Mood Disorders in Children and Adolescents
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Disclosures

- **Research/Grants**: Brain & Behavior Research Foundation, Johnson & Johnson, National Institute of Mental Health (NIMH), National Institute of Aging (NIA), Neuronetrix, Office of Research on Women’s Health, Stanford Child Health Research Institute

- **Advisory Board**: Sunovion Pharmaceuticals
Integrate evidence-based, best-practice options in children and adolescents for the management of major depressive disorder (MDD) and bipolar disorder (BD).
Learning Objective

Review the safety of early intervention strategies for treating youth with and at high risk for developing mood disorders.
Mechanisms of Mood Disorders

Depressed For No Reason

Depressed For A Good Reason

JUST DEPRESSED, DON'T WANT TO ANALYZE IT

UN-DONE
Children vs. Adults

- Overall, the clinical picture of mood disorders in youths is similar to the clinical picture in adults.
- Differences may be attributed to a child’s physical, emotional, cognitive, and social developmental stages.
  - Mood lability, irritability, low frustration tolerance, temper tantrums, somatic complaints, and/or social withdrawal instead of verbalizing feelings of depression.
  - Fewer melancholic symptoms and delusions.
  - More suicide attempts in adolescents than depressed adults.

**Prefrontal cortex:**
- Develops more in adolescence
- Executive function
- Regulates emotion

**Prefrontal cortex**

**Limbic system:**
- Primitive
- Amygdala
- Controls moods
- Fight or flight

**DEPRESSION**
Sad or Irritable
x 2 weeks plus:
Sleep
Interest
Guilt
Energy
Concentration
Appetite
Psychomotor changes
Suicide

**MANIA**
Euphoria (3)/irritability (4)
x 1 week plus:
Distractibility
Increased goal directed activity
Grandiosity
Flight of ideas
Accelerated speech
Sleep, decreased need
Trouble

Treatment Strategies

Balance between behavioral/cognitive/psychosocial and psychopharmacological interventions

“I medicate first and ask questions later.”
**Treatment of Pediatric Depression (Case)**

- Jane and Rob took their 9-year-old son Blue to see a psychiatrist when they became concerned about his behavior during their divorce. When his parents separated, Blue was *irritable* and began defying teachers and having confrontations with other children. Blue’s work began to suffer due to *poor concentration* and unsubmitted homework, and he started having *trouble sleeping*, often waking up as much as four times in the night. He also complained frequently of *no appetite* and *tummy aches*, stopped playing football with his club due to *lack of energy*, and *lost interest* in all of his after school activities.
## FDA-Approved Agents for Pediatric Depression

### Acute Depression

- **1987 Fluoxetine (8-18 years)**
- **2002 Escitalopram (12-17 years)**
- SSRIs most frequently prescribed (63.7%)
- Only 9.2% of the visits with FDA-approved indications
- Visits made to pediatricians (adjusted OR = 2.4; 95%CI: 1.1-5.1), family physicians, and other offices (adjusted OR = 1.9; 95%CI: 1.2-3.1) were more likely to be associated with off-label prescribing as compared with visits to a psychiatrist's office

SSRI = Selective serotonin reuptake inhibitor

Phases of Treatment and Tools

**Phases**
- Acute (6-12 weeks)
- Continuation (to prevent relapses) (6-12 months)
- Maintenance (to prevent recurrences) (≥ 1 year)

**Tools**
- Psychoeducation
- Psychotherapy
  - Psychodynamic Psychotherapies
  - Cognitive Behavioral Therapy (CBT)
  - Interpersonal Psychotherapy (IPT)
  - Supportive Psychotherapy
  - Family Therapy
  - Group Psychotherapy
- Most studies utilize CBT and to a lesser extent interpersonal psychotherapy (IPT)
- Most studies have been done with adolescents
- Overall results: 60%-70% vs. Controls: 30%-50%
- Pharmacotherapy

**Controlled Pediatric MDD Studies**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Reference</th>
<th>Ages</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Emslie et al. [16], Emslie et al. [17], TADS [19], Almeida-Montes &amp; Friederichsen [15]</td>
<td>6–17</td>
<td>4</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Emslie et al. [20]</td>
<td>12–17</td>
<td>1</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Wagner et al. [22] **</td>
<td>6–17</td>
<td>1 (a priori pooled analysis, individual trials negative)</td>
</tr>
<tr>
<td><strong>Negative studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Wagner et al. [21]</td>
<td>6–17</td>
<td>1</td>
</tr>
<tr>
<td>Citalopram</td>
<td>von Knorring et al. [23]</td>
<td>13–18</td>
<td>1</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Keller et al. [25], Emslie et al. [27], Berard et al. [26], Paroxetine Trial 1 [28]</td>
<td>7–17</td>
<td>4</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Emslie et al. [29]**</td>
<td>7–17</td>
<td>2</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Mirtazapine Trials 1 &amp; 2 [30]**</td>
<td>7–17</td>
<td>2</td>
</tr>
</tbody>
</table>

*On primary outcome measure

**References 22, 29 and 30 include two trials in one paper

Additional Negative study: Duloxetine, ages 7-17, 2 studies

Acute Effects of SSRIs for MDD, Anxiety and OCD

Antidepressants Dosages Commonly Used
MDD Treatment in Youth

<table>
<thead>
<tr>
<th>Medication group</th>
<th>Medication</th>
<th>Starting dosage (mg/day)*</th>
<th>Dosage range (mg/day)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>Citalopram**</td>
<td>20</td>
<td>20–40(^a)</td>
</tr>
<tr>
<td></td>
<td>Escitalopram</td>
<td>10</td>
<td>10–20</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>10</td>
<td>10–20</td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine**</td>
<td>25</td>
<td>50–150</td>
</tr>
<tr>
<td></td>
<td>Paroxetine**</td>
<td>20</td>
<td>20–50</td>
</tr>
<tr>
<td></td>
<td>Sertraline**</td>
<td>50</td>
<td>50–200</td>
</tr>
</tbody>
</table>

\(^a\)Dose adjusted by U.S. Food and Drug Administration recently because of concerns about QT prolongation.

*With the exception of escitalopram and fluoxetine, indicated dosages are for adults. In children consider using lower dosages.

**Citalopram, fluvoxamine, paroxetine, and sertraline not FDA-approved for the treatment of MDD in youths [Package Inserts]. Drugs@FDA Website
### Antidepressants Dosages Commonly Used MDD Treatment in Youth (cont.)

<table>
<thead>
<tr>
<th>Medication group</th>
<th>Medication</th>
<th>Starting dosage (mg/day)*</th>
<th>Dosage range (mg/day)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNRIs</td>
<td>Venlafaxine XR**</td>
<td>37.5–75</td>
<td>37.5–225</td>
</tr>
<tr>
<td></td>
<td>Duloxetine**</td>
<td>40–60</td>
<td>60–120</td>
</tr>
<tr>
<td>Others</td>
<td>Bupropion SR**</td>
<td>150</td>
<td>150–400</td>
</tr>
<tr>
<td></td>
<td>Bupropion XL**</td>
<td>150</td>
<td>150–450</td>
</tr>
</tbody>
</table>

SNRI = serotonin-norepinephrine reuptake inhibitor; SR = sustained release; XL = extended release; XR = extended release

*Indicated dosages are for adults. In children consider using lower dosages.

**Not FDA-approved for the treatment of MDD in youths

[Package Inserts]. Drugs@FDA Website.
## Medication for Youth Depression: SSRI Side Effects

Number Needed to Harm (NNH) = 112

### Side Effects of SSRIs: May attenuate over several weeks. In general, any SSRI may cause: nausea, anxiety, agitation, anorexia, tremor, somnolence, sweating, dry mouth, headache, dizziness, diarrhea, constipation, sexual dysfunction

<table>
<thead>
<tr>
<th>Medication</th>
<th>Anticholinergic Side Effects</th>
<th>Sedating Effects</th>
<th>Other Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>+, especially nausea, sexual dysfunction</td>
<td>+</td>
<td>FDA-approved for MDD</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>+</td>
<td>+</td>
<td>FDA-approved for MDD</td>
</tr>
<tr>
<td>Citalopram</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>0, especially diarrhea &amp; male sexual dysfunction</td>
<td>+</td>
<td>FDA-approved for teen OCD</td>
</tr>
</tbody>
</table>

[Package Inserts]. Drugs@FDA Website
# Common Side Effects: Other Agents

<table>
<thead>
<tr>
<th>Name/Class</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>Hypertension, tachycardia, headache, tremors, dizziness &lt;br&gt; <strong>Serious (rare):</strong> seizures, cardiac dysrhythmia, anaphylaxis</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>Tachycardia, hypertension, sweating, weight loss, loss of appetite, nausea, constipation, dizziness, headache, insomnia, somnolence, blurred vision, abnormal ejaculation &lt;br&gt; <strong>Serious (rare):</strong> hyponatremia, hepatitis, seizure, NMS</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Nausea, headache, decreased weight, and abdominal pain.</td>
</tr>
<tr>
<td>Trazadone</td>
<td>Sedation, sweating, constipation, diarrhea, nausea, dizziness, headache, insomnia, memory impairment, blurred vision. &lt;br&gt; <strong>Serious (rare):</strong> Priapism in males, cardiac dysrhythmia</td>
</tr>
<tr>
<td>Nefazadone</td>
<td>Cough; <strong>Serious (rare):</strong> orthostasis, liver failure, seizure</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Sedation, weight gain, hypercholesterolemia, constipation, liver dysfunction, dizziness &lt;br&gt; <strong>Serious (rare):</strong> agranulocytosis, neutropenia, seizure</td>
</tr>
<tr>
<td>Tricyclic Antidepressants</td>
<td>Weight change, bloating, constipation, appetite loss, nausea, dry mouth, asthenia, dizziness, headache, somnolence, blurred vision, fatigue. &lt;br&gt; <strong>Serious (rare):</strong> cardiac dysrhythmia, myocardial infarction, sudden death, agranulocytosis</td>
</tr>
</tbody>
</table>

[Package Inserts]. Drugs@FDA Website.
● Depressed adolescents who failed to respond to an 8 week trial with a SSRI were randomly assigned for another 12 weeks to:
  ● Another antidepressant (citalopram/fluoxetine), venlafaxine, or SSRI + CBT, or venlafaxine plus CBT
● Response rates were better for CBT+ antidepressant (55%) than antidepressants alone (41%)
● Predictors of response: less severe depression, less family conflict, no self-injurious behavior

Treatment Recommendations

- Management of negative events, school issues, etc
- Treatment of Parents – Family
- Ultimate goal is REMISSION
- Management of disorder “side effects”
- Management of comorbid disorders
Treatment Challenge: How should we treat depressed youth who are at high-risk for BD?

Well…definitely therapy first if possible…then…

- SSRI?
- Bupropion?
- Lamotrigine?
- Lithium?
- Quetiapine?

BD = bipolar disorder
At least 29 published case reports describe pediatric patients with treatment emergent mania or hypomania when exposed to SSRIs.

Pooled together these studies report hypomanic or manic symptoms that appear any time between 2 wks to 1 yr after initial SSRI exposure.

In 21% of such patients represented in these studies, there was a family history of BD.

## Pharmacological Studies in High-Risk Bipolar Offspring

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample size and Population</th>
<th>Drug</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Geller</strong> et al., 1998</td>
<td>30 Prepubertal (mean age 10.7 years) depressed children; 80% had Family History of BP-I or mania (40% of parents had BP-I or mania); and 20% with loaded or multigenerational MDD but no mania.</td>
<td>Lithium (N=17) vs Placebo (N=13)</td>
<td>Double-blind placebo controlled</td>
<td>No difference between active and placebo groups.</td>
</tr>
<tr>
<td><strong>Chang</strong> et al., 2003</td>
<td>24 (6-18 year old) youth with mood and behavioral disorders, at least mild affective symptoms, and at least one parent with BD.</td>
<td>Divalproex</td>
<td>12-week Open-label</td>
<td>78% response rate. Well tolerated with no discontinuations due to adverse effects.</td>
</tr>
<tr>
<td><strong>Findling</strong> et al., 2007</td>
<td>56 symptomatic youth (ages 5-17) with bipolar disorder not otherwise specified (NOS) or cyclothymia who also had at least 1 biological parent with bipolar illness.</td>
<td>Divalproex (N=29) vs Placebo (N=27)</td>
<td>Double-blind placebo controlled</td>
<td>No difference in survival time for discontinuation for any reason (p = .93) or due to a mood event (p = .55). Both groups had improved mood sx and psychosocial function.</td>
</tr>
<tr>
<td><strong>DelBello</strong> et al., 2007</td>
<td>20 symptomatic adolescents (12-18 years old) at high risk for developing BD by virtue of having at least one first-degree relative with BD I.</td>
<td>Quetiapine</td>
<td>12-week single blind open label trial</td>
<td>87% responded (CGI-I &lt; or = 2) at week 12. Decreased YMRS and CDRS scores from baseline to endpoint.</td>
</tr>
<tr>
<td><strong>Findling</strong> et al., 2009</td>
<td>9 children (7-16 years old) with MDD and at least one parent with BD</td>
<td>Paroxetine vs Paroxetine + Divalproex</td>
<td>Open-label</td>
<td>Neither treatment was effective. 50% had mania symptoms.</td>
</tr>
</tbody>
</table>

Explosive Outbursts and Irritability

Rare

Neither DMDD Nor bipolar

Change from previous behavior or self

Child

Teen

Frequent

Irritable between Outbursts

Chronic

Fine until frustrated

First R/O Stressor
School-learning probs bullying
Home Family probs abuse

R/O mood disorder
Depression Mania
Anxiety disorder Drugs Psychosis

DMDD +/- ASD

ADHD ODD +/- ASD

DMDD=disruptive mood dysregulation disorder; ASD=Autism spectrum disorder
Psychiatric Approach for Most Children with “Mood Dysregulation”

- Good diagnostic assessment
  - Combined ADHD/ODD is most common (~75%);
  - anxiety, depression and autism are other common primary disorders; it is why they are “rule outs” for DMDD.
  - Keep careful records of frequency, intensity, number, and duration of outbursts.

- Maximize the treatment of the base condition.
  - My experience/most data: it is ADHD, combined
  - If symptoms remain, add another medication – atypical antipsychotic (AAP), conventional antipsychotic (CAP), or mood stabilizer or possibly alpha agonist.
  - Pay attention to weight gain immediately

- We desperately need medications for severe outbursts whatever they are called

- >40% of kids remain symptomatic in spite of best treatment
  - the “press” goes on about giving kids “powerful” drugs. For these kids, the power of their disorder is much greater than our treatments.

Proposed Management

ADHD symptoms

Mood regulation

Social info processing

Family

Medication management

ADHD treatment
“mood stabilizers”
Anti-aggressive/anti Psychotic medications

Psychoeducation
Understand primary condition
? psych and language testing

Psychological
Anger management
Problem solving

Family
Treat parent psychiatric dis.
Understand triggers
Parent training
For Inadequate Response in Youth Consider:

- Conveying hope
- Optimizing dose
- Checking the diagnosis
- Inadequate treatment (meds, therapy, dose, duration)
- Clarify what has not responded: depression, mania, ADHD, anxiety?
- Stressors, abuse, conflicts, parental psychopathology, school issues
- Co-occurring psychiatric/med conditions
- Non-adherence
- Side effects
- Poor fit between patient and therapist
- Managing residual symptoms (e.g., insomnia)
- Pharmacodynamic/pharmakokinetic factors
- Change SSRI or type of antidepressant
- Combine psychotherapy w/ SSRI
- ECT/Transcranial Magnetic Stimulation/Ketamine

- Inadequate treatment (meds, therapy, dose, duration)
## Treatment of Pediatric BD (Case)

Joy is a 15-year-old sophomore in high school who reports that for the past week, she has gone without any sleep in a heightened state of activity, with distractibility from racing thoughts, rapid speech, and rapid mood swings. She describes herself as being “out of control.” She recently proclaimed to a group of friends that she did not menstruate because she was “of a third sex, a gender above the human sexes.” When her friends questioned her on this, she explained that she is a “superwoman” who can avoid human sexuality and still give birth.
Comparing Pediatric BD to ADHD

**BD**
- Unstable Mood
- Internally distracted
- Can’t soothe when angry
- Rage for hours
- Take big risks, look for danger or thrill
- Do better at school
- High energy/inappropriate giggling
- May be overly sexual

**Family History**
- ADHD meds can trigger mania

**Worsen with Age**

**ADHD**
- Stable Mood
- Externally distracted
- Soothing helps
- Lose interest in fighting
- Do not intend to get into big trouble
- Do better at home
- Normal laughing or fun
- Sexuality not a major issue

**No Family History**
- ADHD meds help

**Get better with Age**
Comorbidity-ADHD

- Rates depend on whether or not symptoms of mania and ADHD are “double counted”
- Comorbidity rates are much higher when they are
  - 75-98% children
  - 25-60% in teens;
  - 10-20% in adults
- Even accounting for that, rates of ADHD appear to be somewhat higher than expected by chance
- ADHD comorbidity
  - Lengthens a manic episode
  - Decreases time to relapse
  - Worsens treatment response

## Treatment Challenge: Limited Evidence

### Base/Approved Agents for ADHD in BD

<table>
<thead>
<tr>
<th><strong>Good News</strong></th>
<th><strong>Bad News</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>On average, over time, symptoms</td>
<td>No RCTs have examined efficacy and safety of ADHD treatment in youth at</td>
</tr>
<tr>
<td>become less severe</td>
<td>risk for mood disorders</td>
</tr>
<tr>
<td>A variety of interventions clearly</td>
<td>No existing treatments seem to change the long-term course of ADHD</td>
</tr>
<tr>
<td>can reduce symptoms, at least in</td>
<td>Inadequately treated ADHD makes other developmental goals much harder to</td>
</tr>
<tr>
<td>the short run</td>
<td>attain</td>
</tr>
<tr>
<td></td>
<td>When ADHD occurs with another problem (about 2/3 of the time) outcomes tend</td>
</tr>
<tr>
<td></td>
<td>to be worse</td>
</tr>
<tr>
<td></td>
<td>All treatments have the potential for side effects</td>
</tr>
</tbody>
</table>
Possible Points of Intervention

**Environmental**
- Structural
- Programmatic

**Psychological**
- Cognitive
- Behavioral

**Biological**
- Medications
- Nutritional changes

- Stimulants
  - Methylphenidate
  - Amphetamine
  - Lisdexamfetamine

- Non-Stimulants
  - Atomoxetine
  - Guanfacine
  - Clonidine*
  - Other less well established or less used:
    - Bupropion*
    - Imipramine*
    - Nortriptyline*
    - Venlafaxine*
    - Modafinil*

*Clonidine, bupropion, imipramine, nortriptyline, venlafaxine, and modafinil are not FDA-approved for ADHD
Use of Stimulants in the Context of Mania

● Studies suggest that:
  ● Children with bipolar disorder/severe mood dysregulation/disruptive mood dysregulation disorder (DMDD) are not harmed by stimulants and could help\(^1\)
  ● Children with bipolar disorder find stimulants in addition to mood stabilizers add further to treatment response\(^2\)
  ● Children with ADHD and irritability/aggression respond better to mood stabilizers or atypicals versus placebo if the ADHD is maximally treated first\(^3\)
  ● Conversion from ADHD to BD/severe mood dysregulation happens less often in children given stimulants\(^4\)

## FDA-Approved Agents for Pediatric BD

<table>
<thead>
<tr>
<th></th>
<th>Acute Mania</th>
<th>Acute Depression</th>
<th>Longer-Term</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
<td><strong>Drug</strong></td>
<td><strong>Year</strong></td>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>1970</td>
<td>Lithium&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2014</td>
<td>Olanzapine+fluoxetine</td>
</tr>
<tr>
<td>2007</td>
<td>Risperidone&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2014</td>
<td>combination&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2008</td>
<td>Aripiprazole&lt;sup&gt;b&lt;/sup&gt;, (*-&gt;e)</td>
<td>2014</td>
<td>1974 Lithium&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2009</td>
<td>Quetiapine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2008</td>
<td>Aripiprazole&lt;sup&gt;(b-&gt;e)&lt;/sup&gt;</td>
</tr>
<tr>
<td>2009</td>
<td>Olanzapine&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2015</td>
<td>2015 Asenapine&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2015</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Important unmet needs - well-tolerated treatments for acute depression and maintenance.

*Adjunctive (as well as monotherapy); <sup>a</sup>Age ≥ 12-17; <sup>b</sup>Age 10-17; <sup>c</sup>Age 13-17; (*->e)Extrapolated indication
Adapted from: Ketter TA (ed). Advances in the Treatment of Bipolar Disorder, Am Psych Pub, Inc., Washington, DC, 2015,
Overview of Pediatric Acute Mania Studies
Number Needed to Treat for Response, Rates


<table>
<thead>
<tr>
<th>Treatment</th>
<th>NNT</th>
<th>Percent Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone Vs PBO</td>
<td>3</td>
<td>61% (0.5-2.5 mg/d) 35% (1.8-3.6 mg/d)</td>
</tr>
<tr>
<td>Aripiprazole Vs PBO</td>
<td>4</td>
<td>54% (10 or 30 mg/d) 26%</td>
</tr>
<tr>
<td>Olanzapine Vs PBO</td>
<td>4</td>
<td>45% (2.5-20 mg/d) 26%</td>
</tr>
<tr>
<td>Quetiapine Vs PBO</td>
<td>5</td>
<td>61% (400 or 600 mg/d) 24%</td>
</tr>
<tr>
<td>Asenapine Vs PBO</td>
<td>5</td>
<td>48% (5 or 10 mg/d) 20%</td>
</tr>
<tr>
<td>Ziprasidone Vs PBO</td>
<td>4</td>
<td>62% (80-160 mg/d) 27%</td>
</tr>
</tbody>
</table>

Second generation antipsychotics consistently increased pediatric antimanic response rates.

**p < 0.01
***p < 0.001,
****p < 0.0001 vs. PBO.
Overview of Pediatric Acute Mania Studies
Numbers Needed to Treat and Harm, ≥ 7% Weight Gain Rates

Second generation antipsychotics more variably increased weight in youth.

<table>
<thead>
<tr>
<th>Approved Drugs</th>
<th>NNT/NNH</th>
<th>Percent with ≥ 7% Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone vs Placebo</td>
<td>3/16</td>
<td>12% vs 7%</td>
</tr>
<tr>
<td>Aripiprazole vs Placebo</td>
<td>4/29</td>
<td>8% vs 5%</td>
</tr>
<tr>
<td>Olanzapine vs Placebo</td>
<td>4/3</td>
<td>42% vs 2%</td>
</tr>
<tr>
<td>Quetiapine vs Placebo</td>
<td>5/9</td>
<td>12% vs 12%</td>
</tr>
<tr>
<td>Asenapine vs Placebo</td>
<td>5/12</td>
<td>9% vs 8%</td>
</tr>
<tr>
<td>Ziprasidone vs Placebo</td>
<td>4/34</td>
<td>7% vs 4%</td>
</tr>
</tbody>
</table>

Unapproved Drugs

Lithium vs. Placebo in 81 Youth with Acute Mania

Lithium vs. Placebo: Weight Gain Over 8 Weeks

<table>
<thead>
<tr>
<th>Mood Stabilizers in Pediatric BD: 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lithium:</strong> FDA approved down to age 12 y/o. Lithium superior to PBO in children with BD, little weight gain&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Divalproex:</strong> Extended Release (ER) form with negative pediatric data (24% response) for acute mania. Unpublished data suggests Immediate Release (IR) more effective than PBO&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Carbamazepine:</strong> ER form with open label data showing mild to moderate improvement in pediatric mania.&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Lamotrigine:</strong> Open studies find efficacy in pediatric acute mania, mixed mania, depression. Maintenance study completed, mild-moderate effects.&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Oxcarbazepine:</strong> Negative for acute mania in children and adolescents&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Not FDA-approved for pediatric bipolar disorder

---

8-Week Olanzapine + Fluoxetine in Pediatric Bipolar I Depression
Numbers Needed to Treat and Harm, Response and ≥ 7% Weight Gain Rates


**Benefit (NNT)**
- CDRS-R Response

Olanzapine+Fluoxetine vs PBO
- NNT: 6
- 78.2%
- 19.0%

**Harm (NNH)**
- ≥ 7% Weight Gain

Olanzapine+Fluoxetine vs PBO
- NNH: 3
- 59.2%
- 52%

OLZ-FLX vs. PBO more than twice as likely to yield weight gain as response.

Mean 7.7 + 37.6 mg/d

OLZ + FLX: 170
PBO: 85 = N

OLZ + FLX: 52%
PBO: 48%

OLZ + FLX: 4%
PBO: 4%
<table>
<thead>
<tr>
<th>Agents lacking FDA-Approval for Pediatric Bipolar Disorder*</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Antidepressants (other than fluoxetine + olanzapine) – any</td>
</tr>
<tr>
<td>● Divalproex, carbamazepine, lamotrigine – any</td>
</tr>
<tr>
<td>● Lithium – BD depression</td>
</tr>
<tr>
<td>● Olanzapine, quetiapine, risperidone – BD depression; maintenance</td>
</tr>
<tr>
<td>● Aripiprazole – BD depression; maintenance (LAI)</td>
</tr>
<tr>
<td>● Asenapine – adjunctive mania; BD depression; maintenance</td>
</tr>
<tr>
<td>● Ziprasidone, lurasidone, caripazine, brexipiprazole – any</td>
</tr>
<tr>
<td>● Chlorpromazine – any</td>
</tr>
<tr>
<td>● Armodafinil – any</td>
</tr>
<tr>
<td>● Negative studies in pediatric BD: oxcarbazepine, topiramate</td>
</tr>
</tbody>
</table>

Pediatric Bipolar Depression

First Line: Psychotherapy

Second Line: Lithium, Lamotrigine, Lurasidone* (Olanzapine-Fluoxetine is FDA approved)

Third Line: Quetiapine, Bupropion,* careful SSRI titration

*Not FDA-approved for pediatric bipolar depression.
### Mood Stabilizers: Safety and Tolerability Concerns

<table>
<thead>
<tr>
<th></th>
<th>Lithium</th>
<th>Valproate</th>
<th>Carbamazepine</th>
<th>Lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Weight gain</td>
<td>Weight gain</td>
<td>Gastrointestinal</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>Tremor</td>
<td>Neurotoxicity</td>
<td>Rash</td>
<td>Rash</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>Hepatotoxicity</td>
<td>Hepatotoxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid toxicity</td>
<td>Thrombocytopenia</td>
<td>Thyroid changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair Loss</td>
<td>Hair Loss</td>
<td>Blood dyscrasias</td>
<td></td>
<td>Dream abnormality</td>
</tr>
<tr>
<td>Cardiac toxicity</td>
<td>Pancreatitis</td>
<td>Cardiac toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acne, Psoriasis</td>
<td>PCOS</td>
<td>Hyponatremia</td>
<td></td>
<td></td>
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<tr>
<td>Teratogen</td>
<td>Teratogen</td>
<td>Teratogen</td>
<td></td>
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<tr>
<td>Suicidality</td>
<td></td>
<td></td>
<td></td>
<td>Suicidality</td>
</tr>
</tbody>
</table>

*All mood stabilizers have at least one boxed warning.*

---

= boxed warning in prescribing information.

# Antipsychotic Safety and Tolerability Concerns: All Antipsychotics Have at Least One Boxed Warning

## First-Generation
- Depression
- Akathisia
- Acute dystonia
- Tardive dyskinesia\(^a\)
- Weight gain, Sedation
- Anticholinergic
- Cardiac, Orthostasis
- Hyperprolactinemia
- Neuroleptic malignant\(^a\)
- Leukopenia, Neutropenia,
  
  **Agranulocytosis\(^a\)**
  
  **Cardiac/pneumonia in older adults\(^a\)**

## Second-Generation
- Weight gain, Sedation
- Hyperglycemia, Diabetes\(^b\)
  
  **Suicidality in age ≤ 24\(^c\)**

- Akathisia
- Hyperprolactinemia
- Cerebrovascular in elderly\(^d\)
- Cardiac, Orthostasis
- Tardive dyskinesia\(^a\)
- Neuroleptic malignant\(^a\)
- Leukopenia, Neutropenia,
  
  **Agranulocytosis\(^a\)**
  
  **Cardiac/pneumonia in older adults\(^a\)**

**Warnings -** boxed; \(^a\) Antipsychotic class warning/precaution; \(^b\) Second generation antipsychotic class warning; \(^c\)Aripiprazole, quetiapine, olanzapine + fluoxetine combination (antidepressant class warning); \(^d\) risperidone, olanzapine, aripiprazole.

Ketter TA (ed). Handbook of Diagnosis and Treatment of Bipolar Disorder, APPI., Washington, DC, [Package Insert]. Drugs@FDA Website.
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 wk</th>
<th>8 wk</th>
<th>12 wk</th>
<th>Quarterly</th>
<th>Annually</th>
<th>Every 5 y</th>
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<tbody>
<tr>
<td>Personal/family history</td>
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<td>Weight (BMI)</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Waist circumference</td>
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<td></td>
<td></td>
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<td>Blood pressure</td>
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<td>Fasting plasma glucose</td>
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<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Fasting lipid profile</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*More frequent assessments may be warranted based on clinical status*

SMART Goals

● For every child who presents with mood symptoms, assess for both depression and mania
● Ensure adequate dosing and trial before trying different antidepressant and watch for treatment-emergent mania
● Treat comorbid conditions (e.g. ADHD) after addressing primary mood disorder
● Evidence supports atypical antipsychotic and lithium use for acute mania
● Psychotherapy, and 3 L’s: lurasidone,* lithium,* and lamotrigine* may be effective for bipolar depression; potential for maintenance
● Weight gain and sedation are the most common and problematic adverse effects

*Not FDA-approved for pediatric bipolar depression
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Questions & Answers