DIAGNOSING AND TREATING BIPOLAR DISORDER IN YOUTH
Learning Objectives

• Provide an overview of general principles in the **diagnosis** in pediatric bipolar disorder (BD)
• Discuss the **efficacy** of evidence-based treatments for pediatric BD
• Discuss the **safety** of evidence-based treatments for pediatric BD
• Bipolar Risk and Resilience
Bipolar Spectrum in Children

SMD  ADHD+FH  DEP+FH  BP NOS  BP II  BP I

Possible Prodromal States

Severe Mood Dysregulation

“Full” Bipolar Disorder
Course and Outcome of Bipolar in Youth (COBY)

• 263 subjects, 7–17 yrs.
• 57% BD I, 8% BD II, 35% BD NOS
• Assessed over 1.5 years
• BD NOS defined as one less symptom, 4 hours duration
• BD I recover and recur more frequently than BD NOS
• 12% with psychosis, 15% with suicide attempt/gesture

Birmaher B et al. Arch Gen Psychiatry 2006;63(2):175-83.
Family History Matters

The graph illustrates the rate of conversion to BP/I/II over weeks for both (+) BP Family History and (-) BP Family History groups. The y-axis represents the rate of conversion, ranging from 0% to 100%, while the x-axis represents weeks to conversion, ranging from 0 to 234 weeks.

- (+) BP Family History:
  - 1 year: 26.6%
  - 2 years: 35.1%
  - 4 years: 50.7%

- (-) BP Family History:
  - 1 year: 14.5%
  - 2 years: 19.9%
  - 4 years: 30.4%
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>YOUTH</th>
<th>ADULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability</td>
<td>16.7%</td>
<td>15.8%</td>
</tr>
<tr>
<td>Aggression</td>
<td>15.0%</td>
<td>13.9%</td>
</tr>
<tr>
<td>Rapid speech</td>
<td>14.8%</td>
<td>15.6%</td>
</tr>
<tr>
<td>Grandiosity</td>
<td>10.3%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Increased motor</td>
<td>9.4%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Elevated mood</td>
<td>8.7%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Flight of ideas</td>
<td>7.0%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Sleep decreased</td>
<td>5.8%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Low insight</td>
<td>4.7%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Sexual interest</td>
<td>3.5%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Odd appearance</td>
<td>3.4%</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

### Bipolar Spectrum Symptoms in Youth in Meta-Analysis

<table>
<thead>
<tr>
<th>Percentage</th>
<th>70–80%</th>
<th>60–70%</th>
<th>50–60%</th>
<th>40–50%</th>
<th>&lt;40%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>↑ Energy</strong></td>
<td>Energy</td>
<td>Euphoria</td>
<td>Grandiose</td>
<td>↑ Productivity</td>
<td>Hypersexuality</td>
</tr>
<tr>
<td><strong>Irritability</strong></td>
<td>Irritability</td>
<td>Rapid speech</td>
<td>Inappropriate laughter</td>
<td>Intrusive</td>
<td>Hallucinations</td>
</tr>
<tr>
<td><strong>Lability</strong></td>
<td>Lability</td>
<td>Hyperactive</td>
<td>Racing thoughts</td>
<td>↑ Creativity</td>
<td>Hallucinations</td>
</tr>
<tr>
<td><strong>Distract.</strong></td>
<td>Distract.</td>
<td>Poor</td>
<td>Need for sleep</td>
<td>Flight of ideas</td>
<td>delusions</td>
</tr>
<tr>
<td><strong>Goal-Activity</strong></td>
<td>Goal-Activity</td>
<td>Hyperactive</td>
<td>Racing thoughts</td>
<td>Poor judgment</td>
<td>Poor judgment</td>
</tr>
</tbody>
</table>

## Confusing Symptom Overlap

<table>
<thead>
<tr>
<th></th>
<th>Mania</th>
<th>MDD</th>
<th>ADHD</th>
<th>ODD</th>
<th>Anxiety</th>
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<tbody>
<tr>
<td>Elated mood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
<td>67%</td>
<td>Low frustration tolerance</td>
<td>Touchy Easily annoyed</td>
<td>Irritability</td>
</tr>
<tr>
<td>Hyperactivity Agitation</td>
<td>Agitation</td>
<td>Hyperactivity</td>
<td></td>
<td></td>
<td>Restlessness Agitation</td>
</tr>
<tr>
<td>Distractibility</td>
<td>Poor concentration</td>
<td>Distractibility</td>
<td></td>
<td></td>
<td>Difficulty in concentration</td>
</tr>
<tr>
<td>Flight of ideas</td>
<td></td>
<td>Communication disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grandiosity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor judgment</td>
<td></td>
<td></td>
<td></td>
<td>Impulsivity</td>
<td></td>
</tr>
<tr>
<td>Reduced sleep need</td>
<td>Insomnia</td>
<td>Trouble settling Wakes early</td>
<td></td>
<td>Initial insomnia</td>
<td></td>
</tr>
</tbody>
</table>
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 age, 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

Diagnostic Challenge: 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

BD = bipolar disorder; ADHD = attention-deficit/hyperactivity disorder.
Percentage of time spent with mood symptoms between youth with BP-I vs. adults with BP-I


c.o. Boris Birmaher
DISRUPTIVE MOOD DYSREGULATION DISORDER (DMDD)
Downstream effect of *DSM* changes
ADHD gentrified
Mania episodes poorly defined

No diagnostic home for explosive outbursts/rages
~10% outpatients
90% inpatients

**Managed Care**
No time to evaluation
Must medicate

FDA approval of atypical antipsychotics and divalproex to treat mania in adults and subsequently children
For office-based visits with a mental disorder, rates from .42% (n=25) in 1994 to 6.7% (n=1003)
DMDD Criteria: OI VEY

• Outbursts—frequent (several times/week), impairing, in more than one place (i.e., not just conflict with a parent or teacher)

• Irritable mood when not having outbursts

• Very chronic—has lasted at least a year

• Explained by another [better understood] condition e.g., mania (at least a day), MDD, PTSD, anxiety, autism???, not DMDD
  • The point being that outbursts occur in many conditions that need to be ruled out first

• Young—starts in childhood (after age 6, before age 10, not after age 18)
Explosive Outbursts and Irritability

Rare

Neither DMDD nor bipolar

Change from previous behavior or self

Child

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

Teen

R/O mood disorder

Depression Mania

Anxiety disorder Drugs
Psychosis

Frequent

Irritable between outbursts

DMDD +/- ASD

Chronic

Fine until frustrated

ADHD ODD +/- ASD

DMDD=disruptive mood dysregulation disorder; ASD=Autism spectrum disorder
Treating Youth With Bipolar Disorder Today

- **Antipsychotics** (dopamine, serotonin, norepinephrine receptor antagonists, partial agonists, and reuptake inhibitors) and **mood stabilizers** (glutamatergic, voltage-gated sodium and calcium channel blockers) are current mainstay treatments.

- Most of these medications have side effects (most common: weight gain, metabolic syndrome, sedation) and long-term safety profiles are not well known.

- Compared to adults:
  - Relative risk for ≥7% weight gain, somnolence, nausea, or vomiting was higher, and akathisia was lower in pediatric patients.
  - The magnitude of difference among antipsychotics and mood stabilizers varies widely.
  - Risk of side effects for pediatric patients could be underestimated because doses of studied medications are lower, flexibly dosed, and titration speeds are slower.
  - Differences in study design might impact risk for common side effects when prescribing a medication for BD.

CASE:
Joy is a 15-year-old sophomore who reports that for the past week she has gone without any sleep, running around like an energizer bunny, 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.”
### FDA-Approved Treatments for Pediatric Bipolar Disorder

#### Acute Mania

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
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<tbody>
<tr>
<td>1970</td>
<td>Lithium &lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2007</td>
<td>Risperidone &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2008</td>
<td>Aripiprazole &lt;sup&gt;b,(*-&gt;e)&lt;/sup&gt;</td>
</tr>
<tr>
<td>2009</td>
<td>Quetiapine &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2009</td>
<td>Olanzapine &lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2015</td>
<td>Asenapine &lt;sup&gt;b&lt;/sup&gt;</td>
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</tbody>
</table>

#### Acute Bipolar Depression

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>Olanzapine+fluoxetine combination&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2018</td>
<td>Lurasidone&lt;sup&gt;b&lt;/sup&gt;</td>
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</table>

#### Longer-Term

<table>
<thead>
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<th>Year</th>
<th>Drug</th>
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<tbody>
<tr>
<td>1974</td>
<td>Lithium &lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2008</td>
<td>Aripiprazole (b-&gt;e)</td>
</tr>
</tbody>
</table>

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*Adjunctive (as well as monotherapy); <sup>a</sup>Age ≥ 12–17; <sup>b</sup>Age 10–17; <sup>c</sup>Age 13–17; (<sup>->e</sup>)Extrapolated indication

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

Unmet Need
Overview of Pediatric Bipolar I Acute Mania/Mixed Studies

Numbers Needed to Treat Response

Second-generation antipsychotics consistently increased pediatric antimanic response rates.

Approved

<table>
<thead>
<tr>
<th>NNT</th>
<th>Drug</th>
<th>vs</th>
<th>Placebo</th>
<th>Percent Responders</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td>3</td>
<td>Risperidone</td>
<td>vs</td>
<td>Placebo</td>
<td>61%</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35%</td>
</tr>
<tr>
<td>4</td>
<td>Olanzapine</td>
<td>vs</td>
<td>Placebo</td>
<td>45%</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19%</td>
</tr>
<tr>
<td>4</td>
<td>Quetiapine</td>
<td>vs</td>
<td>Placebo</td>
<td>61%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>37%</td>
</tr>
<tr>
<td>5</td>
<td>Aripiprazole</td>
<td>vs</td>
<td>Placebo</td>
<td>48%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28%</td>
</tr>
</tbody>
</table>

Unapproved

| 4   | Ziprasidone| vs    | Placebo | 62%                | 27%        |

** p < 0.01, *** p < 0.001, **** p < 0.0001 vs. PBO. LOCF = Last Observation Carried Forward; OC = Observed Cases.

Overview of Pediatric Bipolar I Acute Mania/Mixed Studies
Numbers Needed to Harm, ≥ 7% Weight Gain Rates

Second-generation antipsychotics more variably increased weight in youth.

Approved

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo</th>
<th>NNT/NNH</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>Placebo</td>
<td>3/16</td>
<td><strong>p &lt; 0.0001</strong></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Placebo</td>
<td>4/29</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Placebo</td>
<td>4/3</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Placebo</td>
<td>5/9</td>
<td></td>
</tr>
<tr>
<td>Asenapine</td>
<td>Placebo</td>
<td>5/12</td>
<td></td>
</tr>
</tbody>
</table>

Unapproved

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo</th>
<th>NNT/NNH</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone</td>
<td>Placebo</td>
<td>4/34</td>
<td></td>
</tr>
</tbody>
</table>

Second-generation antipsychotics more variably increased weight in youth.

Overview of Pediatric Bipolar I Depression Studies
Numbers Needed to Treat and Harm, Response and ≥ 7% Weight Gain Rates

**p < 0.01, ***p < 0.001, ****p < 0.0001 vs PBO.

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

NNT / NNH

Olanzapine+Fluoxetine vs Placebo

Benefit (NNT) Response

Olanzapine+Fluoxetine

Response

6

≥ 7% Weight Gain

3

Harm (NNH)

Olanzapine+Fluoxetine vs Placebo

≥ 7% Weight Gain

3

Lurasidone vs Placebo

≥ 7% Weight Gain

20

Lurasidone vs Placebo

0

Percentage With Benefit or Harm (%)

10

20

30

40

50

60

70

80

OLZ + FLX

PBO

59.2%

19.0%

Mean 7.7 + 37.6 mg/d

52%

48%

OLZ + FLX vs Placebo more than twice as likely to yield weight gain as response.

LUR

PBO

59.5%

23.0%

Mean 32.5 mg/d

59.5%

23.0%

Mean 36.5 mg/d

59.2%

19.0%

LUR vs Placebo

170

8

OLZ + FLX vs Placebo

173

17

PBO

5.3%

4%

LUR

PBO

59.5%

23.0%

Mean 36.5 mg/d

59.2%

19.0%

LUR vs Placebo

170

8

OLZ + FLX vs Placebo

173

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PBO

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4%

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PBO

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Mean 36.5 mg/d

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59.5%

23.0%

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19.0%

LUR vs Placebo

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OLZ + FLX vs Placebo

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17

PBO

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4%

LUR

PBO

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23.0%

Mean 36.5 mg/d

59.2%

19.0%

LUR vs Placebo

170

8

OLZ + FLX vs Placebo

173

17

PBO

5.3%

4%

LUR

PBO

59.5%
Possible Treatment Algorithm for Pediatric Bipolar Depression

First-Line: Psychotherapy
Next: Lurasidone, Olanzapine-Fluoxetine (with metformin?)
Consider
Lithium, Lamotrigine, Abilify
Next: Quetiapine, Bupropion,
careful SSRI titration

Schneck et al. JCAP 2017; DelBello et al. JAACAP 2017; Findling et al. JAACAP 2017.
# Antipsychotic Safety and Tolerability

<table>
<thead>
<tr>
<th>First-Generation</th>
<th>Second-Generation</th>
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</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Weight gain, Sedation</td>
</tr>
<tr>
<td>Akathisia</td>
<td>Hyperglycemia, Diabetes&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Acute dystonia</td>
<td>Suicidality in age ≤ 24&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tardive dyskinesia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Akathisia</td>
</tr>
<tr>
<td>Weight gain, Sedation</td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>Cardiac, Orthostasis</td>
</tr>
<tr>
<td>Cardiac, Orthostasis</td>
<td>Tardive dyskinesia&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Neuroleptic malignant&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Neuroleptic malignant&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Leukopenia, Neutropenia,</td>
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<td>Leukopenia, Neutropenia,</td>
<td></td>
</tr>
<tr>
<td>Agranulocytosis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Agranulocytosis&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cardiac/pneumonia in older adults&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cardiac/pneumonia in older adults&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Warnings** - boxed;  
<sup>a</sup> Antipsychotic class warning/precaution;  
<sup>b</sup> Second-generation antipsychotic class warning;  
<sup>c</sup> Aripiprazole, Quetiapine, Olanzapine + fluoxetine combination (Antidepressant class warning);  
<sup>d</sup> Risperidone, Olanzapine, Aripiprazole.

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All antipsychotics have at least one boxed warning.

ADA Consensus on Antipsychotic Drugs: Monitoring Protocol for Patients on SGAs*

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

<table>
<thead>
<tr>
<th></th>
<th>Short-Term</th>
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<th>Long-Term</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>4 wk</td>
<td>8 wk</td>
<td>12 wk</td>
<td>Quarterly</td>
<td>Annually</td>
<td>Every 5 y</td>
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<td>Personal/family history</td>
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<td></td>
<td></td>
<td></td>
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<td>Weight (BMI)</td>
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<td>Blood pressure</td>
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<td>Fasting plasma glucose</td>
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<td>Fasting lipid profile</td>
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Lithium vs. Placebo in 81 Youth With Acute Mania

Lithium vs. Placebo: Weight Gain Over 8 Weeks

Positive Studies for Mood Stabilizers in Pediatric BD

- **LITHIUM**: FDA-approved down to age 12 y/o; lithium superior to placebo in children with BD, little weight gain

- **DIVALPROEX**: Extended-release form was negative for acute mania; unpublished data suggests immediate-release more effective than placebo; inferior to quetiapine and risperidone

- **CARBAMAZEPINE**: ER form with open-label data showing mild to moderate improvement in pediatric mania

- **LAMOTRIGINE**: Open studies find efficacy in pediatric acute mania, mixed mania, depression; maintenance RCT study showed benefit as an adjunct

DelBello 2006; Pavuluri 2010; Wagner 2009; Kowatch 2009; Joshi 2010; Chang 2006; Biederman 2010; Findling 2015a; Findling 2015b.
All mood stabilizers have at least one boxed warning.
Selected Agents Lacking FDA-Approval Used Off-Label in Pediatric Bipolar Disorder

- Antidepressants (other than fluoxetine + olanzapine)—any
- Divalproex, carbamazepine, lamotrigine, topiramate—any
- Lithium—BD depression
- Tamoxifen (protein kinase C inhibitor—adjunctive to lithium)—reductions in mania and depression after 4 weeks
- Quetiapine, risperidone—BD depression; maintenance
- Paliperidone—BD (open-label)
- Aripiprazole—BD depression; maintenance
- Asenapine—BD depression; maintenance
- Ziprasidone, cariprazine, brexpiprazole—any
- Vitamin D3 (2000 IU)—open-label, reduced mania and depressive symptoms
- Uridine (pyrimidine nucleoside)—open-label, reduced depressive symptoms
- Adverse effects may limit utility for cariprazine (akathisia) and brexpiprazole, paliperidone (weight gain)
- Ketamine

NEGATIVE STUDIES IN CHILDREN: for acute mania: oxcarbazepine, divalproex ER, omega-3 FA, celecoxib (adjunctive to lithium/risperidone), marginally nonsignificant treatment response by global assessment but significant mania reduction after 8 weeks; for bipolar depression: quetiapine and quetiapine ER
Intranasal Ketamine for Fear of Harm and Longitudinal Treatment of Youth With Bipolar Disorder

- Ketamine every 2–5 days had sustained benefits in the fear of harm bipolar phenotype
- Treatment-resistant patients receiving ketamine had marked reduction in CGI scores
- Intranasal ketamine administration every few days was tolerable for months to years
- Most adverse events were time limited and persisted for 15–120 minutes
- Intensity of most adverse events decreased over time without loss of benefits

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?
Mania in SSRI Trials in Youth

- 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 weeks to 1 year after initial SSRI exposure
- In 21% of such patients represented in these studies, there was a family history of BD
Theories for Why Antidepressant-Induced Mania Occurs

• **Ignition hypothesis**: Antidepressant interacts with genetic predisposition to trigger mania

• **Scar hypothesis**: No genetic predisposition, but new predisposition created by antidepressant

• **Side effect hypothesis**: Simply an adverse effect, no scar created

• **Natural course hypothesis**: Coincidence of mania naturally following depression

## Pharmacological Studies in High-Risk Offspring

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample Population and Size</th>
<th>Drug</th>
<th>Design</th>
<th>Outcome</th>
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<tr>
<td>Geller, 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) versus placebo (n=13)</td>
<td>Double-blind placebo-controlled</td>
<td>No difference between active and placebo groups</td>
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<td>Chang, et al. 2003.</td>
<td>24 (6–18 years old) youth with mood and behavioral disorders and at least one parent with BD</td>
<td>Divalproex</td>
<td>12-week open-label</td>
<td>78% response rate; no discontinuations due to adverse effects</td>
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<td>Findling, et al. 2007.</td>
<td>56 symptomatic youth (5–17 years old) with BD-NOS or cyclothymia with at least one parent with BD</td>
<td>Divalproex (n=29) versus placebo (n=27)</td>
<td>Double-blind placebo-controlled for up to 5 years</td>
<td>No difference in survival time for discontinuation for any reason (p=.93) or due to a mood event (p=.55)</td>
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<td>DeiBello, et al. 2007.</td>
<td>20 symptomatic adolescents (12–18 years old) with at least one first-degree relative with BD I</td>
<td>Quetiapine</td>
<td>12-week single blind open-label trial</td>
<td>87% response (CGI-I ≤ 2) at week 12; decreased YMRS and children's depression rating scale (CDRS) scores from baseline to endpoint</td>
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<td>Findling, et al. 2009.</td>
<td>9 children (7–16 years old) with MDD and at least one parent with BD</td>
<td>Paroxetine versus paroxetine+ divalproex</td>
<td>Open-label</td>
<td>Neither treatment was effective; 50% had mania symptoms</td>
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<td>Findling et al. 2017.</td>
<td>59 youth (5–17 years old) with BD-NOS or cyclothymia and at least one parent with BD, another first- or second-degree relative with a mood disorder, and not responsive to psychotherapy</td>
<td>Aripiprazole versus placebo</td>
<td>12-week double-blind placebo-controlled</td>
<td>Aripiprazole was superior to placebo in reducing symptoms of mania; youth who received aripiprazole vs. placebo had significantly more weight gain (mean=2.3 vs 0.7 kg).</td>
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</table>

**Take Away Points:** Jury is out! Need more RCTs, and watch out for AEs!
Managing Arousal Induced By Medication When It Presents

• Rule out organic etiology

• Evaluate for potential contributors:
  • Diagnosis (mania), co-occurring conditions (e.g., ADHD, substance use)
  • Family and other psychosocial factors
  • Medication adherence

• Decrease dose of inciting agent, avoiding abrupt discontinuation (e.g., serotonin discontinuation syndrome)

• Supportive individual/family psychotherapy

• Consider role of short-term mono- or adjunctive pharmacological treatment:
  • Benzodiazepines
  • Mood stabilizers
  • Atypical antipsychotics
Adherance Challenge: Discontinuation Symptoms

- **F**—flu-like symptoms (i.e. headache, etc)
- **I**—insomnia
- **N**—nausea, vomiting, diarrhea
- **I**—imbalance (dizziness, vertigo, ataxia)
- **S**—sensory disturbances (paresthesia, numbness, tingling)
- **H**—hyperarousal (anxiety, agitation, irritability, over-activity, aggression, crying spells, low mood)

Arise within 2–3 days of discontinuing SSRI, and can persist for 2–3 weeks; usually mild, self-limited; slow taper can prevent these symptoms
How do we make decisions about youth with depression with or at risk for mania who don’t or only partially respond to psychotherapy?

**History or Symptoms of Mania in Youth 10+ Years of Age With Depression**

- **Family History of Bipolar Disorder**
  - Yes
    - ✓ Past response
    - ✓ Family response
    - If AD fails or AIM (monotx/adjunct) lamotrigine lithium quetiapine lurasidone?
  - No
    - ✓ Past/Family response
    - escitalopram sertraline citalopram bupropion?

- **Antidepressant-induced mania?**
  - Yes
    - Lurasidone OFC (√ wt)
    - lamotrigine lithium quetiapine lurasidone?
  - No
    - Yes
    - No RCTs; treat as BD I cariprazine?

- **Antidepressant-induced mania?**
  - No
    - Lamotrigine monotherapy? or combination mood stabilizer + sertraline, fluoxetine, venlafaxine (based on adults)
  - Yes
    - quetiapine lurasidone cariprazine?

Schneck et al. JCAP 2017.
Evaluation: Who will be resilient? Who will develop a mood disorder?

Family history of depression is our model system.

Singh et al. Bipolar Disorders 2014.
Resilience Is an Intriguing Solution

Defined as:

• a complex and dynamic process

• the ability to adapt successfully to adversity, stressful life events, significant threat, or trauma

• being on a continuum and can be cultivated with the potential for change across the life span
What makes humans resilient?

Mount Sinai Health System, 2018.
1. Evaluation: The Brain Can Provide Clues About Stages of Depression

Risk Marker

Disorder Marker

n.s. = not significant; * p<0.05, ** p<0.01, *** p<0.001
Stronger Brain Connectivity Predicts Resilient Outcomes After 3 Years and Tracks With More Prosocial Behaviors

Treatment: Can we cultivate prosocial behaviors to change the brain and change the outcome?
How do we cultivate prosocial behaviors?

Traditional

- Educate about symptoms

Add Prosocial Behavior Training

- Communication Skills
- Problem Solving Skills

Enhanced Care (EC)

Family-Focused Therapy (FFT)
Family-Focused Therapy (FFT) Delays New Mood Episodes By 20 More Weeks Than Enhanced Care (EC)

Finding: Family prosocial skills-training for youths at high risk for bipolar disorder is associated with longer intervals between depressive episodes.

Future Direction: Clarify the relation between changes in family function and changes in the course of high-risk syndromes.

Differences in Brain Connectivity in High Risk (HR) Versus Healthy Comparison (HC) Youth

Independent Components Analysis

Singh et al. JAACAP 2020.
FFT Is Associated With Increased Connectivity Which Tracks With Improved Depression Outcome

Singh et al. JAACAP, In Press.
Putative Mechanisms of Action of Psychotherapy in Pediatric Mood Disorders

**Finding:** We found that family-focused therapy is associated with improved functional connectivity between networks in the brain important for emotion processing and regulation.

**Future Directions:** Clarifying treatment-related changes in these neural pathways may lead to earlier identification of bipolar disorder, personalized interventions, and potentially more adaptive long-term outcomes.

- Improves emotion regulation
- Targets parent-expressed emotion (treats the system)
- Improves quality of family relationships and physical well-being
- Improves prosocial behavior
- Interactive effect of medication plus psychotherapy (adherence)
- Neuroplasticity?

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Singh et al. In Review.
Yatham et al. Bipolar Disorders 2018;20;97-120.
Let’s Leverage the Science of Resilience to Prevent Depression From Lasting a Lifetime

1. Biomarkers for early detection.
2. Preemptive interventions for those at risk or in presymptomatic stages.
3. Better treatments for people living with depression that PREDICT and TRACK outcomes.

Insel. A bridge to somewhere, Translational Psychiatry 2011.
Summary

• PRINCIPLES OF PSYCHOPHARMACOLOGY:
  • Children are not just younger versions of adults

• EFFICACY OF CURRENT EVIDENCE-BASED TREATMENTS:
  • Strongest evidence for atypical antipsychotics (>mood stabilizers) from large randomized controlled trials
  • Combined medication + psychotherapy may yield better results than either alone
  • Psychotherapy, lurasidone, olanzapine-fluoxetine may be effective for bipolar depression; potential for maintenance

• SAFETY OF CURRENT EVIDENCE-BASED TREATMENTS:
  • Weight gain and sedation are the most common and problematic adverse effects for atypical antipsychotics
  • Youth with a familial risk of bipolar disorder may be at higher risk for side effects from antidepressants than the general population

• RISK:
  • Family history

• RESILIENCE:
  • Prosocial behaviors promote resilience
Key Take-Aways

• Children are not mini-adults but classic mania can be assessed in youth

• Youth with or at risk for bipolar disorder may show early signs of neurobiological dysfunction even before symptom onset

• Effective and safe preventive, pharmacological, and psychotherapeutic interventions exist

• More combination, comparative effectiveness, and maintenance trials designed to examine longer-term outcomes are needed
Future Directions to Fulfill Clinical Unmet Need

• More research comparing available psychototropic medications and nonpharmacological alternatives is needed

• More maintenance studies and studies on long-term outcomes are needed

• More combination (pharmacotherapy and psychotherapy) trials are needed
Acknowledging our Village at Stanford

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Stanford Children’s Health | Lucile Packard Children’s Hospital
Stanford
Why is bipolar disorder challenging to treat in youth?

A. Mania is a stable phenotype across the lifespan
B. The long-term safety of medication is unknown
C. There are no FDA-approved treatments for pediatric bipolar disorder
D. There is a strong placebo effect in randomized controlled trials for pediatric bipolar disorder
The only drug that is FDA-approved for pediatric bipolar depression is:

A. Aripiprazole
B. Olanzapine
C. Lurasidone
D. Quetiapine
Posttest Question

Which is not FDA-approved for the treatment of pediatric bipolar depression?

A. Aripiprazole  
B. Lurasidone  
C. Olanzapine-fluoxetine  
D. None of the above