixed mania:

- A four-week trial compared ziprasidone with placebo in 237 children and adolescents [27]. The mean modal dose in patients weighing <45 kg was 69 mg/day and for patients ≥45 kg

was 119 mg/day. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients treated with ziprasidone than placebo (53 versus 22 percent).

- Another four-week trial compared ziprasidone with placebo in 171 youth; the mean modal dose in patients weighing <45 kg was 66 mg/day and for patients ≥45 kg was 96 mg/day. Improvement of mania was greater with ziprasidone, and the clinical effect was moderate to large [28].

Ziprasidone is generally started at 20 mg/day at bedtime, and is subsequently administered two times per day with food [27]. The dose is titrated up by 20 mg/day increments approximately every two days, over one to two weeks; increases of 20 mg every day can be used in more severely ill patients. The target dose is 40 to 160 mg/day, depending upon weight (eg, 60 to 80 mg/day for patients <45 kg, and 80 to 160 mg/day for patients ≥45 kg).

Common side effects with ziprasidone include akathisia, nausea, and sedation [6,27]. The randomized trial found that sedation occurred in more patients treated with ziprasidone than placebo (33 versus 6 percent), as did nausea (14 versus 7 percent) [27].

It is prudent to avoid using ziprasidone in patients who are at risk of developing arrhythmias due to electrolyte disturbances, cardiac abnormalities, long QT syndrome, or family history of sudden cardiac death, because of concerns that ziprasidone increases the duration of intracardiac conduction. Nevertheless, in children and adolescents with mania who are otherwise healthy and treated with ziprasidone, the data indicate that the risk of corrected QT (QTc) interval prolongation is modest [6]. As an example, a meta-analysis of randomized trials and prospective observational studies examined increases in QTc interval in youth with various psychiatric diagnoses who were treated with ziprasidone (n = 10 studies and 523 youth; mean dose 63 mg/day) or placebo (n = 19 studies and 962 youth) [29]. The average increase in the QTc was greater with ziprasidone than placebo (9 versus 1 millisecond). However, the incidence of QTc prolongation (defined as QTc >450 milliseconds or increase in QTc >60 milliseconds) was comparable for ziprasidone and placebo. In addition, one of the observational studies found that QTc prolongation occurred in the absence of QTc dispersion and thus concluded that the arrhythmogenic potential of ziprasidone was low [30].

There is no established practice for cardiac monitoring of patients receiving ziprasidone. In our practice, we obtain baseline electrocardiograms and repeat them during dose titration (eg, after increasing the dose by 40 or 60 mg/day) [6,31].

Clozapine — Retrospective studies of youth with mania suggest that clozapine may potentially benefit patients who are refractory to multiple trials of second-generation antipsychotics, lithium, carbamazepine, and first-generation antipsychotics [32-34]. However, clozapine is

generally reserved for highly refractory patients due to concerns about agranulocytosis, myocarditis, and seizures [6,31,35]. The administration, monitoring, and adverse effects of clozapine are discussed separately in the context of adult schizophrenia. (See "Schizophrenia in adults: Guidelines for prescribing clozapine".)

CLASS-WIDE SIDE EFFECTS

Patients treated with second-generation antipsychotics should be monitored for side effects that are common in this drug class, including weight gain, extrapyramidal symptoms, and sedation, as well as serious but rare side effects such as the neuroleptic malignant syndrome and tardive dyskinesia [35]. In addition, clinicians should monitor patients for drug-specific adverse effects. (See 'Specific drugs' above and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects", section on 'Adverse effects'.)

Weight gain — Children and adolescents who are treated with aripiprazole, asenapine, clozapine, olanzapine, paliperidone, quetiapine, and risperidone are at risk for age inappropriate weight gain and other metabolic effects (eg, increases in total cholesterol and triglycerides) [36-40]. By contrast, ziprasidone does not appear to cause weight gain or dyslipidemia [27].

Amongst aripiprazole, olanzapine, quetiapine, and risperidone, aripiprazole may cause less weight gain and olanzapine the most. A pooled analysis included 25 studies in which different second-generation antipsychotics were used to treat a variety of psychiatric disorders; the median duration of treatment ranged from 4 to 11 weeks, and the results found that [38]:

- Weight gain was less with aripiprazole than:
  - Olanzapine by 4 kg
  - Quetiapine by 2 kg
  - Risperidone by 2 kg
- Weight gain was greater with olanzapine than:
  - Quetiapine by 6 kg
  - Risperidone by 3 kg

In addition, the pooled analysis found that weight gain was comparable with quetiapine and risperidone.

We suggest that clinicians monitor patients who are prescribed aripiprazole, asenapine, clozapine, olanzapine, paliperidone, quetiapine, or risperidone for metabolic effects (table 1) [41,42]. The frequency of monitoring is increased if there are significant changes from baseline. Management of metabolic side effects is discussed separately in the context of adults with schizophrenia. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Metabolic dysregulation'.)

Diabetes — Multiple observational studies suggest that second-generation antipsychotics are associated with an increased risk of type 2 diabetes, but the absolute risk seems small. A meta-analysis of six observational studies compared youth exposed to antipsychotics (n >290,000) with unexposed psychiatric controls (n >2,000,000) [43]. The incidence rate of type 2 diabetes was greater in antipsychotic-exposed youth than controls (3.1 versus 1.7 cases per 1000 patient years of follow-up). The risk was higher in males, youth taking olanzapine, and youth with a longer duration of follow-up. The increased incidence of diabetes observed in youth is consistent with the association between use of antipsychotics in adults and increased rates of weight gain, diabetes, and dyslipidemia. (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects", section on 'Metabolic syndrome' and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects", section on 'Metabolic syndrome'.)

Extrapyramidal symptoms — Pediatric patients who are treated with second-generation antipsychotics can develop extrapyramidal symptoms such as akathisia, bradykinesia, dystonia, and tremor [6,26]. The Abnormal Involuntary Movement Scale (form 1) should be performed at baseline and repeated every 6 to 12 months. In addition, inquiry and examination for extrapyramidal symptoms should occur at each follow-up appointment, particularly during dose titration. Management of extrapyramidal symptoms is discussed separately. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Extrapyramidal symptoms'.)

Sedation — All second-generation antipsychotics can cause sedation, which should be monitored at each visit [26]. Adjunctive stimulants for comorbid attention deficit hyperactivity disorder may attenuate sedation caused by atypical antipsychotics. By contrast, other adjunctive drugs for bipolar disorder (eg, divalproex) may exacerbate somnolence.

Serious but rare effects — In youth treated with atypical antipsychotics, serious but rare side effects include cardiovascular events [44], the neuroleptic malignant syndrome (table 2) [45] and tardive dyskinesia [46]. These adverse effects are discussed separately. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects", section

on 'Cardiovascular events' and "Neuroleptic malignant syndrome" and "Tardive dyskinesia: Etiology, risk factors, clinical features, and diagnosis".)

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".)

SUMMARY

- **Efficacy** – Placebo-controlled, randomized trials have demonstrated the efficacy of aripiprazole, asenapine, olanzapine, quetiapine, risperidone, and ziprasidone for children and adolescents with mania and mixed mania. Other trials have found that risperidone was superior to divalproex or lithium, and that quetiapine was superior to divalproex or lithium. (See 'Specific drugs' above.)

- **Target doses and drug specific side effects** – The target dose and frequent drug specific side effects of second-generation antipsychotics for pediatric mania or mixed mania are as follows:

  - **Aripiprazole** – 5 to 30 mg/day; akathisia, sedation, nausea, vomiting, and weight gain (see 'Aripiprazole' above)

  - **Asenapine** – 5 to 20 mg/day; oral hypo/paresthesia, sedation, and weight gain (see 'Asenapine' above)

  - **Olanzapine** – 10 mg/day, ranges from 2.5 to 20 mg/day; weight gain, sedation, and increases in systolic blood pressure, pulse, total cholesterol, triglycerides, glucose, hepatic enzymes, prolactin, and uric acid (see 'Olanzapine' above)

  - **Quetiapine** – 400 to 600 mg/day, ranges from 200 to 800 mg/day; dizziness, sedation, tachycardia, and weight gain (see 'Quetiapine' above)

  - **Risperidone** – 1 to 4 mg/day; extrapyramidal symptoms, headache, sedation, and weight gain (see 'Risperidone' above)

  - **Ziprasidone** – 40 to 160 mg/day; akathisia, nausea, sedation, and increases in the duration of intracardiac conduction (see 'Ziprasidone' above)

- **Class-wide adverse effects**

- **Metabolic effects** – Children and adolescents who are treated with aripiprazole, asenapine, clozapine, olanzapine, paliperidone, quetiapine, or risperidone are at risk and monitored for metabolic effects (table 1). By contrast, ziprasidone does not appear to cause weight gain or dyslipidemia. (See 'Weight gain' above.)

- **Extrapyramidal symptoms** – Pediatric patients who are treated with second-generation antipsychotics can develop extrapyramidal symptoms such as akathisia, bradykinesia, dystonia, and tremor, and are monitored with the Abnormal Involuntary Movement Scale (form 1). (See 'Extrapyramidal symptoms' above.)

- **Sedation** – All second-generation antipsychotics can cause sedation, which should be monitored at each visit. (See 'Sedation' above.)

- **Serious but rare side effects** – Serious but rare side effects caused by atypical antipsychotics include cardiovascular events, the neuroleptic malignant syndrome (table 2) and tardive dyskinesia. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects", section on 'Cardiovascular events' and "Neuroleptic malignant syndrome" and "Tardive dyskinesia: Etiology, risk factors, clinical features, and diagnosis".)

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