The phenomenology of bipolar disorder in the pediatric population is different from that seen in adults. This can present a major obstacle in the accurate diagnosis of the illness and may also hinder the initiation of appropriate treatment. Historically, the mood stabilizers lithium, divalproex, and carbamazepine have been studied in the pediatric population with varying degrees of methodologic rigor. Recently, a body of literature has grown regarding the use of atypical antipsychotics for the treatment of pediatric bipolar disorder. Atypical antipsychotics have shown promise in the treatment of young people who present with symptoms of mania, but long-term adverse effects such as weight gain and tardive dyskinesia might be a concern with these agents and may be particularly worrisome. Children and adolescents tend to be more susceptible to antipsychotic-related adverse effects than adults; therefore, the risk of adverse effects must be balanced against the potential benefits associated with these agents.

The pediatric population presents special considerations regarding the safe and effective use of antipsychotic medications and thereby forms a group distinct from adults. What is known about psychotropics in adults does not always translate to the pediatric population, and children and adolescents may not respond to drugs that work in adults (or vice versa). Developmental changes in the central nervous system (CNS) and in the way drugs are metabolized affect drug effectiveness and tolerability. Thus, dosing regimens for young patients may be different from those for adults and may vary considerably by disorder.

Developmental changes in the CNS may have substantial implications for pharmacotherapy. For example, various neurotransmitter systems mature at different times during childhood. In addition, children have a greater density of striatal dopamine D2 receptors compared with adults, and it has been hypothesized that this is the reason why children have a greater propensity for developing extrapyramidal side effects (EPS) during antipsychotic treatment.

Sensitivity to medication-related adverse effects is a key concern for all pediatric patients. Long-term, if not lifelong, treatment may be required for children with bipolar disorder; therefore, it is imperative that adverse effects associated with psychopharmacologic treatment be kept to a minimum and be carefully monitored. Even under ideal circumstances, adherence to long-term therapy in children and adolescents can be problematic. Adverse effects such as weight gain, which appears to be one of the most common reasons for noncompliance with antipsychotics in the pediatric population, can be particularly distressing for children. Beyond the burden of drug-induced adverse effects, adolescents may be at particularly high risk for poor adherence to treatment regimens because of their developmentally appropriate desire for increased autonomy. This paper focuses on published data from prospective open-label and randomized placebo-controlled trials of medications used for the treatment of pediatric bipolar disorder.
**Pediatric Bipolar Disorder**

Bipolar disorder can develop during childhood or adolescence, but accurate diagnosis is often difficult because the clinical manifestations may differ greatly between adult and pediatric populations. Pediatric bipolar disorder tends to be associated with chronic and continuous symptoms rather than acute exacerbations. Pediatric bipolarity is often characterized by complex cycling patterns. Features of bipolar disorder in children and adolescents include prominent mood instability, hyperactivity, aggression, irritability, and dysphoric or mixed states. Several studies have demonstrated that comorbidity of bipolar disorder with attention-deficit/hyperactivity disorder (ADHD), conduct disorder, and other psychiatric disorders is common in this patient population.

According to criteria of the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV), bipolar I disorder is characterized by 1 or more manic or mixed episodes, and bipolar II disorder patients experience hypomanic but not manic episodes. Psychotic symptoms such as hallucinations or paranoia indicate bipolar I disorder, and the presence of such symptoms rules out bipolar II disorder. Adolescents with bipolar disorder and “subsyndromal” bipolar disorder (cyclothymia, bipolar disorder not otherwise specified) have equivalent degrees of psychosocial impairment by age 24, highlighting an equal need for treatment of both subgroups of pediatric patients with bipolar disorder.

Familial aggregation and genetic transmission of bipolar disorder have been consistently demonstrated in family, twin, and adoption studies. Children who have 1 parent with bipolar disorder have been reported to have a 38% chance of developing bipolar disorder. A 1% lifetime prevalence of bipolar disorder and a 5% lifetime prevalence of subsyndromal bipolar disorder have been reported in adolescents, although the data for children are less clear.

**Treatment of Pediatric Bipolar Disorder**

**Mood Stabilizers**

Lithium is the only US Food and Drug Administration-approved medication for adolescent mania. However, the pediatric indication for mania was grandfathered in, and to date, no placebo-controlled studies of the drug in children or adolescents with mania have been undertaken. In a small, 6-week, placebo-controlled study (n = 25) (the first placebo-controlled trial in this field), Geller and colleagues found that lithium may be effective in improving functioning in some adolescents with comorbid substance abuse and bipolar disorder. It should be noted, however, that mood state was not an outcome measure because this was not an acute mania study. Although lithium is generally well tolerated and beneficial in children and adolescents with symptoms of mania, children and teenagers may develop lithium-induced hypothyroidism at a similar rate to adults, which necessitates close monitoring of thyroid function. Despite its shortcomings, lithium is the best-studied agent in this field.

Other mood stabilizers used in adult bipolar disorder include divalproex, carbamazepine, and lamotrigine. Open-label prospective studies suggest that divalproex and carbamazepine may also be effective in children and adolescents with bipolar disorder, but similar to lithium, they may not lead to full syndromal recovery, thereby necessitating cotreatment with another mood-stabilizing agent. Limited data of adequate methodologic rigor are available regarding the use of lamotrigine in pediatric patients, and prospective studies must be carried out for this drug. Table 1 summarizes some selected published studies of mood stabilizers in pediatric bipolar disorder.

Combination therapy with mood stabilizers. Treatment with 1 mood stabilizer (lithium, carbamazepine, divalproex) can be helpful in pediatric patients, but residual symptoms have led investigators to explore the effects and potential benefits of combining 2 of these agents (a strategy that has been reported to be useful in adults). Kowatch and colleagues studied children and adolescents with bipolar disorder and determined that, although more than 50% of patients did not respond to monotherapy with the mood stabilizer carbamazepine, lithium, or divalproex, patients responded very well to a combination therapy that included different mood stabilizers. Kafantaris and colleagues studied lithium in combination with traditional atypical antipsychotics or risperidone and found an improvement in adolescents with mania and psychosis. Mood stabilizers coadministered with adjunctive atypical antipsychotics appear to be another effective strategy for some children and adolescents. This form of treatment is reviewed in the following section.
**Atypical Antipsychotics**

*Rationale for atypical antipsychotics.* Although lithium, carbamazepine, and divalproex may be effective in children and adolescents with bipolar disorder, these agents require ongoing serum monitoring. In addition, adverse effects such as sedation and tremors may affect adherence to treatment in this patient population. Thus, researchers should continue to develop new drugs that might be efficacious for the treatment of psychotic disorders in the pediatric population.

---

Table 1. Selected Published Studies of Mood Stabilizers in Pediatric Bipolar Disorder

<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug</th>
<th>Average Dose</th>
<th>Patients (n)</th>
<th>Study Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geller et al, 1998</td>
<td>Lithium</td>
<td>1769 ± 401 mg/day (ITT group)</td>
<td>25</td>
<td>Double-blind lithium, n = 13 placebo, n = 12</td>
<td>Significant differences in global functioning and urine assays for drugs of abuse between lithium and placebo groups</td>
</tr>
<tr>
<td>Kafantaris et al, 2003</td>
<td>Lithium</td>
<td>1355 ± 389 mg/day</td>
<td>100</td>
<td>Open-label lithium, n = 14; divalproex, n = 15</td>
<td>Response (YMRS score ≥33% and CGI = 1 or 2) 63%, with 26 patients achieving remission of manic symptoms (YMRS scores ≤6) at week 4 assessment</td>
</tr>
<tr>
<td>Kowatch et al, 2000</td>
<td>Lithium, divalproex, carbamazepine</td>
<td>Mean serum levels: lithium, 0.8-1.2 mEq/L; divalproex, 85-110 µg/L; carbamazepine, 7-10 µg/L</td>
<td>42</td>
<td>Open-label lithium, n = 14; divalproex, n = 15; carbamazepine, n = 13</td>
<td>Response rates on YMRS (50% change from baseline to exit): lithium, 38%; divalproex, 53%; carbamazepine, 38%</td>
</tr>
<tr>
<td>Wagner et al, 2002</td>
<td>Divalproex</td>
<td>813 ± 338 µg/day (corresponding mean serum level, 83.4 ± 25.4 µg/mL)</td>
<td>40</td>
<td>Open-label</td>
<td>Significant improvement in MRS, MSS, BIS, BPRS, CGI-S, HAM-D vs baseline</td>
</tr>
<tr>
<td>Findling et al, 2003</td>
<td>Lithium + divalproex</td>
<td>Lithium, 923.3 ± 380.0 mg/day (corresponding mean serum level, 0.9 ± 0.3 mmol/L); divalproex, 862 ± 397.5 µg/day (corresponding mean serum level, 79.8 ± 25.9 µg/mL)</td>
<td>90</td>
<td>Open-label</td>
<td>Significant improvement in YMRS, CDRS-R, CGI-C, CGAS</td>
</tr>
<tr>
<td>Kowatch et al, 2003</td>
<td>1 or 2 mood stabilizers + stimulant/ atypical antipsychotic/ antidepressant n = 20</td>
<td>N/A</td>
<td>35</td>
<td>Open-label</td>
<td>80% of subjects responding to combination therapy with 2 mood stabilizers</td>
</tr>
</tbody>
</table>

ITT = intention-to-treat; YMRS = Young Mania Rating Scale; CGI = Clinical Global Impression; MRS = Mania Rating Scale; MSS = Manic Symptom Scale; BIS = Behavior and Ideation Scale; BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression - Severity of Illness; HAM-D = Hamilton Rating Scale for Depression; CDRS-R = Children’s Depression Rating Scale Revised; CGI-C = Clinical Global Impression - Change; CGAS = Children’s Global Assessment Scale.
Atypical antipsychotics have been shown to be beneficial in adults with bipolar disorder, which has prompted investigators to study the effectiveness of these compounds in children and adolescents. Although large, randomized, placebo-controlled trials in children with bipolar disorder have yet to be published, small investigations of atypical antipsychotics have yielded optimistic findings (Table 2).

The use of atypical versus traditional antipsychotics may be particularly attractive to clinicians who treat pediatric bipolar disorder.

### Table 2. Selected Published Studies of Atypical Antipsychotics in Pediatric Bipolar Disorder

<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug</th>
<th>Average Dose</th>
<th>Patients (n)</th>
<th>Study Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kowatch et al, 1995</td>
<td>Clozapine</td>
<td>128 ± 46 mg/day</td>
<td>10</td>
<td>Open-label Monotherapy, n = 3</td>
<td>Significant improvement on CGI-S and CGAS scales</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(n = 1 BP; n = 2 schizophrenia); adjunct with lithium n = 7 (n = 4 BP; n = 2 schizophrenia; n = 1 psychotic disorder NOS)</td>
<td></td>
</tr>
<tr>
<td>Masi et al, 2002</td>
<td>Clozapine</td>
<td>142.5 ± 73.5 mg/day</td>
<td>10</td>
<td>Open-label Monotherapy, n = 2; adjunct with mood stabilizers, n = 8</td>
<td>Significant improvement on CGI-S scale</td>
</tr>
<tr>
<td>Frazier et al, 1999</td>
<td>Risperidone</td>
<td>1.7 ± 1.3 mg/day</td>
<td>28</td>
<td>Chart review Adjunct with mood stabilizers, n = 18; adjunct with anti-ADHD treatments, n = 16; adjunct with other antipsychotics, n = 4</td>
<td>Significant improvement in 82% for both manic and aggressive symptoms, 69% in psychotic symptoms, 8% in ADHD symptoms on the CGI-I (criteria ≤2)</td>
</tr>
<tr>
<td>Frazier et al, 2001</td>
<td>Olanzapine</td>
<td>9.6 ± 4.3 mg/day</td>
<td>23</td>
<td>Open-label Monotherapy</td>
<td>Response in 61% (response criteria ≥30% reduction in YMRS and CGI-S mania score ≤3 at endpoint)</td>
</tr>
<tr>
<td>McConville et al, 2000</td>
<td>Quetiapine</td>
<td>Starting at 25 mg twice daily, reaching 400 mg twice daily by day 20</td>
<td>10</td>
<td>Open-label Adjunct with lithium if part of a stable regimen</td>
<td>Significant improvement on the BPRS, CGI-S, CGI-I, and SANS</td>
</tr>
<tr>
<td>Delbello et al, 2002</td>
<td>Quetiapine + divalproex</td>
<td>Divalproex, 20 mg/kg; quetiapine, 450 mg/day</td>
<td>30</td>
<td>Placebo-controlled Divalproex + placebo, n = 15; divalproex + quetiapine, n = 15</td>
<td>Significantly greater improvement in YMRS for divalproex + quetiapine vs divalproex + placebo</td>
</tr>
</tbody>
</table>

BP = bipolar disorder; NOS = not otherwise specified; CGI-S = Clinical Global Impression - Severity of Illness; CGAS = Children’s Global Assessment Scale; ADHD = attention-deficit/hyperactivity disorder; CGI-I = Clinical Global Impression - Global Improvement; YMRS = Young Mania Rating Scale; BPRS = Brief Psychiatric Rating Scale; SANS = Modified Scale for the Assessment of Negative Symptoms.
young patients because these newer agents are associated with a lower incidence of EPS than are the older drugs. This is an important advantage for young people because they often face long-term or lifelong pharmacotherapy. Clozapine. Several case series have reported on the use of clozapine in children and adolescents with bipolar disorder and mania and have noted mood stabilization, as well as amelioration of symptoms of aggression and psychosis.27-28,32,33 Kowatch and colleagues reported a significant response, as documented by the Clinical Global Impression of Severity (CGI-S) and Children’s Global Assessment Scales.27 Adverse effects observed in this study included increased appetite, sedation, enuresis, sialorrhea, and a mean weight gain of approximately 7 kg after 6 months. In addition, Masi and colleagues found that all 10 patients in their study responded positively to clozapine according to the CGI-S, and adverse effects and weight gain were similar to those noted by Kowatch and colleagues.27,28 However, despite the therapeutic benefit of clozapine, this drug is generally used only in treatment-resistant patients because of its associated risks for serious adverse effects such as agranulocytosis, seizures, and changes in blood pressure and pulse.34

Risperidone. Adjunctive treatment with risperidone has resulted in significant improvement in symptoms of mania and aggression in children with bipolar disorder in a case series report (n = 28).29 Although prolactin elevation and weight gain may be of concern with risperidone, some prospective data from long-term studies in children with disruptive behavior disorders suggest otherwise. In a post hoc analysis of 5 clinical trials, Findling and colleagues showed that at a mean risperidone dose of 1.23 mg/day, prolactin levels increased, with peak levels occurring at 4 to 7 weeks; they then decreased over the subsequent 40 to 48 weeks of the trial.35 Although these results are promising, empiric data are still needed regarding risperidone in the treatment of pediatric patients with bipolar disorder. Although risperidone may cause weight gain, generally low dropout rates due to this adverse effect have been reported.36,37

Olanzapine. Olanzapine is approved for the treatment of bipolar disorder in adults. An open-label study (n = 23) of children with bipolar disorder showed response rates of 61% with olanzapine (response criteria defined as ≥30% reduction in the Young Mania Rating Scale from baseline to endpoint and a CGI-I mania score ≤3 at endpoint).30 It should be noted, however, that the response criteria used in this study were not as stringent as those used in other studies, thus suggesting that these higher response rates might have been due to the use of more liberal response criteria. Of note, a mean weight gain of approximately 5 kg was observed during the 8-week trial.

Quetiapine. In an open-label pharmacokinetic study that examined the effectiveness of quetiapine in the treatment of bipolar disorder in children, McConville and colleagues studied 10 adolescent patients with chronic and intermittent psychosis (n = 7 with schizoaffective disorder; n = 3 bipolar disorder with psychotic features) who had received oral treatment with quetiapine.31 Quetiapine therapy led to improvements in positive and negative symptoms of psychosis. The pharmacokinetics of quetiapine were noted to be dose proportionate in adolescents, a finding similar to that previously reported in adults. The most common adverse effects noted were postural tachycardia and insomnia. A mean weight gain of 1.5 kg was seen in 6 of 10 patients over a 23-day trial period. Adjunctive therapy with quetiapine and a mood stabilizer has also been shown to be beneficial in young people. Delbello and colleagues demonstrated in a randomized, placebo-controlled study of 30 adolescent inpatients with mania or mixed bipolar I disorder that treatment with divalproex and quetiapine was more efficacious than treatment with divalproex with placebo.32

Ziprasidone. Although its effectiveness in children with bipolar disorder is unknown, ziprasidone has been shown to be beneficial in children and adolescents with Tourette syndrome. In a double-blind, placebo-controlled study, ziprasidone and placebo were studied in 28 children and adolescents for 56 days.33 Ziprasidone at a relatively low mean daily dose of 28.2 mg was found to be significantly more effective than placebo for relieving the symptoms of Tourette syndrome. Sedation was the most common adverse effect for ziprasidone. A mean weight gain of 0.7 (1.5 kg) for ziprasidone-treated patients was compared with a gain with placebo of 0.8 (2.3 kg). Although an assertion about the putative benefits of ziprasidone in young patients with Tourette syndrome can be supported, empiric data regarding the use of this drug in pediatric patients with bipolar disorder are needed.

Aripiprazole. Although no published studies are available on the use of aripiprazole in the treatment of pediatric bipolar disorder, an unpublished retrospective chart review of children and adolescents with bipolar disorder reported that 67% of subjects who received
Aripiprazole (mean duration, 4 ± 2.7 mo; mean final dose, 10.3 ± 3.1 mg/d) responded to therapy (n = 30; 9 on monotherapy, 21 as adjunctive therapy). Adverse effects reported for aripiprazole included sedation and akathisia. This chart review suggested that aripiprazole might have a low propensity to increase weight, although care should be taken in the interpretation of these data until larger, prospective, more methodologically rigorous published studies are available. Aripiprazole also produced high response rates in a study of pediatric patients with conduct disorder. Because of its partial dopamine antagonism, aripiprazole theoretically might be particularly beneficial for children with comorbid bipolar disorder and ADHD.

**USE OF ATYPICAL ANTIPSYCHOTICS IN BIPOLAR DISORDER**

**DOSING**

In the absence of definitive evidence from controlled trials in pediatric patients, the dosing of atypical antipsychotics in this patient population is often guided by evidence and experience in adults and is not always based on pediatric pharmacokinetic studies or prospective dose-ranging studies. However, the dosing regimen of atypical antipsychotics is especially important when young people are treated because they appear to be more vulnerable than adults to adverse effects (some of which may be dose related), which can lead to intolerance and nonadherence.

When adolescents with psychosis (such as schizophrenia) are treated, the final target doses of atypical antipsychotics appear to be similar to the target doses used in adults. Nonetheless, because pediatric patients have an increased risk for adverse effects, EPS in particular, the optimal time required to get to the target dose appears to be 1.5 to 2 times longer in teenagers with psychotic illness. The physician should “start low and go slow” to minimize adverse effects and the risk for EPS, and dose titration should be guided by symptomatic response. Consequently, use of available dose strengths of the drug is important so that slow increases in doses can be implemented. To avoid unnecessarily high doses of medication, medication dose should be aimed at treating target symptoms—not the behaviors that are sometimes associated with these conditions.

**ADVERSE EFFECTS ASSOCIATED WITH ANTIPSYCHOTICS: UNIQUENESS OF THE PEDIATRIC POPULATION**

Atypical antipsychotics provide equal efficacy and superior EPS profiles compared with conventional antipsychotics in adults with psychotic disorders. Given that the risk for EPS is higher in children than in adults, the lower propensity of atypical antipsychotics to cause EPS is particularly pertinent in the treatment of young people. With the atypical antipsychotic class of drugs, experience in adults shows that the relative propensity for EPS varies between agents. However, it should be noted that relative rates of EPS in young people as a result of atypical antipsychotic treatments have not been fully characterized because of the dearth of data from comparative trials in youths.

Despite the favorable EPS profile of atypical antipsychotics, these drugs are associated with other important adverse effects that can affect treatment in the pediatric population. These adverse effects are discussed in the following section.

**Weight gain.** Weight gain appears to be one of the main reasons why children discontinue treatment with atypical antipsychotics. Increased weight can have a significant negative effect on the physical and emotional development of children and adolescents. Weight gain appears to be an important issue with atypical antipsychotics and is of particular concern in youths, who may be more sensitive than adults to atypical antipsychotic-induced weight gain. Although the propensity for weight gain in adults varies among the different atypical antipsychotics, head-to-head studies of these compounds in pediatric patients must be carried out before any definitive comparative conclusions can be made for children and adolescents.

**Sedation.** Although it is an adverse effect, sedation in modest degrees may be temporarily advantageous in the pediatric population because it may help calm aggressive behavior and improve sleep during manic episodes. However, sedation is deleterious in the long term because it can affect attention and learning, routine activities of day-to-day living, and social and family relationships. Sedation, which can be minimized through gradual dose escalation, is a common adverse effect of treatment with most atypical antipsychotics.

**Prolactin increase.** The atypical antipsychotics risperidone and olanzapine have been reported to increase serum prolactin levels in children and adolescents. Adverse effects that might occur as a result
of this include breast enlargement, menstrual disturbance, galactorrhea, and sexual dysfunction, all of which may be especially distressing to adolescents. Based on available data from Findling and associates, it appears that prolactin levels do not need to be monitored as part of routine care; however, they should be measured if adverse effects that might be a result of hyperprolactinemia become manifest.

**Summary**

Although the quantity of relevant studies is limited, some atypical antipsychotics have been reported to be beneficial in the treatment of pediatric bipolar disorder. To unequivocally establish safety and efficacy in children with bipolar disorder, it is imperative that large, randomized, placebo-controlled, as well as head-to-head, trials of atypical antipsychotics both as monotherapy and as combination therapy with mood stabilizers be performed. Long-term randomized maintenance studies will also be important in revealing the long-term safety and tolerability of these drugs in children and adolescents with bipolar disorder.

**REFERENCES**


27. Kowatch RA, Suppes T, Gillillan SK, Fuentes RM,


34. Clozaril (clozapine tablets) prescribing information. Dorval, Quebec: Novartis Pharmaceuticals Canada Inc; 2000.


