Update on Pediatric Bipolar Disorder

Benjamin I. Goldstein, MD, PhD, FRCPC

Associate Professor
Departments of Psychiatry & Pharmacology
Sunnybrook Health Sciences Centre
University of Toronto Faculty of Medicine
benjamin.goldstein@sunnybrook.ca

Financial Disclosures

BMS: consultant
Purdue Pharma: speaker’s honoraria
Symptoms of Mania

• “A distinct period of abnormally and persistently elevated, expansive, or irritable mood”, plus:
  • Increased self-esteem, grandiosity
  • Decreased need for sleep
  • More talkative or pressure to keep talking
  • Racing thoughts, stream of ideas
  • Distractible
  • Increased purposeful activity
  • Risky, thrill-seeking behaviors

Types of Bipolar Disorder

• Bipolar I Disorder
• Bipolar II Disorder
• Bipolar Disorder Not Otherwise Specified (NOS)
• Cyclothymic Disorder
Severity of Early-onset Bipolar Disorder

- 32-65% of adults have onset ≤18 years old
- More anxiety, substance abuse
- More episodes and symptoms
- More suicidality, violence, psychosis
- Longer delay until treatment
- Greater functional impairment
- Less time well

Goldstein & Levitt, 2006; Leverich et al. 2007; Perlis et al. 2004

Epidemic of Adolescent Bipolar Disorder?

Lifetime rates of bipolar disorder among adolescents = 2.7%

>40-fold increase?

0.01% of MD visits
0.42% of psychiatry visits

0.44% of MD visits
6.67% of psychiatry visits

Epidemic of Pediatric Bipolar Disorder?

- Lifetime bipolar disorder in adolescents = 2.7%
- No significant increase over time
- No significant difference of U.S. vs. elsewhere


Bipolar Disorder among 191 Canadian Adolescents and Young Adults

<table>
<thead>
<tr>
<th></th>
<th>15-18yo</th>
<th>19-24yo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>64.9%</td>
<td>52.3%</td>
</tr>
<tr>
<td>White</td>
<td>72.7%</td>
<td>77.7%</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>41.8%</td>
<td>48.6%</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>32.1%</td>
<td>46.0%</td>
</tr>
<tr>
<td>Suicidality</td>
<td>54.6%</td>
<td>48.6%</td>
</tr>
<tr>
<td>Received treatment</td>
<td>45.8%</td>
<td>60.3%</td>
</tr>
</tbody>
</table>

Kozloff et al, J Affect Disord 2010
### Why is this a Challenging Diagnosis?

- Symptom overlap with other disorders
- Less time well vs. adults
- More likely to have “mixed” states, involving both manic and depressive symptoms
- Historical recall affected by current mood
- Often need repeated visits, follow-up
Clinical Pearls

• Establish a “baseline”
• Identify an episode
• Look for a change in trajectory
• Determine onset, including precipitants
• Ensure there’s “enough”:
  – Enough symptoms
  – Enough duration
  – Enough distress and/or functional impairment

Recovery in COBY

After 2.5 years, 81.5% recovered

Less likely to recover if:
  BD-NOS
  <12yo at intake
  Minority race
  Longer illness

More like to recover if:
  Living with both parents and high SES

Birmaher et al, Arch Gen Psychiatry 2009
Recurrence in COBY

Among recovered, 62.5% had ≥1 recurrence within 1.5 yrs
Polarity of index episode predicted polarity of recurrence

More likely to recur if:
- BD-I or BD-II
- Low SES
- Family history of BD

Weekly Symptoms Status Comparing Youth with BP-I (Birmaher et al., 2006) vs. Adults with BP-I (Judd et al., 2002)
Longitudinal Course of Bipolar Disorder

• 12-mo. follow-up of adolescents hospitalized for mania:
  – Psychotherapy predicts longer time to recurrence
  – Antidepressants, alcohol use disorders predict shorter time to recurrence
  – 86% syndromic recovery, ~40% functional recovery
  – Predictors of lack of recovery: ADHD, anxiety, DBD, non-adherence, low SES

DelBello et al, Am J Psychiatry 2007

Longitudinal Course of Bipolar Disorder

• 8-yr. follow-up of childhood and early-adolescent BD-I:
  – 88% recovery, 73% relapse to mania
  – Low maternal warmth predicted relapse and more weeks ill
  – 34% developed new-onset substance use disorders
  – 44% of subject >18yo had manic episodes as adults

Geller et al, Arch Gen Psychiatry 2008
### Comorbidity in Large Clinical Samples

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean Age</th>
<th>Female</th>
<th>Anxiety</th>
<th>ADHD</th>
<th>ODD</th>
<th>CD</th>
<th>SUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axelson et al, 2006</td>
<td>438</td>
<td>12.7y</td>
<td>47%</td>
<td>39%</td>
<td>60%</td>
<td>40%</td>
<td>13%</td>
<td>0%/16%</td>
</tr>
<tr>
<td>Biederman et al, 2005</td>
<td>299</td>
<td>~10.7y</td>
<td>36%</td>
<td>49%</td>
<td>84%</td>
<td>85%</td>
<td>42%</td>
<td>0%/22%</td>
</tr>
<tr>
<td>Findling et al, 2001</td>
<td>90</td>
<td>10.8y</td>
<td>~33%*</td>
<td>14%</td>
<td>68%</td>
<td>47%</td>
<td>17%</td>
<td>0%/18%</td>
</tr>
<tr>
<td>Geller et al, 2004</td>
<td>86</td>
<td>10.8y</td>
<td>38%</td>
<td>17%</td>
<td>86%</td>
<td>78%</td>
<td>13%</td>
<td>---</td>
</tr>
</tbody>
</table>

*Tabulated

### Differential Diagnosis of Manic Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Bipolar Mania/Hypomania</th>
<th>ADHD(^1)</th>
<th>ODD(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elation</td>
<td>Episodic, prolonged, pathological (inappropriate to context, uncharacteristic), associated with change in functioning, &quot;travels&quot; with ≥3 other manic symptoms</td>
<td>If present, not clearly episodic or pathological</td>
<td>If present, not clearly episodic or pathological</td>
</tr>
<tr>
<td>Irritability</td>
<td>Episodic, prolonged, pathological, associated with change in functioning, &quot;travels&quot; with ≥4 other manic symptoms</td>
<td>Can be an associated feature, related to stimulant rebound, or due to a comorbid illness (e.g. ODD)</td>
<td>Diagnostic criterion, lacks distinct prolonged episodes, does not &quot;travel&quot; with other manic symptoms</td>
</tr>
<tr>
<td>Sleep</td>
<td>Reduced need for sleep, i.e. significantly less sleep than usual without increased daytime fatigue or somnolence, mood-related</td>
<td>Insomnia, i.e. difficulty falling asleep, can be an associated feature or associated with stimulants, but need for sleep is unchanged</td>
<td>Not a symptom or common characteristic, may defy bedtime rules or routine</td>
</tr>
<tr>
<td>Grandiosity</td>
<td>Distinct uncharacteristic increase in confidence or self-importance, mood-related</td>
<td>Not a symptom or common characteristic</td>
<td>Defiance toward authority figures is common, but not necessarily mood-related</td>
</tr>
<tr>
<td>Hyperactivity, Distractibility</td>
<td>Episodic, if comorbid ADHD then distinctly &quot;worse than usual&quot;, mood-related</td>
<td>Diagnostic criteria, non-episodic</td>
<td>Not prominent or episodic</td>
</tr>
</tbody>
</table>
Irritability Without Elation in a Large Bipolar Youth Sample: Frequency and Clinical Description

Irritability without elation:
- Overall highly similar to those with elation
- Younger
- More family history of alcohol abuse, depression
- Conclusion: irritable-only hypo/mania is infrequent

Hunt et al, JAACAP 2009

Neurocognitive Dysfunction in Pediatric Bipolar Disorder

- Ten studies, N=352
- @50-80% with ADHD
- Mix of symptomatic and asymptomatic
- 60-90% medicated

<table>
<thead>
<tr>
<th>Neurocognitive Domain</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-scale IQ</td>
<td>0.32</td>
</tr>
<tr>
<td>Reading achievement</td>
<td>0.40</td>
</tr>
<tr>
<td>Attention</td>
<td>0.62</td>
</tr>
<tr>
<td>Motor speed</td>
<td>0.33</td>
</tr>
<tr>
<td>Executive function</td>
<td>0.55</td>
</tr>
<tr>
<td>Working memory</td>
<td>0.60</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>0.45</td>
</tr>
<tr>
<td>Visual-perceptual</td>
<td>0.48</td>
</tr>
<tr>
<td>Visual memory</td>
<td>0.51</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Joseph et al, J Child Adoles Psychopharm 2008
Summary of Neurobiological Findings Regarding Bipolar Disorder vs. “Severe Mood Dysregulation”

- Posner task accuracy: Control>BD>SMD
- Response reversal accuracy: Controls=BP>SMD (response reversal)
- Frustration P3: Control=SMD>BD
- Post-frustration reaction time: BD>Control=SMD
- Face emotion labeling: Control>BD=SMD
- Affective prosody labeling: Control>BD=SMD
- Neural activation during failed inhibition: BD<SMD=Control
- Neural activation to negative feedback: BD different, SMD=Control
- Attention interference of emotional stimuli: SMD<BD=Control
- Neural response to emotion processing of neural faces: SMD<BD=Control<ADHD

Like the phenotypes, many behavioral and neural differences between SMD and BD, and many similarities
Who is at Highest Risk?

- Adolescents with Major Depression
  - With psychosis
  - With medication-induced mania
- Offspring of parents with bipolar disorder
  - With anxiety disorders
  - With disruptive behavior
  - With both parents affected
- Youth with BP-NOS (40% conversion)
  - With family history

Family History at Intake associated with Progression to BP-I or II

- 31.1% of those with family history converted to BP-I or II within the first year of follow-up.
- 58.5% of those without family history converted to BP-I or II within the first year of follow-up.

Axelson et al, JAACAP 2011
The Child Behavior Checklist (CBCL) and the CBCL-Bipolar Phenotype Are Not Useful in Diagnosing Pediatric Bipolar Disorder

- Compared youth with BP (N=157), MDD/Anx (N=101), DBD (N=127), and healthy controls (N=128)
- 41% of BP youth did not have elevated CBCL-PBD
- Sensitivity = 57%, specificity = 70-77%
- Accuracy (AUC) 0.72-0.78

Diler et al, J Child Adolesc Psychopharm 2009

Parent General Behavior Inventory, 10-item short form (PGBI-SF10)

Example items:
- Has your child experienced periods of several days or more when, although he/she was feeling unusually happy and intensely energetic (clearly more than your child’s usual self), he/she was also physically restless, unable to sit still, and had to keep moving or jumping from one activity to another?
- Have there been periods of several days or more when your child’s friends or other family members told you that your child seemed unusually happy or high – clearly different from his/her usual self or from a typical good mood?
- Has your child’s mood or energy shifted rapidly back and forth from happy to sad or high to low?

http://www.whatsupdoc.us/Common/PCP/PGBI-sf10%20mania%20modified%20again.pdf
### Likelihood of Having Bipolar Disorder Based on PGBI 10-item Mania Short Form

<table>
<thead>
<tr>
<th>Score Range</th>
<th>Risk</th>
<th>Likelihood Ratio</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0-0.9</td>
<td>Very low</td>
<td>0.01</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>1.0-4.9</td>
<td>Low</td>
<td>0.16</td>
<td>100</td>
<td>21</td>
</tr>
<tr>
<td>5.0-9.9</td>
<td>Low to neutral</td>
<td>0.56</td>
<td>94</td>
<td>54</td>
</tr>
<tr>
<td>10-14.9</td>
<td>Neutral</td>
<td>1.55</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>15.0-17.9</td>
<td>High</td>
<td>2.67</td>
<td>56</td>
<td>90</td>
</tr>
<tr>
<td>18.0-30.0</td>
<td>Very high</td>
<td>7.25</td>
<td>39</td>
<td>95</td>
</tr>
</tbody>
</table>


### Mean Scores on PGBI 10-item Mania Short Form

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar I</td>
<td>178</td>
<td>17.12 (6.86)</td>
</tr>
<tr>
<td>Other bipolar</td>
<td>116</td>
<td>12.90 (6.66)</td>
</tr>
<tr>
<td>Unipolar mood</td>
<td>131</td>
<td>6.10 (5.25)</td>
</tr>
<tr>
<td>ADHD/DBD</td>
<td>130</td>
<td>7.03 (6.03)</td>
</tr>
<tr>
<td>Residual diagnosis</td>
<td>19</td>
<td>6.63 (7.80)</td>
</tr>
<tr>
<td>No Axis I diagnosis</td>
<td>60</td>
<td>1.28 (3.82)</td>
</tr>
<tr>
<td>Total</td>
<td>637</td>
<td>10.17 (8.10)</td>
</tr>
</tbody>
</table>

Take-Home Messages

• Bipolar disorder among youth can be parsed from normal or comorbid disorders
• Difficult to diagnose (over- and under-diagnosed)
• Billing diagnoses have increased; prevalence has not
• Diagnosis and comorbidity have treatment implications
• Pediatric BD is a severe, impairing, familial illness, frequently complicated by multiple comorbidities
• Both neurobiological differences and similarities with chronic irritability

AACAP Guidelines for Treatment of Acute Mania

Psychosis?

No

Yes

MS (Li, VPA, CBZ), or SGA (OLZ, RISP, QUET, ARI)

Li, VPA, or CBZ + OLZ, RISP, QUET, or ARI

Switch to other class

Li + VPA, or MS + SGA

Li + VPA + SGA or Li + CBZ + SGA

Some response

No response

Some response

Some response

Li + VPA + SGA or Li + CBZ + SGA

Li + VPA + SGA or Li + CBZ + SGA

Li + VPA + SGA or Li + CBZ + SGA

MS = mood stabilizer
SGA = second generation antipsychotic
Li = lithium; VPA = valproate; CBZ = carbamazepine;
OLZ = olanzapine; RISP = risperidone; QUET = quetiapine; ARI = aripiprazole

Slide courtesy of Kiki Chang, MD, APA 2010
Acute Mania Response Rates in Recent Large Trials

Wagner et al, JAACAP 2009; Correll et al, Bipolar Disord 2010;
Geller et al, Arch Gen Psychiatry 2012
Slide courtesy of David Axelson, MD

Age Differences in Antipsychotic and Mood Stabilizer Efficacy and Tolerability in Acute Mania

Correll et al, Bipolar Disord 2009
Adolescent Bipolar Depression Open Studies

Lamotrigine:
- 8 wk, N=20, any BP subtype
- Mean 132mg/d; target 100-200mg (1/2 if VALP)
- Titration: wk 1-2=25mg → wk 3-4=50mg → wk 5=100mg; wk 6-8 increase 25mg/wk prn
- 63% response, 58% remitted
- Side effects: H/A 84%, fatigue 58%, nausea 53%

Chang et al, JAACAP 2006

Adolescent Bipolar Depression Open Studies

Lithium:
- 6 wk, N=27, BP-I
- Titration: 30mg/kg/d (bid); 70% therapeutic<19d
- Mean level @ endpoint, 0.9mEq/L (1356mg/d)
- 48% response
- Side effects: H/A 74%, N/V 67%

Patel et al, JAACAP 2006
Quetiapine vs. Placebo for Adolescent Bipolar Depression

- DBPC, N=32, two-sites (UC & Stanford)
- 8-weeks monotherapy (300-600mg/day, no changes after day 28) BP I, depressed
- Inpatients or outpatients, ages 12-18 years

Good News for Quetiapine!
- 71% response, 35% remission

Good News for Placebo!
- 67% response, 40% remission

DelBello et al, Bipolar Disord 2009

Double-Blind 18-Month Trial of Lithium Versus Divalproex Maintenance Treatment in Pediatric Bipolar Disorder

- BD-I or -II, stabilized on lithium/divalproex
- Randomized to one medication (N=30/group)
- No difference in relapse
  - 114 days for lithium
  - 112 days for divalproex

Findling et al, JAACAP 2005
Comorbid ADHD:
AACAP Treatment Guidelines

- Treat BD symptoms first

- Treat ADHD if impairing symptoms persist, stimulants are first-line in this setting

- Atomoxetine, stimulants, TCAs can induce switches to mania/cycling

Kowatch et al, JAACAP 2005

Take-Home Messages

- Response rates for acute manic and mixed episodes among youth are comparable to those among adults

- Less is known about combination, continuation, maintenance, depression, and some comorbidities

- Youth are highly responsive to SGAs, and especially sensitive to their metabolic side effects

- Use SSRIs with caution; consider psychosocial treatment first-line for bipolar depression or anxiety

- Once mood is stabilized, stimulant treatment of comorbid ADHD appears to be safe and effective

Goldstein, Sassi, Diler, Child & Adol Psych Clinics 2012
What Are The Goals Of Psychotherapy For Adolescent Bipolar Disorder?

Decrease Risk Factors
- Stress
- Family conflict
- Substance use
- Irregular daily routines
- Poor sleep patterns

Increase Protective Factors
- Medication adherence
- Social support
- Coping skills
- Problem solving skills
- Access to resources

Promising Psychotherapies for Youth with Bipolar Disorder

Individual Approaches
- Cognitive Behavioral Therapy (CBT; Danielson et al., 2004)
- Interpersonal & Social Rhythm Therapy (IPSRT-A; Hlastala & Frank, 2006)

Family Approaches
- Family-Focused Therapy (FFT-A; Miklowitz et al., 2004)
- Child & Family-Focused CBT* (Pavuluri et al., 2004)

Group Approaches
- Multi-Family Psychoeducation Groups* (MFPG; Fristad et al., 2003)

Combination Approaches
- Dialectical Behavior Therapy (DBT-A; Goldstein et al., 2007)

*Focus on children <13yo

Psychotherapy slides courtesy of Tina R. Goldstein, PhD
Common Elements of Psychotherapies for Youth with Bipolar Disorder

- Psychoeducation about bipolar disorder
  - symptoms, course, treatment
- Sleep hygiene
- Medication adherence
- Mood Monitoring
- Skill Building
  - Communication
  - Problem Solving
  - Emotion Regulation
  - Impulse Control
- Enhance relationships
- Relapse prevention and safety planning

AACAP Treatment Guidelines for Children and Adolescents with Bipolar Disorder, 2005

Family-Focused Treatment for Adolescents with Bipolar Disorder

Treatment targets:
- Criticism, hostility, and over-involvement

χ² = 4.36, p = .04. HR = 1.85, 95% CI 1.04-3.29.

EC = enhanced care. HR = hazard ratio. CI = confidence interval.

Take-Home Messages

• There is strong evidence that specific psychotherapies are helpful for adults with bipolar disorder

• Psychotherapy is complementary to pharmacotherapy, and provides a forum for psychoeducation

• Benefits of psychotherapy may be most evident for depression and suicidality (vs. mania)

• Different psychotherapies share several core elements

• Youth-specific developmental considerations are key

• Involvement of families is suggested

Bipolar SAQs

1. List three ways in which early-onset bipolar disorder can be considered a more severe variant than adult-onset bipolar disorder. Bipolar II Disorder

hospitalization, comorbidity, symptom burden, impairment, suicidality

2. List three factors that may contribute to the greater challenge of diagnosing bipolar disorder in youth as compared to adults.

   symptom overlap with other diagnoses, less time well than adults, historical recall affected by current mood, more likely to have mixed states
Bipolar SAQs

3. A 12 year-old girl presents with severe irritability accompanied by hyperactivity and distractibility. List three key aspects of the history that would be needed in order to rule in or rule out a diagnosis of bipolar disorder

- Irritability is episodic
- Irritability has sufficient duration (eg 4 days for hypomania)
- Irritability episodes are accompanied by changes in at least 4 other manic symptoms

Bipolar SAQs

4. List three neurocognitive deficits/problem areas that have been observed among youth with bipolar disorder

- verbal memory
- attention
- working memory
- executive function
- face emotion recognition
Bipolar SAQs

5. A 12 year-old girl presents with severe irritability accompanied by hyperactivity and distractibility. List three key aspects of the history that would be needed in order to rule in or rule out a diagnosis of bipolar disorder

- Irritability is episodic
- Irritability has sufficient duration (eg 4 days for hypomania)
- Irritability episodes are accompanied by changes in at least 4 other manic symptoms

Acknowledgments

Research participants and their families

Collaborators:
Ana Andreazza, PharmD, PhD
David Axelson, MD
Boris Birmaher, MD
James Kennedy, MD
Daphne Korczak, MD
Krista Lanctôt, PhD
Brad MacIntosh, PhD
Alan Moody, MD
Brad Strauss, MD, PhD
Trevor Young, MD, PhD

Research Team:
Katelyn Collinger, MA
David Crane, MSc
Jessica Hatch, BSc
Rachel Mitchell, MD, MSc
Tiffany Ou, BSc
Antonette Scavone
Brenda Swampillai, BSc
Vanessa Timmins, BSc
Sinthujah Varatharajah, MSc

Funding Support:
Canadian Institutes of Health Research
Depressive & Bipolar Disorder Alternative Treatment Foundation (US)
Heart & Stroke Foundation of Ontario
National Institute of Mental Health
Ontario Mental Health Foundation
Sunnybrook Foundation