Is Pediatric Bipolar Disorder a Valid Disorder?

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Pediatric BPD: History of a Controversy

- 1960: Childhood mania exists but is rare (Anthony and Scott)
- 1970-1980: Childhood mania may be more common than we thought (Weller et al., Carlson et al.)
  - It may be under-diagnosed due to developmentally variable symptom expression
- 1990-2000: Childhood mania is a serious source of morbidity in child psychiatric clinics (Biederman et al., Geller et al.)
- 2000-2010: Childhood mania is over-diagnosed and over-treated (or is it?)
Pediatric Mania
Are We Giving Kids Too Many Drugs?

A medicated generation is growing up with quick fixes for mood and behavior. Here are the benefits—and the risks.
Growing Up Bipolar
In February, the American Psychiatric Association released draft revisions for the next iteration of its diagnostic manual (the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM-V]). As reported by Moreno and colleagues, the number of children with a diagnosis of bipolar disorder visiting outpatient clinics increased by a factor of 40. These children, some preschoolers, were...
National Trends in Visits with a Diagnosis of Bipolar Disorder as a Percentage of Total Office-Based Visits by Youth (aged 0-19 years) and adults (aged ≥20 years)
National Trends in Visits with a Diagnosis of Bipolar Disorder as a Percentage of Total Office-Based Visits

Moreno et al., Arch Gen Psych, 2007)
Most bipolar adults in STEP-BD reported onset in childhood or adolescence

- 65% of adults with onset < 18
- Almost a third with onset < 13

Perlis, Miyahara, Marangell, Wisniewski, Ostacher, DelBello, Bowden, Sachs, Nierenberg, Biol Psych 2004;55:875-881
Bipolar adults with childhood and adolescent onset had more lifetime suicide attempts and violence

Perlis, Miyahara, Marangell, Wisniewski, Ostacher, DelBello, Bowden, Sachs, Nierenberg, Biol Psych 2004;55:875-881
Population Studies of Bipolar Disorder and Severe Mood Dysregulation in Youth

- Benjet 2009 Mexico: 2.5
- Lynch 2006 Ireland: 0
- Canals 1997 Spain: 2.4
- Kim-Cohen 2003 New Zealand: 1.8
- Stringaris 2010 UK: 1.2
- Holtzmann 2010 German: 0.7
- Verhulst 1997 Dutch: 2.8
- Costello 1996 USA: 0
- Kessler 2009 USA: 6.3
- Gould 1998 USA: 1.3
- Andrade 2006 USA: 1.5
- Kashani 1987 USA: 0.7
- Lewinsohn 1995 USA: 1
- Merikangas 2010 USA: 2.9

Not USA: 1.9%*
USA: 1.7%*

*from Van Meter et al., JCP, in press
Number of Patients with a New Diagnosis of Bipolar Disorder by Age Group

Without New Diagnosis: 1,271,819

With New Diagnosis: 2,907 (0.23%)

Diagnosed <7: 4.5%
Diagnosed 7-12: 24.8%
Diagnosed 13-17: 70.7%

Robins & Guze Criteria for Validity of Psychiatric Diagnosis

- Clinical presentation
- Family history
- Treatment response
- Course and outcome
- Laboratory studies
Clinical Presentation
Euphoria and Irritability in BPD Probands
Are All Forms of Irritability the Same?

Heterogeneity of Irritability
Heterogeneity of Irritability in Children

Mick et al, 2007
Stratified Prevalence of Irritability in ADHD Subjects With and Without Mood Disorder

- ADHD (N=274)
- Non-Mood ADHD (N=144)

ODD Irritability
Mad/Cranky
Super Angry/Grouchy/Cranky

Geller et al (2002) JCAP

Juvenile Mania

- The type of irritability observed in manic children is very severe, persistent, and often violent.
- The outbursts often include threatening or attacking behavior towards others, including family members, other children, adults, and teachers.

Heterogeneity of Irritability

- Labile mood/hot temper: ODD
- Severe irritability: MDD
- Explosive/violent irritability: BPD

Differential Diagnosis with ADHD

- Overlapping symptoms include:
  
  a) Distractibility
  
  b) Physical hyperactivity
  
  c) Talkativeness
Bipolar Disorder in Girls and Boys With and Without ADHD

Patterns of Comorbidity in ADHD Adults

Clinical Presentation:

Two Cohorts
1) Assessed in the early 1990’s
2) Assessed 1995-2002
2002 MGH Study of Pediatric BPD

Diagnostic Overlap of BPD and ADHD [Second Cohort]

N=450
N=112
N=17

2002 MGH Study of Pediatric BPD

**BPD Illness Age of Onset**

<table>
<thead>
<tr>
<th>Years (mean)</th>
<th>BPD 1st Cohort</th>
<th>BPD 2nd Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4</td>
<td></td>
<td>4.8</td>
</tr>
</tbody>
</table>

2002 MGH Study of Pediatric BPD

2002 MGH Study of Pediatric BPD

BPD Illness Duration

BPD 1st Cohort: 3 years (mean)
BPD 2nd Cohort: 3.5 years (mean)

2002 MGH Study of Pediatric BPD

Comorbid Disorders by Bipolar Cohort

2002 MGH Study of Pediatric BPD

Treatment History: Hospitalization

Clinical Presentation

- Frequently irritable
- Frequently non-episodic
- Frequently chronic
- Frequently mixed
- Highly comorbid with ADHD, ODD, CD, and anxiety
Robins & Guze Criteria for Validity of Psychiatric Diagnosis

Is Pediatric BPD Familial?
Familial Risk of BP-I Disorder in First Degree Relatives

Wozniak et al. In Press
Robins & Guze Criteria for Validity of Psychiatric Diagnosis

Does Pediatric BPD have a unique course?
Types of Remission

- Syndromatic Remission
  - Loss of full diagnostic status

- Symptomatic Remission
  - Loss of subthreshold diagnostic status

- Functional Remission
  - Loss of subthreshold diagnostic status with functional recovery

Figure 1. Persistence of DSM-IV BP-I in youth at 4-year Follow-up

Wozniak, Biederman et al. 2010 in press
Persistence of DSM-IV BP-I in youth at 4-year Follow-up

**Full BP-I disorder**: 73.1%
- **Subthreshold BP-I disorder**: 6.4%
- **Euthymic**: 6.4%
- **Treated**: 9.0%
- **Full or subthreshold MDD**: 5.1%

Wozniak, Biederman et al. 2010 in press
Robins & Guze Criteria for Validity of Psychiatric Diagnosis

Does Pediatric BPD have unique laboratory findings?
MRI Findings
Bipolar MRI Results

Frazier et al. 2003.
Proton Spectrum (b) acquired from the anterior cingulate cortex (a) of a child with bipolar disorder.

Ino: myo-Inositol
Cho: choline
Cr: creatine
Glx: glutamate and glutamine
NAA: N-acetyl aspartate

Robins & Guze Criteria for Validity of Psychiatric Diagnosis

Does Pediatric BPD have a unique pharmacological response?
Pharmacologic Dissection Strategy: ADHD and BPD Naturalistic Study

Olanzapine in the Treatment of Pediatric Bipolar Mania: Change in YMRS Total Score from Baseline to Endpoint

OPEN LABEL 8-WEEK STUDY (n=23)
Mean dose: 9.6±4.3mg/day

-14 points

-19 points

CGI-S of Mania: 40% improvement, p<0.001
Mean Weight Gain: 5.0±2.3kg, p<0.001

DOUBLE BLIND 3-WEEK STUDY (n=161)
Mean dose: 8.9mg/day

-17.65 points, p<0.001

Mean Weight Gain: 5.0±2.3kg, p<0.001

**p<0.001

Tohen et al. AJP 2007; 164:1547–1556
Aripiprazole in the Treatment of Pediatric Bipolar Mania: Change in YMRS Total Score from Baseline to Endpoint

OPEN LABEL 8-WEEK STUDY (n=19)  
Mean dose: 9.4±4.2mg/day

-15 points, p<0.001

Mean Weight Gain: 1.8±1.7kg, p=.2

DOUBLE BLIND 4-WEEK STUDY (n=296)

-14 points, p<0.0001

Mean Weight Gain: 0.55kg, p>0.5

Biederman et al. CNS Spectr 2007; 12(9)  
Nyilas et al (2008) APA Meeting
Risperidone in the Treatment of Pediatric Bipolar Mania: Change in YMRS Total Score from Baseline to Endpoint

OPEN LABEL 8-WEEK STUDY (n=30)
Mean dose: 1.25 ± 1.5 mg/day
-14.4 points, \( p<0.0001 \)

DOUBLE-BLIND 3-WEEK STUDY (n=137)
-18.5 points, \( p<0.001 \)

Mean Weight Gain: 2.1±2.0kg; \( p<0.001 \)
Mean Weight Gain: 1.9±1.7kg

Pandina et al. (2007) AACAP Meeting
Divalproex ER in the Treatment of Pediatric Bipolar Mania: Change in YMRS Total Score from Baseline to Endpoint

**OPEN LABEL 8-WEEK STUDY**

<table>
<thead>
<tr>
<th>Week, Post-Baseline</th>
<th>Mean Change from Baseline (LOCF)</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>-7 points, p=0.4</td>
</tr>
<tr>
<td>2</td>
<td></td>
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<tr>
<td>3</td>
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\[ F(8,17) = 1.2, p = 0.4 \]

**DOUBLE BLIND 4-WEEK STUDY (n=229)**

-8.8 points, p = .604

Mean Weight Gain: 1.0kg; p > 0.05

Wozniak et al. CNS Spectrums 2008 submitted

Wagner et al., JAACAP 48:5, May 2009
Is Pediatric BPD Without the Distinct Episode Qualifier a Valid Clinical Entity?

- Fully satisfies Robins & Guze criteria for a valid clinical entity
- Severe and highly dysfunctional clinical presentation highly consistent with adult bipolar disorder
- Positive family history of BPD
- Selective treatment response to antimanic agents
- Compromised course and outcome
Is Mood Instability Characterized by Severe Irritability and Frequent Absence of Discrete Episodes in Children, BPD?

- Chronic and severe irritability and absence of discrete episodes may represent developmentally specific associated features of pediatric onset BPD.

- “Atypical” form is the most common presentation of BPD in children.
First scientific article to present a coherent conceptual perspective on Pediatric Bipolar Disorder as a developmental subtype of Bipolar Disorder

Pediatric Mania: A Developmental Subtype of Bipolar Disorder?

Joseph Biederman, Eric Mick, Stephen V. Faraone, Thomas Spencer, Timothy E. Wilens, and Janet Wozniak

Despite ongoing controversy, the view that pediatric mania is rare or nonexistent has been increasingly challenged not only by case reports, but also by systematic research. This research strongly suggests that pediatric mania may not be rare but that it may be difficult to diagnose. Since children with mania are likely to become adults with bipolar disorder, the recognition and characterization of childhood-onset mania may help identify a meaningful developmental subtype of bipolar disorder worthy of further investigation. The major difficulties that complicate the diagnosis of pediatric mania include: 1) its pattern of comorbidity may be unique by adult standards, especially its overlap with attention-deficit/hyperactivity disorder, aggression, and conduct disorder; 2) its overlap with substance use disorders; 3) its association with trauma and adversity; and 4) its response to treatment is atypical by adult standards. Biol Psychiatry 2000;48:458–466 © 2000 Society of Biological Psychiatry.
Can a Subtype of Conduct Disorder Linked to Bipolar Disorder Be Identified? Integration of Findings from the Massachusetts General Hospital Pediatric Psychopharmacology Research Program

Joseph Biederman, Eric Mick, Janet Wozniak, Michael C. Monuteaux, Maribel Galdo, and Stephen V. Faraone

Our intent was to investigate systematically the overlap between conduct disorder (CD) and bipolar disorder (BPD). We hypothesized that neither CD nor manic symptoms were secondary to the other disorder and that children with the two disorders would have correlates of both. Results from a series of programmatic studies examining phenotypic features of bipolar and conduct disorder alone or combined in probands and relatives were evaluated within and without the context of ADHD. Examination of the clinical features, patterns of psychiatric comorbidity, functioning in multiple domains, and familiality showed that children with CD and BPD had similar features of each disorder irrespective of the comorbidity with the other disorder. Our data suggest that when BPD and CD co-occur in children, both are correctly diagnosed. In these comorbid cases, CD symptoms should not be viewed as secondary to BPD, and manic symptoms should not be viewed as secondary to CD. Biol Psychiatry 2003;53:952–960 © 2003 Society of Biological Psychiatry
“He’s just doing that to get attention.”