Juvenile Bipolar Disorder: Further Complicated by Comorbidity
Learning Objectives

• Utilize evidence-based strategies to accurately diagnose pediatric patients with bipolar disorder and mania

• Identify current best practices for the treatment of pediatric bipolar disorder and mania
Tony is an 11-year-old patient with bipolar disorder I. In discussion with the patient and his parents, it is determined that an atypical antipsychotic may be the best choice of treatment. Which of the following atypical antipsychotics is currently FDA-approved for the treatment of bipolar disorder in children 10 years and older?

1. Asenapine
2. Olanzapine
3. Paliperidone
4. All of the above
5. None of the above
Case of Joey

- Joey is a 14-year-old male with a history of trauma referred because of "fights" with his mother.
- Mother complains of quick temper, "rapid mood swings," agitation, inappropriate "jokes" and "touching," and times of poor sleep (and not tired).
- Marginally passing school (on educational plan).
- Previous trials of stimulants for ADHD were "ineffective and made him angry;" previous SSRI for early mood "set him in a rage."
- No medical history; no hospitalizations.
- MSE: Joey reports sad/mad, angry with mother; reactive; laughs inappropriately; appears disinhibited; no psychosis; no suicidality/homicidality.
- Diagnosis(es)?
Juvenile Bipolar Disorder (BPD)

- Prevalence: 2.9% of children and adolescents (Merikangas 2010)
- Estimated 10-15% of cases in child psychiatric practices (Carlson et al. 1999, Wozniak et al. 1995)
Mean Age of Onset for Bipolar Disorder; Many Adult Cases Onset in Childhood

FIGURE 1.
Frequency curve for AAO in years for patients with bipolar and schizoaffective disorders (n=353). The mean(±SD) AAO is 20.22±7.60 years.

Kennedy et al. CNS Spectrums 2011;16.
Pediatric-Onset Bipolar Disorder: Mood History

**MANIA**
- **Irritable**, angry, grouchy, cranky, snappy, swearing, disrespectful, threatening, rage attacks
- **Explosions**: how often, how long, how destructive, how aggressive
- **Giddy**, goofy, silly, high, "on drugs," laughing fits, class clown

**DEPRESSION**
- **Depressed**, sad, no pleasure, down on self, suicidal, self-destructive, whiney, complaining, lower-level irritability
Distribution of Irritable Mood in Children With ADHD

Essential Features of Pediatric BPD

• Mania is cardinal symptom:
  – Without mania = depressive disorder
• Several types of BPD based on duration, patterns
• Manic episodes (≥1 week); Hypomania (4-6 days)
  – Persistently elevated/irritable mood
  – May alternate between irritable/expanded mood
  – If only irritable, then need grandiosity/inflated self esteem, reduced sleep (not tired), pressured speech, flight of ideas, severe distractibility, increased goal directed and high risk behaviors
• DSM IV vs V: Change in mixed episodes- now mixed features ([hypo]mania+depressive symptoms)
Disruptive Mood Dysregulation Disorder (DMDD)

- The symptoms of DMDD include:
  - Severe temper outbursts at least 3 times a week
  - Sad, irritable, or angry mood almost every day
  - Reaction is bigger than expected
  - Child must be at least 6 years old
  - Symptoms begin before age 10
  - Symptoms are present for at least a year
  - Child has trouble functioning in more than one place (eg, home, school, and/or with friends)
- DDX: bipolar disorder, oppositional + mood disorder, ADHD

Axelson et al. J Clin Psychiatry 201;73(10):1342-50;
Predictors of Manic Switches

- **Family history of mood (major depressive and bipolar) disorders** (5/7 studies)
  - FHx of MDD, FHx of BPD
  - Multigenerational FHx
  - Family loading (>3 affected relatives per family)
- **Aggression, conduct, and behavioral difficulties** (2/7 studies)
  - Comorbid conduct disorder
  - Comorbid oppositional defiant disorder
  - Aggressive and bullying behaviors
- **Emotional dysregulation** (2/7 studies)
- **Medication-induced hypomania** (3/3 studies)
Factors That Differentiate Bipolar Depression From Unipolar Depression

- Family history of psychiatric illness (3/4 studies)
- Comorbid conduct or oppositional defiant disorders/aggressive behaviors (4/4 studies)
- High severity of depression (2/4 studies)
- High level of impairment (2/4 studies)

COBY BP Spectrum Conversion to BP-I/II

Either 1st or 2nd Degree Relative with Mania/Hypomania

- No (n=69)
- Yes (n=71)

Psychiatric Comorbidity is Common in Adolescent BPD

Psychiatric Comorbidity in Youth With BPD Stratified by Presence of Psychosis

- Avoidant Disorder
- OCD
- Agoraphobia
- Simple Phobia
- Social Phobia
- Panic
- PTSD
- GAD

OCD: obsessive compulsive disorder
PTSD: posttraumatic stress disorder
GAD: generalized anxiety disorder
BPD: bipolar disorder

Lowest Past GAF Score

- BPD-Psychosis: 40.3 ± 5.8
- BPD+Psychosis: 35.8 ± 5.6

$t = 5.93, p < 0.01$

Global Assessment of Functioning (GAF) Associated With Psychosis in Pediatric BPD

High Rates of Neuropsychologically Defined Executive Function Deficits in Bipolar Disorder

Treatment of Bipolar Disorder

- Thorough diagnostics (use of DSM-5)
- Education assessment (remember neuropsychological issues, comorbidity)
- Family evaluation
- Level of care if acute crisis
- Pharmacotherapy
- Psychotherapy
Psychotherapy for Juvenile BPD

- Psychoeducation family groups
- Family-focused therapy
- Cognitive behavioral therapy
- Group therapy

## Effect Size for Change in Manic Youth With Mood Stabilizers

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect Size</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Divalproex-IR/ER</td>
<td>0.28</td>
<td>0.01-0.54</td>
</tr>
<tr>
<td>Lithium</td>
<td>0.31</td>
<td>-0.12-0.73</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>0.11</td>
<td>-0.26-0.49</td>
</tr>
<tr>
<td>Topiramate</td>
<td>0.51</td>
<td>0.03-1.04</td>
</tr>
<tr>
<td><strong>Weighted</strong></td>
<td><strong>0.24</strong></td>
<td><strong>0.06-0.41</strong></td>
</tr>
</tbody>
</table>

YMRS = Young Mania Rating Scale

Courtesy M. Delbello

## Effect Size for Bipolar Change in Manic Youth With Second-Generation Antipsychotics (SGAs)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect Size</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>0.69</td>
<td>0.44-0.94</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.75</td>
<td>0.41-1.08</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.60</td>
<td>0.35-0.86</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.81</td>
<td>0.48-1.14</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>0.48</td>
<td>0.21-0.76</td>
</tr>
<tr>
<td>Weighted SGAs</td>
<td>0.65</td>
<td>0.53-0.78</td>
</tr>
</tbody>
</table>

YMRS = Young Mania Rating Scale

Correll et al. Bipolar Disord 2010. Courtesy M. Delbello
<table>
<thead>
<tr>
<th>Medication</th>
<th>Age Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>12+ years*</td>
</tr>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>10+ years</td>
</tr>
<tr>
<td>Asenapine (Saphris)</td>
<td>10+ years</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>13+ years</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>10+ years</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>10+ years</td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td>10+ years</td>
</tr>
</tbody>
</table>

*Under consideration for label change
Adverse Effects of Medications for Juvenile BPD

- **SGAs**
  - Weight gain, sedation, metabolic abnormalities, dyskinesias, prolactin elevation, EPS/TD
  - Risk depends on agent

- **Mood stabilizers**
  - Weight gain, sedation (general), thyroid abnormalities/renal/dermatological (Li), polycystic ovary syndrome (valproic acid), blood dyscrasia, rash (carbamazepine)

- **Monitoring required**
  - Height, weight, BMI, glucose/lipid panel, levels, other depending on agent

De Hert et al. Eur Psychiatry 2011;26:144-58:
TREATING COMORBIDITY WITH BPD
Diagnostic Overlap Between Conduct Disorder and BPD

ADHD in BPD Youth

Mania
N=43

ADHD
N=206

N=42
Juvenile BPD MGH Sample

• 17% of outpatient psychopharmacology referrals under age 12 met criteria for BPD

• 91% comorbid with ADHD

• 87% (81/93) of BPD sample with ADHD
• Subjects with comorbid ADHD were significantly younger (10 years vs. 14 years, $p<0.001$)
• Comorbidity with ADHD occurred more often in males than females (98% vs. 69%, $p<0.001$)

ADHD Rates in Children, Adolescents, and Adults With BPD

Rates of ADHD

- **Manic Children**: N=68, p<0.05 vs. controls & manic adols (adolescent onset)
- **Manic Adolescents (Childhood Onset)**: N=25, p<0.05 vs. manic adols (adolescent onset)
- **Manic Adolescents (Adolescent Onset)**: N=108, p<0.05 vs. non-mood adol
- **Manic Adults**: N=500

Volumetric Differences Between ADHD Patients and Controls

Blue: volumetric decrease
Red: volumetric increase
Light blue: trend towards volumetric decreases

CGa: anterior cingulate gyrus
F1: superior frontal gyrus
F3o: inferior frontal gyrus, pars opercularis
F3t: inferior frontal gyrus, pars triangularis

Biederman et al. 2006.
Volumetric Differences Between BPD Patients and Controls

Blue: volumetric decreases in the BPD group
Red: volumetric increases in the BPD group

FOC: frontal orbital cortex

Biederman et al. 2006.
Emotional Impulsivity in Adults With ADHD vs. Community Controls

Adults With ADHD and BPD

**DSM-IV ADHD: Inattention Symptoms**

- Difficulty Sustaining Attention
- Easily Distracted
- Doesn't Listen
- Forgetful
- Difficulty Following Instructions
- Careless/Sloppy
- Difficulty Organizing Tasks/Activities
- Difficulty Concentrating
- Loses Things

Adults With ADHD and BPD

Mean Bipolar Symptoms

## ADHD vs Bipolar Disorder

### Distinguishing Factors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ADHD</th>
<th>Bipolar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Course</td>
<td>Constant</td>
<td>Chronic (cycling)</td>
</tr>
<tr>
<td>Impairment</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Effect of structure</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Environmental role</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

MGH Open Study: Bupropion for ADHD in Adults With Bipolar Disorder


Baseline: 34.7

DSM-IV ADHD Checklist

Mean Change to Endpoint

Baseline: 34.7

YMRS

Baseline: 9.4

Difference: -18.44

Difference: -6.90

p < 0.005

p = 0.0016
Treating Juvenile BPD+ADHD

- Study of BPD spectrum youth
- Ages 6-17 (9 ± 2.4 years)
- Design
  - 8-week open (N=40) with DPK
  - 4-week double-blind (N=30) DPK + Adderall (5 mg BID) or PBO

YMRS scores (endpoint)
- PBO 5.9
- Amph 7.1 (pNS)

Effect of Methylphenidate on ADHD in Stabilized Youth With BPD

N=16; ages 4-17 (mean 11 years)
Euthymic-stable on thymoleptic
1 week Tx
No effect on mania

*ARS-IV: parent-completed ADHD Rating Scale-IV

Emerging data suggests a bidirectional over-representation of BPD and SUD across the life cycle.

About half of referred and community samples of adults with BPD have a lifetime history of SUD.

Himmelhoch, 1979; Reich, 1974; Strakowski, 1998; Winokur, 1995.
Impact of SUD in Juvenile BD

MSIT: Multisource Interference Task
HC: healthy controls

Development of Nicotine Dependence in BPD Youth

Failure Curve for Nicotine Dependence

$\text{p} = 0.001$

Bipolar

Control

Development of Substance Use Disorders (SUD) in BD Youth

Failure Curve for Any Substance Use Disorder

Lifetime Prevalence

$\textbf{Bipolar}$

$\textbf{Control}$

$p=0.004$

Persistence of Adolescent BPD: BPD Status From Ages 14 to 19 (N=68)

% of subjects with different BPD status:

- No BPD
- Subthreshold BPD
- Full BPD

DX based on KSAD/SCID

66% have BPD

Development of SUD in BPD Youth

BPD Adolescent Substance Use and Self-Medication

Start to Aid Sleep, \( p=0.5 \)

Start to Get High, \( p=0.7 \)

Cont to Change Mood, \( p=0.1 \)

Start to Change Mood, \( p=0.02 \)

Motivation from 1="very true" to 4="not true at all"

Deficits in Emotional Regulation Are Related to SUD in Bipolar Youth

Association remained significant when controlling for both BP and ADHD (HR: 5.16; 95% CI: 2.06, 12.90; \( p < 0.001 \)). Association lost significance when controlling for ADHD, CD, and BP (\( p = 0.06 \); trend). CBCL = Child Behavior Checklist.

Wilens et al. Drug Alcohol Dependence; epub: 3 2013.
Deficits in Emotional Regulation Are Associated With Polysubstance Abuse

*\( p < 0.05 \) vs. CBCL < 180

Wilens et al. Drug Alcohol Dependence; epub: 3 2013.
Temporal Association of BPD and SUD

• Assess youth with **severe** or **binge** substance use disorders for BPD

• Assess all adolescents with **BPD** for cigarette smoking and substance use disorders
Controlled Study of Lithium for Bipolar Adolescents With SUD

Mean age = 16 years
Alcohol and/or drugs (marijuana)
Dose: [lithium] = 0.9-1.3 mEq/L

Quetiapine Plus Topiramate Reduces Cannabis Use in Adolescents With BPD

BPD YMRS scores improved with both treatments
-14 quetiapine + topiramate
-16 quetiapine + placebo

Delbello et al. AACAP presentation, 2011.
Juvenile BPD and Comorbidity

- BPD often onsets in childhood
- BPD may manifest differently than adult BPD
- BPD assessment requires consideration of the mood, educational, environmental, and family needs
- Multimodal treatment is necessary
- Pharmacologically, second-generation antipsychotics are often first-line agents (and FDA-approved)
Juvenile BPD and Comorbidity

• Juvenile BPD is commonly comorbid with other major psychiatric disorders
• Evidence suggests that these disorders are not just a manifestation of BPD
• ADHD, conduct disorder, and substance use disorders are among the most common and disconcerting disorders
• Treatment of both the underlying BPD and comorbidity is often necessary