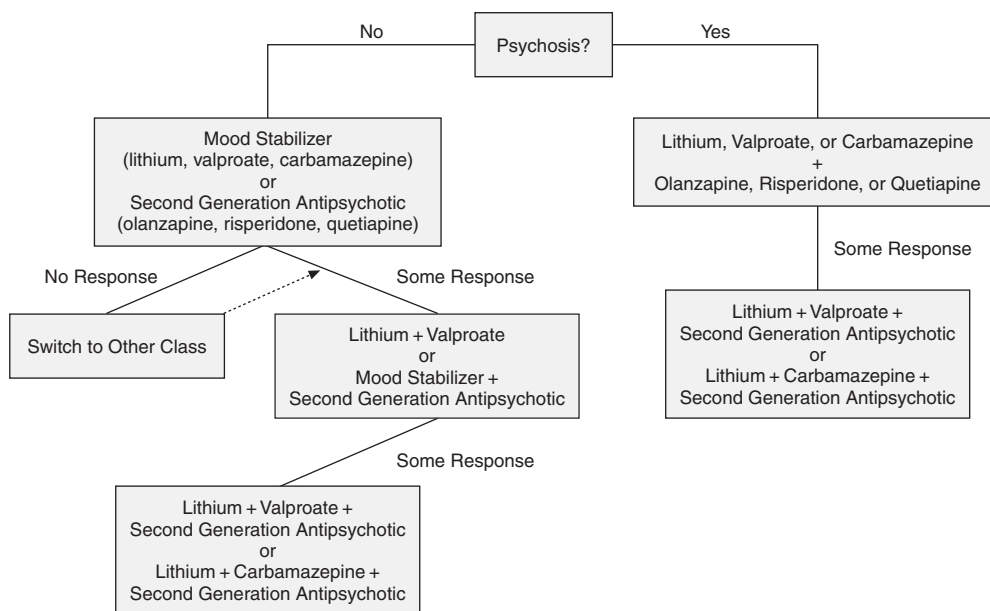




Figure 1. Consensus Treatment Recommendations for Acute Mania in Pediatric Bipolar Disorder<sup>a</sup>

<sup>a</sup>Adapted with permission from Madaan and Chang.<sup>11</sup>

disorder with other atypical antipsychotics, including ziprasidone and aripiprazole.

### Studies of Atypical Antipsychotics in Pediatric Patients With Manic or Mixed States

Since the guidelines<sup>5,10</sup> were developed, the results of several studies, some of which were controlled, have become available that examined olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole in youths with acute manic or mixed states.

**Olanzapine.** The efficacy and safety of olanzapine for the treatment of adolescents with acute manic or mixed episodes of bipolar disorder were evaluated by Tohen and colleagues.<sup>12</sup> The 3-week study included 161 adolescents between 13 and 17 years old who had a score of  $\geq 20$  on the Adolescent Structured Young Mania Rating Scale (YMRS).<sup>13</sup> Participants were randomly assigned in a double-blind fashion to receive either placebo or olanzapine at doses of 2.5 to 5.0 mg/day. The olanzapine dose could be increased up to 20 mg/day depending on response.

Youths treated with olanzapine experienced a greater reduction in manic symptoms and higher rates of response and remission than those receiving placebo.<sup>12</sup> At baseline, the mean mania score of participants was more than 30 on the YMRS, indicating moderate-to-severe mania. The olanzapine group had a mean decrease of 17.65 points, compared with a decrease of 9.99 points in the placebo group, which was a significant ( $p < .001$ ) difference. The significant change became evident after 1 week of treatment and extended throughout the study. Response rates

(defined by a  $\geq 50\%$  reduction in YMRS scores) were significantly ( $p = .002$ ) higher in the olanzapine group (48.6%) compared with the placebo group (22.2%). The rates of remission (defined as a YMRS score  $\leq 12$ ) were also greater in the olanzapine group (35.2%) compared with the placebo group (11.1%;  $p = .001$ ).

Greater weight gain occurred in the olanzapine group compared with placebo (3.7 kg vs. 0.3 kg); the olanzapine group also had increases in prolactin levels. The olanzapine group showed a significantly greater increase in fasting glucose levels compared with the placebo group (0.15 mg/dL vs. -0.21 mg/dL,  $p = .002$ ) and a significantly greater increase in fasting total cholesterol levels (0.37 mg/dL vs. 0.03 mg/dL,  $p = .010$ ). No extrapyramidal symptoms occurred.<sup>12</sup>

Few controlled longer-term data are available in pediatric patients with bipolar disorder, but after completion of the acute study described above,<sup>12</sup> 146 adolescents continued in an open-label study<sup>14</sup> of olanzapine for up to 26 weeks. At endpoint, participants showed a 63% response rate (50% reduction in YMRS score and a Clinical Global Impressions-Bipolar Disorder [CGI-BP] severity score  $\leq 3$ ). Weight gain from baseline to endpoint was about 7.5 kg, and 69% of the adolescents had a  $\geq 7\%$  increase in body weight. Abnormally high prolactin levels developed in 40.5% of participants. Adverse effects of antipsychotic medications are discussed in more detail by Correll elsewhere in this supplement.<sup>15</sup>

**Olanzapine or risperidone.** Biederman and colleagues<sup>16</sup> studied the efficacy of open treatment with either

olanzapine or risperidone in 31 children aged 4 to 6 years old who met DSM-IV-TR<sup>17</sup> criteria for bipolar I disorder, bipolar II disorder, or bipolar disorder not otherwise specified (NOS). The children were in manic or mixed states with or without psychosis. After 8 weeks, treatment with either medication resulted in significant decreases in YMRS score from baseline (18.3 points in the risperidone group and 12.1 points in the olanzapine group,  $p < .001$  each). The response rates to the 2 medications were also not significantly different (69% for the risperidone group and 53% for the olanzapine group).

**Risperidone.** The use of risperidone for short-term treatment of acute manic or mixed episodes of bipolar I disorder in youths between 10 and 17 years of age received approval from the U.S. Food and Drug Administration (FDA) in 2007.<sup>18</sup> An 8-week open-label study<sup>19</sup> of 30 youths aged 6 to 17 years who had manic or hypomanic symptoms showed a 70% response rate to risperidone treatment.

In the study<sup>16</sup> of children aged 4 to 6 years mentioned above, the mean dose of risperidone was 1.4 mg/day, and in the study<sup>19</sup> of youths aged 6 to 17 years the mean dose of risperidone was 1.25 mg/day, so children and adolescents in both studies needed less than 2 mg/day of risperidone to effectively treat mania. Over the 8 weeks of the study<sup>19</sup> of youths aged 6 to 17 years, participants experienced a weight gain of 2.1 kg ( $p < .001$ ) and a 4-fold elevation in prolactin levels ( $p < .001$ ) from baseline.

The efficacy of risperidone was demonstrated in a 3-week, double-blind, placebo-controlled trial<sup>20</sup> in which 169 youths were randomly assigned to receive placebo; risperidone, 0.5 to 2.5 mg/day; or risperidone, 3 to 6 mg/day. Both dose ranges showed significantly higher response rates compared with placebo ( $p = .002$  and  $p = .001$ , respectively). The response rate ( $\geq 50\%$  reduction in YMRS) was 59% in the low-dose risperidone group, 63% in the high-dose risperidone group, and 26% in the placebo group. Decreases in YMRS score were 18.5 (low-dose group), 16.5 (high-dose group), and 9.1 points (placebo group). Doses greater than 2.5 mg/day did not lead to greater efficacy but did lead to an increase in certain types of adverse effects such as somnolence, fatigue, and agitation. The incidence of potentially prolactin-related adverse effects was 5% in the high-dose group, 4% in the low-dose group, and 2% in the placebo group; similarly, mean weight gain over the 3 weeks of the study was greater in the high-dose group (1.4 kg) and the low-dose group (1.9 kg) than in the placebo group (0.7 kg).

**Quetiapine.** The efficacy of quetiapine has been compared with that of divalproex or placebo in studies of youths with bipolar disorder. In a 28-day, double-blind study,<sup>21</sup> 50 adolescent inpatients who were 12 to 18 years of age, diagnosed with bipolar I disorder (manic or mixed episode), were randomly assigned to receive either divalproex or quetiapine. Both treatment groups had significant improvements in YMRS score from baseline to endpoint

( $p < .0001$ ). The between-group YMRS score difference was not significant. Side effect rates were also similar between the 2 groups, but a greater percentage of patients treated with quetiapine had sedation, and weight increase was numerically greater in patients taking quetiapine than in patients treated with divalproex.

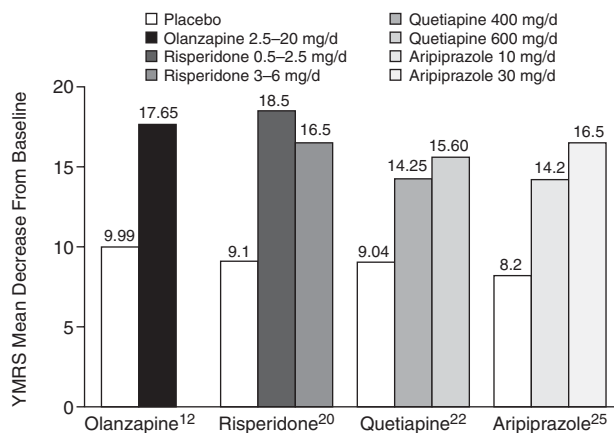
Quetiapine was compared with placebo in a 3-week, double-blind, randomized, controlled study of 277 youths, 10 to 17 years of age, with bipolar I mania.<sup>22</sup> Doses of quetiapine were either 400 or 600 mg/day. The 15% of subjects with comorbid attention-deficit/hyperactivity disorder (ADHD) were allowed to continue stimulant medication throughout the study. Compared with placebo, both quetiapine dosage groups showed greater efficacy ( $p < .001$ ) in reducing YMRS scores by endpoint, but the best response rate was in the 400-mg/day group (64%), followed by the 600-mg/day group (58%) and the placebo group (37%). Reductions in YMRS score were 14.25 (400-mg/day group), 15.60 (600-mg/day group), and 9.04 (placebo group). Participants receiving quetiapine experienced higher rates of somnolence, sedation, dizziness, and weight gain (1.7 kg vs. 0.4 kg) than those who received placebo.

A study<sup>23</sup> of 30 adolescents, 12 to 18 years old, who were in manic or mixed episodes of bipolar I disorder showed that quetiapine plus divalproex was more effective than placebo plus divalproex. The divalproex plus quetiapine group had a significantly greater reduction in YMRS scores from baseline to endpoint than the divalproex plus placebo group ( $p = .03$ ).

**Ziprasidone.** The efficacy of different dose levels of ziprasidone was examined in Versavel and colleagues' 3-week study<sup>24</sup> of 46 children and adolescents, 10 to 17 years of age, with bipolar I disorder, mixed or manic episode. A low dose of ziprasidone (40 mg/2 times a day) was compared with a high dose of ziprasidone (80 mg/2 times a day). YMRS scores were improved from baseline by a mean 14.9 points in the low-dose group and 11.1 points in the high-dose group. A recently completed placebo-controlled trial will provide more information.

**Aripiprazole.** Data about different dose levels are available for aripiprazole from a multicenter, 4-week study<sup>25</sup> of 296 youths with bipolar I disorder (manic or mixed episode) who were 10 to 17 years old. Participants were randomly assigned to receive aripiprazole doses of either 10 mg/day or 30 mg/day or placebo. Although a washout period took place before the trial, patients were allowed to take benzodiazepines or anticholinergic agents as needed. At endpoint, the 10-mg/day group's YMRS scores had decreased 14.2 points, and the 30-mg/day group's YMRS scores had decreased 16.5 points, whereas the placebo group's YMRS scores had decreased 8.2 points. Both dosage arms of the study had significantly better response rates than placebo (low-dose group 44.8%,  $p < .05$  vs. placebo; high-dose group 63.6%,  $p < .0001$  vs. placebo; and

Figure 2. Comparison of Decreases in YMRS Scores in Youths With Bipolar Disorder (manic or mixed state) Treated With Atypical Antipsychotics<sup>a</sup>



<sup>a</sup>Data from Tohen et al.,<sup>12</sup> Pandina et al.,<sup>20</sup> DelBello et al.,<sup>22</sup> and Chang et al.<sup>25</sup>  
Abbreviation: YMRS = Young Mania Rating Scale.

placebo group 26.1%). The 3 most commonly reported adverse events were somnolence, extrapyramidal disorder, and fatigue. Weight gain in the groups treated with aripiprazole was not significantly different from weight gain in the placebo group (low-dose group 0.55 kg, high-dose group 0.90 kg, placebo group 0.54 kg).

**Summary of evidence on atypical antipsychotics.** Data from the placebo-controlled studies described here show that the atypical antipsychotics olanzapine,<sup>12</sup> risperidone,<sup>20</sup> quetiapine,<sup>22</sup> and aripiprazole<sup>25</sup> are more effective than placebo for the treatment of acute manic or mixed states in children and adolescents with bipolar disorder. As shown in Figure 2, in youths who received placebo, the mean decrease in YMRS score from baseline ranged from 8.2 to 9.99 points, whereas in those treated with atypical antipsychotics, the decrease in YMRS scores ranged from 14.2 to 18.5 points. Although it is not possible to compare the studies directly because of methodological differences, it is possible to see that similar mania score decreases occurred across all the atypical antipsychotics.

### Treatment of Depression

While data have become available for the treatment of pediatric mania with atypical antipsychotics, no published placebo-controlled studies are available for bipolar depression in youths. However, a study<sup>26</sup> of the phenomenology of bipolar spectrum disorders in children and adolescents showed a 53% rate of a depressive episode, a 76% rate of suicidal ideation, and a 31% rate of history of suicide attempt. Therefore, more information is needed about the efficacy of atypical antipsychotics in youths with bipolar depression. For example, although quetiapine and the olanzapine-fluoxetine combination are approved by

the FDA for the treatment of bipolar depression in adults, it is unknown whether these agents or other atypical antipsychotics are effective for bipolar depression in children and adolescents. Current recommendations<sup>5,10</sup> for depressive presentations of bipolar disorder in youths are generally based on clinical consensus rather than on data; they recommend lithium or lamotrigine, or the augmentation of mood stabilizers with bupropion or selective serotonin reuptake inhibitors (SSRIs). SSRIs should not be used as monotherapy in this population because many children have manic reactions to SSRIs.<sup>27</sup> Treatment alternatives need to be examined in controlled trials.

### EARLY INTERVENTION IN AT-RISK YOUTHS

The use of atypical antipsychotics is being explored in the treatment of children who have rapidly shifting moods that do not meet the duration criteria for a manic episode and thus are considered to have bipolar disorder NOS or who have other mood problems that do not meet full criteria for mania but have a family history of bipolar disorder that puts them at higher genetic risk than the general population for developing full mania. For example, children with major depression who have a parent with bipolar disorder are thought to be at high risk for progressing to bipolar disorder.<sup>28</sup> This burgeoning area of research is somewhat controversial because it concerns treating children who do not yet meet full criteria for bipolar disorder. However, research is needed because these children have mood symptoms and substantial impairment of functioning and thus may already be receiving treatment in the community with agents used to treat bipolar disorder even though they do not meet the full criteria for bipolar disorder.

One single-blind study<sup>29</sup> of early intervention treatment with an atypical antipsychotic has been published. Quetiapine was given to 20 adolescents (12 to 18 years old) with at least 1 first-degree relative with bipolar I disorder and who themselves had a disorder such as bipolar disorder NOS, bipolar II disorder, dysthymia, cyclothymia, or major depression. At baseline, participants had a mean YMRS score of 18.1 or a mean Children's Depression Rating Scale-Revised Version (CDRS-R) score of 38.2. At the 12-week endpoint, the mean YMRS score was 8.7 and the mean CDRS-R score was 27.7. Somnolence was the most frequently reported adverse effect. Longer-term studies are needed to identify whether atypical antipsychotics could help prevent full manic episodes in at-risk youths.

### CONCLUSION

Pediatric bipolar disorder requires much research attention. Early reports suggest that atypical antipsychotics are effective in acute mania and mixed states in youths with bipolar disorder, but more information is needed about the

long-term efficacy and safety of these medications as well as their use in bipolar depression in children and adolescents. In addition, further studies in this population are needed to determine the efficacy of antipsychotics for comorbid psychiatric conditions such as anxiety or ADHD and whether adjunctive medication would be necessary. Additional reliable, large-scale, controlled trials are needed to provide empirical data (both positive and negative) to guide our treatment of children and adolescents with bipolar spectrum disorders.

**Drug names:** aripiprazole (Abilify), bupropion (Wellbutrin and others), carbamazepine (Tegretol, Eptol, and others), divalproex (Depakote), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine-fluoxetine (Symbyax), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

**Disclosure of off-label usage:** The author has determined that, to the best of his knowledge, aripiprazole and risperidone are not approved by the U.S. Food and Drug Administration for pediatric use other than for the treatment of schizophrenia in adolescents aged 13 to 17 years and the short-term treatment of bipolar disorder in children and adolescents aged 10 to 17 years; aripiprazole, bupropion, carbamazepine, divalproex, lamotrigine, lithium, olanzapine, olanzapine-fluoxetine, quetiapine, risperidone, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder in children under 18 years old.

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