Bipolar Disorder (Acute Mania or Mixed Episodes) in Children and Adolescents Ages 6 to 17 Years Old

**Level 0**
Comprehensive assessment. Use systematic interview covering mania and depression symptoms, family history of psychopathology including depression and mania, and information from teachers if possible to establish duration of manic symptoms over the day.

- Classic bipolar disorder has clear episodes representing a change from usual behavior; DSM-5 symptoms consist of elevated and/or irritable mood and increased energy occurring most of the day, every day; Co-occurring symptoms include grandiosity, decreased need for sleep, rapid speech and flight of ideas (no current validity under age 6).
- If ADHD is comorbid with bipolar I or II disorder, symptoms should intensify with the episode. If it is truly comorbid, mania should be treated and stabilized before treating ADHD.
- If the diagnosis of mania cannot be distinguished from ADHD, and especially combined ADHD and oppositional defiant disorder, ADHD should be treated first with discussion with family members about advantages and disadvantages. Refer to ADHD guidelines.
- If rage outbursts are the primary focus of treatment, track the frequency, intensity, number and duration of episodes. Treat the primary disorder first. Refer to aggression treatment guidelines.
- There are no guidelines on treating Disruptive Mood Dysregulation Disorder.

**Level 1**
Monotherapy with one of these three agents:
- Aripiprazole
- Risperidone
- Quetiapine
  - For euphoric mania in adolescents, consider lithium.

**Level 2**
Monotherapy with atypical antipsychotic listed in Level 1 and augmentation with mood stabilizer(s) (lithium, VPA/divalproex), but not two antipsychotics. Olanzapine has been approved for children ages 13 and older. Monitoring weight is especially important with combinations and with olanzapine.

**Level 3**
Monotherapy with antipsychotic (except clozapine) not listed in Level 1 or combination with mood stabilizer(s).

**Level 4** Clozapine or ECT.

Notes:
1. Oxcarbazepine is not recommended. There is little consensus to support the use of this agent for acute mania in pediatric patients. The only randomized controlled trial of oxcarbazepine failed to find a difference from placebo; only open treatment data available for carbamazepine in children and adolescents. No evidence for topiramate or lamotrigine as acute antimanic agents. Divalproex has not been effective in children with manic symptoms and a high rate of co-occurring ADHD and ODD.
2. Avoid antidepressants; use with caution with comorbid anxiety or OCD.
3. There is insufficient data to provide recommendations for treatment of bipolar depression.
Dosing Recommendations for Atypical Antipsychotics in Bipolar Disorder in Children and Adolescents Ages 6 to 17 Years Old*

*Clinicians should realize that data below age 10 for treating mania and mixed states are limited and caution in using pharmacological treatment below age 10 is warranted.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Starting Dose</th>
<th>Maximum Dose</th>
<th>FDA Approved Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>2-5 mg/day</td>
<td>30 mg/day</td>
<td>10-17 years old</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Children: 0.25 mg/day Adolescents: 0.5 - 1 mg b.i.d.</td>
<td>Children: 4 mg/day Adolescents: 6 mg/day</td>
<td>10-17 years old</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Children: 12.5 mg b.i.d. Adolescents: 25 mg b.i.d.</td>
<td>Children: 400 mg/day Adolescents: 600 mg/day</td>
<td>10-17 years old</td>
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<tr>
<td>Lithium</td>
<td>300 - 600 mg/day Goal: acute mania: Blood level 0.8 – 1.2 mEq/L Goal maintenance: Blood level 0.6 – 1 mEq/L</td>
<td>Blood level: 1.2 mEq/L</td>
<td>12-17 years old</td>
</tr>
<tr>
<td>Valproate</td>
<td>10-15 mg/kg/day in divided dose Goal: 80-125 mcg/mL</td>
<td>Dose determined by blood level. Max blood level should be 125 mcg/mL</td>
<td>Not approved</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Children: 0.25 mg -0.5 mg/day Adolescents: 0.5 - 1 mg/day</td>
<td>Children: 4 mg/day Adolescents: 10 mg/day</td>
<td>Not approved for pediatric mania</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Children: 25-50 mg/day Adolescents: 25 -100 mg/day</td>
<td>Children (under 12): 200 mg/day Adolescents: 500 mg/day</td>
<td>Not approved for pediatric mania</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5-5 mg once daily Weekly titration by 2.5-5 mg increments</td>
<td>20 mg/day</td>
<td>13-17 years old</td>
</tr>
</tbody>
</table>

Minimizing side effects when switching psychotropic medications:

- Start low! Go slow! And stop slowly! Avoid abrupt stopping, starting, and/or switching to reduce risk of rebound and withdrawal phenomena.
- Do not switch until the primary disorder has been treated according to target disorder guidelines at adequate dose and duration.
- Only stop and/or switch abruptly if a serious adverse effect necessitates it (i.e., severe neutropenia, agranulocytosis, diabetic ketroacidosis, neuroleptic malignant syndrome, acute pancreatitis, lithium toxicity, Stevens-Johnson syndrome, etc.).
- Slow switch using cross-titration is the preferred method; an even slower switch can be done using the plateau-cross titration method, with therapeutic dose overlap of medications (when switching to a less sedating cholinergic medication, or one with a much longer half-life).
- If time permits, do not reduce the first medication by more than 25-50% per 5 half-lives.


**ADDITIONAL CONSIDERATIONS:**

- When switching medications, the more different the binding affinity for the same receptor (between the two drugs), the greater risk for side effects and rebound and withdrawal phenomena (especially sedating; anti-cholinergic; dopaminergic).

- The more different the half-life of the medications with the same physiological effect (desired or undesired), the greater the risk for rebound and withdrawal phenomena. Withdrawal and rebound phenomena are most likely when discontinuing from a short half-life medication.

- Withdrawal and rebound phenomena are most likely to occur when switching from a strongly antihistaminergic (sedating) or anti-cholinergic medication (i.e., clozapine, olanzapine, quetiapine), to a less strong binding medication (i.e., haloperidol, molindone, paliperidone, aripiprazole, ziprasidone); or from a strongly binding anti-dopaminergic (i.e. FGA AP, risperidone paliperidone) to a less strongly binding antipsychotic (i.e., clozapine, quetiapine, clozapine); or a full antagonist, to a partial agonist (aripiprazole).

- Insufficient efficacy or increased side effects may occur during a switch when medications metabolized by cytochrome P450 liver enzymes are paired with a medication that affects that same enzyme.

- Never discontinue lithium or clozapine abruptly to avoid potentially severe rebound of mania or psychoses.

- Quetiapine and mirtazapine can lead to more sedation at lower doses (below 250-300 mg for quetiapine and below 15 mg for mirtazapine) because of its high affinity for histamine receptors. This is offset by increased alpha adrenergic activity at higher doses that counteract this.

**References**
