Pediatric Bipolar Disorder: Assessment and Management

Joseph Biederman, MD
Professor of Psychiatry
Harvard Medical School
Chief, Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD
Director, Bressler Program for Autism Spectrum Disorders
Trustees Endowed Chair in Pediatric Psychopharmacology
Massachusetts General Hospital
Disclosures 2020-2021

My spouse/partner and I have the following relevant financial relationships with commercial interests to disclose:

- **Consulting fees:** Akili, Avekshan LLC, Jazz Pharma, and Shire/Takeda
- **Honorarium for scientific presentation:** Tris
- **Royalties paid to the Department of Psychiatry at MGH, for a copyrighted ADHD rating scale used for ADHD diagnoses:** Biomarin, Bracket Global, Cogstate, Ingenix, Medavent Prophase, Shire, Sunovion, and Theravance
- Through Partners Healthcare Innovation, I have a partnership with MEMOTEXT to commercialize a digital health intervention to improve adherence in ADHD.
Basic Overview

**Scope:** Pediatric Bipolar disorder is a highly morbid condition that affects a significant minority of young children.

**Diagnostic description:** Pediatric bipolar disorder can be reliably diagnosed and is often mixed and highly irritable and sometimes violent.

**Persistence:** Pediatric bipolar disorder persists over time.
Pediatric Bipolar disorder should always be considered in the differential diagnosis of children with mood symptoms.

Consecutively referred children ≤ 12 years:

1991-1995 16% Bipolar Disorder (N=262)
1995-2002 17% Bipolar Disorder (N=768)

Wozniak, 1995; Biederman, 2004
The symptoms of mania are the same in children and adults with presentations appropriate to developmental stage.

A. A distinct period of abnormally and persistently elevated, expansive or irritable mood and persistently increased goal-directed activity or energy.

B. At least 3/7 (4/7 if mood is irritable)
   1) D Distractibility
   2) I Increased activity/psychomotor agitation
   3) G Grandiosity or inflated self-esteem
   4) F Flight of ideas or racing thoughts
   5) A Activities with painful consequences
   6) S Sleep decreased
   7) T Talkative or pressured speech

Diagnostic and Statistical Manual (DSM-5)
What Have We Learned About Children with Mania?

**IRRITABLE**
- The major mood disorder and chief complaint of parents is severe irritability (rather than euphoria)

**MIXED**
- The children have mostly mixed states (mania and depression overlapping)

**CHRONIC**
- The children are seldom well with many cycles and chronic mood variability

- Very high comorbidity with ADHD

Wozniak, 1995; Biederman, 2004
Problem: Large Overlap Between ADHD and Pediatric BP-I Disorder

Overlapping symptoms:

- Distractibility (very severe in BP disorder)
- Motoric hyperactivity (vs. agitation)
- Talkativeness (vs. pressured speech)
Diagnostic Overlap of BPD and ADHD [Second Cohort]

N=450

ADHD

N=112

BPD

N=17

Despite overlapping symptoms between ADHD and Pediatric BP Disorder, Pediatric BP disorder requires mood symptoms to diagnose.

Differentiating overlapping symptoms between ADHD and Pediatric BP Disorder:

- **Distractibility**: very severe in bipolar disorder
- **Hyperactivity**: vs. an agitated state
- **Talkativeness**: vs. pressured speech
- **Bipolar disorder requires severe mood symptoms**: euphoria/irritability

Biederman JAACAP 1996
Diagnosis of Bipolar Disorder Vs. ADHD

• KEY DISTINGUISHING FEATURE: Unlike ADHD, BP disorder requires the presence of both aberrant, persistent and severe mood symptoms (euphoria or irritability)
BP disorder in adults is Highly Comorbid with ADHD:

The National Epidemiologic Survey on Alcohol and Related Conditions

N=34,000 adults
2.5% ADHD
34% with ADHD had bipolar disorder vs. 6% without ADHD

The National Comorbidity Survey Replication

N=3199 adults
4.4% ADHD
19% with ADHD had BP disorder vs. 3% without ADHD

Most bipolar adults in STEP-BD (N=983) reported onset of their disorder in childhood or adolescence.

65% of bipolar adults had onset prior to age 18.

28% of bipolar adults had age of onset prior to age 13.

Perlis  Biol Psych 2004
In study of 10,000+ US adolescents, 3% were BP and in a meta-analysis of international studies, the rate of pediatric bipolar disorder was 2%
Pediatric BP disorder is prevalent across the world: In a meta-analysis of international studies, the rate of pediatric bipolar disorder was close to 2%.

**Results:** The overall rate of bipolar disorder was 1.8% (95% CI, 1.1%–3.0%). There was no significant difference in the mean rates between US and non-US studies, but the US studies had a wider range of rates. The highest estimates came from studies that used broad definitions and included bipolar disorder not otherwise specified. Year of enrollment was not a study methodology significant difference.

**Conclusions:** Mean rates of bipolar disorder were higher than commonly acknowledged and not significantly different in US compared to non-US samples, nor was there evidence of an increase in rates of bipolar disorder in the community over time. Differences in diagnostic criteria were a main driver of different rates across studies.

*Bipolar Disorder affects 1.8% children worldwide*
A new disorder was created in DSM V called Disruptive Mood Dysregulation Disorder to ‘decrease the number of pediatric BP bipolar diagnoses’
DMDD is “common, transient, difficult to distinguish from ODD and CD

Examining the Proposed Disruptive Mood Dysregulation Disorder Diagnosis in Children in the Longitudinal Assessment of Manic Symptoms Study

David Axelson, MD; Robert L. Findling, MD, MBA; Mary A. Fristad, PhD, ABPP; Robert A. Kowatch, MD, PhD; Eric A. Youngstrom, PhD; Sarah McCue Horwitz, PhD; L. Eugene Arnold, MD; Thomas W. Frazier, PhD; Neal Ryan, MD; Christine Demeter, MA; Mary Kay Gill, MSN; Jessica C. Hauser-Harrington, PhD; Judith Depew; Shawn M. Kennedy, MA; Brittany A. Gron, BS; Brieana M. Rowles, MA; and Boris Birmaher, MD

• Temper outbursts >3 per week
• Persistently irritable mood
• present for 12 or more months. Throughout that time, the person has not had 3 or more consecutive months when they were without the symptoms

Exclusionary:
Euphoria for 1+ day with 3/7 B criteria
During MDD episode
History of (hypo)mania

Conclusions: In this clinical sample, DMDD could not be delimited from oppositional defiant disorder and conduct disorder, had limited diagnostic stability, and was not associated with current, future-onset, or parental history of mood or anxiety disorders. These findings raise concerns about the diagnostic utility of DMDD in clinical populations.

© Copyright 2012 Physicians Postgraduate Press, Inc.

Axelson JClinPsych 2012
How Valid is the Dx of Pediatric BP-Disorder?
A framework for the validation of psychiatric disorders can be applied to pediatric bipolar disorder

Establishment of Diagnostic Validity in Psychiatric Illness: Its Application to Schizophrenia

BY ELI ROBINS, M.D., AND SAMUEL B. GUZE, M.D.

A method for achieving diagnostic validity in psychiatric illness is described, consisting of five phases: clinical description, laboratory study, exclusion of other disorders, follow-up study, and family study. The method was applied in this paper to patients with the diagnosis of schizophrenia, and it was shown by follow-up and family studies that poor prognosis cases can be validly separated clinically from good prognosis cases. The authors conclude that good prognosis "schizophrenia" is not mild schizophrenia, but a different illness.

Since Bleuler (3), psychiatrists have recognized that the diagnosis of schizophrenia includes a number of different disorders. We are interested in distinguishing these various disorders as part of our long-standing concern with developing a valid classification for psychiatric illnesses(6, 7, 10, 11). We believe that a valid classification is an essential step in science. In medicine, and hence in psychiatry, classification is diagnosis.

The authors are with the department of psychiatry, Washington University School of Medicine, 4940 Audubon Ave, St. Louis, Mo. 63110, where Dr. Robins is Wallace Renard professor and head of the department and Dr. Guze is professor. Dr. Robins is also psychiatrist-in-chief, Barness and Renard Hospitals, and Dr. Guze is associate psychiatrist.

This work was supported in part by Public Health Service grants MH-13002 and MH-07081 from the National Institute of Mental Health.

Amer J. Psychiat. 126:7, January 1970

1. Unique Clinical characteristics
2. Familiality
3. Course
4. Unique Pharmacological Responsivity
5. Laboratory Studies/Biomarkers

Robins & Guze, Am J Psych 1970
The symptoms of mania are the same in two cohorts of pre-adolescent age (<12 years) youth with BP disorder. 

Age at presentation: 8 years 
Age of onset: 4.5 years 
Duration of illness: >3 years 

Wozniak, 1995; Biederman, 2004
The symptoms of mania are the same in two cohorts of pre-adolescent age (<12 years) youth with BP disorder.

Wozniak, 1995; Biederman, 2004

N=43

N=12

Age at presentation: 8 years
Age of onset: 4.5 years
Duration of illness: >3 years

Wozniak, 1995; Biederman, 2004
Euphoria and Irritability in BPD Youth
The symptoms of mania are the same in children and adults

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and persistently increased goal-directed activity or energy

B. At least 3/7 (4/7 if mood is irritable)
   1) D Distractibility
   2) I Increased activity/psychomotor agitation
   3) G Grandiosity or inflated self-esteem
   4) F Flight of ideas or racing thoughts
   5) A Activities with painful consequences
   6) S Sleep decreased
   7) T Talkative or pressured speech

Diagnostic and Statistical Manual (DSM-5)
Are All Forms of Irritability the Same?

Heterogeneity of Irritability
Heterogeneity of Irritability in Children

Mick et al, 2007
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.

Mixed presentations are the most common mood abnormality in pediatric BP disorder

- Mixed: 84%
- Mania only: 14%
- Biphasic only: 2%

Wozniak, 1995; Biederman, 2004
BPD Illness Age of Onset

Years (mean)

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

MGH Study of Pediatric BPD

BPD Illness Duration

<table>
<thead>
<tr>
<th>Years (mean)</th>
<th>BPD 1st Cohort</th>
<th>BPD 2nd Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
<td>3.5</td>
</tr>
</tbody>
</table>

MGH Study of Pediatric BPD

Comorbid Disorders by Bipolar Cohort

MGH Study of Pediatric BPD

Treatment History: Hospitalization

- Bipolar 1st Cohort: 21%
- Bipolar 2nd Cohort: 23%
- ADHD 2nd Cohort: 2%

Summary of Clinical Presentation

• Frequently irritable
• Frequently chronic
• Frequently mixed
• Highly comorbid with ADHD, ODD, CD, anxiety and ASD
Is Pediatric BP-I Disorder Familial?
Familial risk of bipolar I disorder is greatest in first-degree relatives of BP-I versus ADHD and control probands.

The MGH Pediatric Bipolar Disorder family is the largest controlled family study.

*\(p<0.01\) versus ADHD and controls.
Meta-analysis of previous family studies

<table>
<thead>
<tr>
<th>Author</th>
<th>BP-1</th>
<th>Age of Relatives,</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Publication Date)</td>
<td>Probands, N</td>
<td>Probands N</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Kutcher (1991)*</td>
<td>23</td>
<td>17</td>
<td>81</td>
</tr>
<tr>
<td>Wozniak (1995)</td>
<td>16</td>
<td>&lt;=12</td>
<td>46</td>
</tr>
<tr>
<td>Faraone (1997)</td>
<td>15</td>
<td>10.4</td>
<td>51</td>
</tr>
<tr>
<td>Geller (2006)</td>
<td>95</td>
<td>10.8</td>
<td>284</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.579)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*It is important to note that Kutcher et al. only included probands who were referred from an inpatient or outpatient treatment at a medical center.
Does Pediatric BPD have a unique course?
We followed-up children ascertained for a family study of pediatric-onset bipolar disorder to assess persistence

78 of 105 youth with Bipolar I Disorder participating in family study followed-up after 4 years

- Baseline age 10 years
- 76% male
- Age of onset bipolar disorder: 5 years
- Duration of BPD at baseline: 7 years
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%
- Full or subthreshold MDD: 5.1%
- Euthymic: 6.4%
- Treated: 9.0%

Wozniak, Biederman et al. 2012
Can We Screen for Pediatric BP Disorder?: The CBCL
CBCL Clinical Scales
(Biederman et al., JAACAP, 1995)

Significantly elevated in children of BPD parents (Wals et al., JAACAP, 2001)

* p<0.01 Bipolar vs. ADHD
The CBCL avoids cultural differences or methodological factors that could account for regional diagnostic differences.

More diagnoses made in the US sample using the KSADS-PL than in Holland.
ROC analysis: BP-I probands & Controls

CBCL Scores ≥210:
- Sensitivity: 57%
- Specificity: 99.2%
- Positive Predictive Value: 99%
- Negative Predictive Value: 66%
- Area Under the Curve: 99%
ROC analysis: BP-I probands & ADHD probands

CBCL Scores ≥210:
  - Sensitivity: 57%
  - Specificity: 92%
  - Positive Predictive Value: 92%
  - Negative Predictive Value: 56%
  - Area Under the Curve: 85%
Does It Matter?

Risk for Completed Suicide
Risk Factors for Adolescent Suicide
Brent et al. AGP, 1988

Bipolar Disorder

- Completed Suicide: N=27
- Suicidal Inpatients: N=56

p = 0.007
20TH-CENTURY - CHANGES IN YOUTH SUICIDE RATES
— United States, Ages 15–24 —

Bipolar adults with childhood and adolescent onset have more lifetime suicide attempts

Rate per 100,000

Year 1900-2000

BOYS
5X AS MANY COMPLETED SUICIDES

GIRLS
3X AS MANY ATTEMPTS

Everyday I think why am I still here?
CONCLUSIONS AND RELEVANCE Children with high irritability and depressive/anxious mood and, to a lesser extent, with moderate irritability only had a higher suicidal risk during adolescence compared with children with low symptom levels. Early manifestation of chronic irritability during childhood, especially when combined with depressive/anxious mood, may be associated with an elevated risk for adolescent suicidality. The putatively causal role of irritability should be investigated.
Does Pediatric BP Disorder have Unique Biomarkers?

Risk for Completed Suicide
Proton Spectrum (b) acquired from the anterior cingulate cortex (a) of a child with bipolar disorder.
Solid lines represent the linear fits to the low score group data (blue) and high score group data (green). Dashed lines represent 95% confidence intervals.
Significant Correlations Between CBCL-ED Score & Mean and Axial Diffusivity Surrounding the Cingulum Bundle

- Track-Based Spatial Statistics (TBSS) using voxelwise analysis showed a significant positive correlation between the CBCL-ED score and median diffusivity (MD; \( p < 0.05 \)) and axial diffusivity (AD; \( p < .05 \)) overlapping in cingulum bundle areas, the genu of the corpus callosum, and the superior longitudinal fasciculus (SLF).

- Findings indicate that greater severity the emotional dysregulation as indexed through the CBCL-ED profile is associated with more impaired matter abnormalities in the cingulum bundle areas as indexed through mean diffusivity and axial diffusivity values.
Converging evidence from GWAS supports the notion that BP + ADHD is an early onset genetic subtype of either BP disorder or ADHD.

Age of onset is one source of the variance in what we call ‘bipolar’.

Early onset bipolar disorder (with high rates of ADHD) may be caused by a different genetics than later onset forms of the disorder.

van Hulzen BiolPsych 2017
Archival Report

Genetic Overlap Between Attention-Deficit/Hyperactivity Disorder and Bipolar Disorder: Evidence From Genome-wide Association Study Meta-analysis

METHODS: Genome-wide association study data were available for 4609 individuals with ADHD, 9650 individuals with BPD (5167 thereof with early-onset BPD), and 21,363 typically developing controls. We conducted a cross-disorder genome-wide association study meta-analysis to identify whether the observed comorbidity between ADHD and BPD could be due to shared genetic risks.

ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BPD) are frequently co-occurring and highly heritable mental health conditions. We hypothesized that BPD cases with an early age of illness onset would have genetic overlap with ADHD, due to overlap in genetic etiology.

CONCLUSIONS: The single nucleotide polymorphism–based genetic correlation between ADHD and BPD is substantial, significant, and consistent with the existence of genetic overlap between ADHD and BPD, with potential differential genetic mechanisms involved in early and later BPD onset.

BPD in the full and age-restricted samples (\(r_{\text{full}} = .64, p = 3.13 \times 10^{-14}; r_{\text{restricted}} = .71, p = 4.09 \times 10^{-16}\)). The meta-analysis between the full BPD sample identified two genome-wide significant \(p\) values: 2.47 \(\times\) 10\(^{-8}\), \(\rho_{\text{61754538}} = 4.36 \times 10^{-8}\) regions located on chromosomes 6 (CEP85L) and 10 (TAF9BP2). Restricting the analyses to BPD cases with an early onset yielded one genome-wide significant association \(p_{\text{606,005,027-97}} = 2.11 \times 10^{-3}\) on chromosome 5 in the ADCY2 gene. Additional nominally significant regions identified contained known expression quantitative trait loci with putative functional consequences for NT5DC1, NT5DC2, and CACNB3 expression, whereas functional predictions implicated ABLIM1 as an allele-specific expressed gene in neuronal tissue.

CONCLUSIONS: The single nucleotide polymorphism–based genetic correlation between ADHD and BPD is substantial, significant, and consistent with the existence of genetic overlap between ADHD and BPD, with potential differential genetic mechanisms involved in early and later BPD onset.

Keywords: Attention-deficit/hyperactivity disorder, bipolar disorder, cross-disorder meta-analysis, genetic correlation, genetic overlap, GWAS

http://dx.doi.org/10.1016/j.biopsych.2016.08.040
Unique Treatment Responsivity

Risk for Completed Suicide
FDA approved treatments for youth with BP Disorder

- Lithium: manic or mixed states, patients age 13-17
- Risperidone: manic or mixed states, age 10-17
- Aripiprazole: manic or mixed states, age 10-17
- Olanzapine: manic or mixed states, age 13-17
- Quetiapine: monotherapy or adjunct to lithium or divalproex sodium, manic states, age 10-17
- Asenapine manic or mixed episodes in BP-I, age 10-17
- Aripiprazole: irritability associated with autistic disorder age 6-17
- Risperidone: irritability associated with autism age 5-16
Large number of Youth participated in pediatric BP trials

- Atypical Antipsychotics: n=1474
- Traditional Mood Stabilizers: n=915
- Other Anticonvulsants: n=244
- Naturopathic Treatments: n=71

The mean change in YMRS is much greater for the SGA’s than for other agents.

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>YMRS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional Mood Stabilizers</td>
<td>-10.99</td>
</tr>
<tr>
<td>Other Anticonvulsants</td>
<td>-11.03</td>
</tr>
<tr>
<td>Atypical Antipsychotics</td>
<td>-16.8</td>
</tr>
<tr>
<td>Naturopathic Treatments</td>
<td>-5.6</td>
</tr>
</tbody>
</table>
The risk-benefit analysis of treatment must include the risks associated with not treating Pediatric BP Disorder.
Both childhood onset and treatment delay were associated with a persistently more adverse course of illness. Conclusions: These data converge with other evidence that onset of bipolar disorder in childhood is common and often associated with extraordinarily long delays to first pharmacologic treatment. Ultradian cycling, and fewer days euthymic (all P < .05).

J Clin Psychiatry 2010;71(7):864–872
© Copyright 2010 Physicians Postgraduate Press, Inc.
Not treating is not an option due to the severity of symptoms associated with early onset bipolar disorder

983 bipolar adult participants

Perlis, Biol Psych 2004;55:875-881
20TH-CENTURY - RISING RATE OF SUICIDE IN YOUTH
UNITED STATES, AGES 15–24

Rate per 100,000

BP adults with pediatric onset have more lifetime suicide attempts

Year 1900-2000

Boys
5X AS MANY COMPLETED SUICIDES

Girls
3X AS MANY ATTEMPTS
SGAs are a robust treatment for adults with BP disorder

Atypical Antipsychotics in the Treatment of Mania: A Meta-Analysis of Randomized, Placebo-Controlled Trials

Roy H. Perlis, M.D.; Jeffrey A. Welge, Ph.D.; Lana A. Vornik, M.S.; Robert M. A. Hirschfeld, M.D.; and Paul E. Keck, Jr., M.D.

Data Synthesis: Data from 12 placebo-controlled monotherapy and 6 placebo-controlled adjunctive therapy trials involving a total of 4,175 placebo-treated subjects with bipolar mania were obtained. Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone all demonstrated significant efficacy in monotherapy (i.e., all confidence intervals exclude zero). However, after adjusting for multiple comparisons, pairwise comparisons of individual effects identified no significant differences in efficacy among antipsychotics. Magnitude of improvement was similar whether the antipsychotic was utilized as monotherapy or adjunctive therapy.

Perlis J Clin Psychiatry 2006; 64(4):509-516
Tardive dyskinesia is a dreaded complication of TX with SGAs, but children at low risk (although data limited by small sample sizes, low doses and limited durations)

The weighted mean annual incidence of tardive dyskinesia for second generation antipsychotics (SGA):

- 0% children
- 0.8% adult
- 6.8% adult and elderly
- 5.4% adults haloperidol

There is a lower risk for tardive dyskinesia associated with SGAs versus first generation antipsychotics

- N=2769
- 11 studies
- 1+year

Correll AmJPsych 2004
Unfortunately, weight gain is very common: Data from 8-week open label trials of SGA monotherapy in children with BP disorder

Parallel trials
Total N=116

Biederman 2007 AACAP Boston

SGA=second generation antipsychotic
Weight gain associated with SGA medications in Youth: Data from 34 studies

SGA = second generation antipsychotic

- **olanzapine** n=353: 3.8 to 16.2 kg
- **clozapine** n=97: 0.9 to 9.5 kg
- **risperidone** n=571: 1.9 to 7.2 kg
- **quetiapine** n=133: 2.3 to 6.1 kg
- **aripiprazole** n=451: 0 to 4.4 kg

Correll JChildAdolescPsychopharm 2011
Lithium, divalproex sodium, carbamazepine are used for pediatric BP disorder but they are not as effective than SGAs and can have serious AEs.

**Trials notable for:**
- high drop out rates
- need for rescue medications

Kowatch JAACAP 2000
Lithium has long been FDA-approved for pediatric BP disorder, but the first double blind RCT study for pediatric BP-I was in 2015

Lithium in the Acute Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled Study

Robert L. Findling, MD, MBA; Adelaide Robb, MD; Nora K. McNamara, MD; Mani N. Pavuluri, MD, PhD; Vivian Kafantaris, MD; Russell Scheffer, MD; Jean A. Frazier, MD; Moira Rynn, MD; Melissa DelBello, MD; Robert A. Kowatch, MD, PhD; Briana M. Rowles, MA; Jacqui Lingler, BS; Karen Martz, MS; Revinder Anand, PhD; Traci E. Clemons, PhD; Perdita Taylor-Zapata, MD

**BACKGROUND:** Lithium is a benchmark treatment for bipolar disorder in adults. Definitive studies of lithium in pediatric bipolar I disorder (BP-I) are lacking.

**METHODS:** This multicenter, randomized, double-blind, placebo-controlled study of pediatric participants (ages 7–17 years) with BP-I/manic or mixed episodes compared lithium (n = 53) versus placebo (n = 29) for up to 8 weeks. The a priori endpoint of interest: mean change.

**RESULTS:** The change in YMRS score was significantly larger in lithium-treated participants (5.51 [95% confidence interval: 0.51 to 10.50]) after adjustment for baseline YMRS score, age group, weight group, gender, and study site (P = .03). Overall Clinical Global Impression–Improvement scores favored lithium (n = 25; 47% very much/much improved) compared with placebo (n = 6; 21% very much/much improved) at week 8/FT (P = .03).

47% lithium vs 21% placebo “much/very much improved”

Findling Pediatrics 2015
SGAs perform better than valproate for pediatric BP disorder

SGA=second generation antipsychotic

3 double blind RCTs
1 chart review

valproate versus second generation antipsychotics

greater reduction of manic symptoms

more rapid onset of effect

Chen 2014
SGAs performed better than mood stabilizers with less discontinuations and less need for augmentation

N=7423
mean age 12.73
57% adolescents
54% males

66.60% SGA
33.40% mood stabilizer
(valproate/oxcarbazepine/lithium)

Comparable risk of psychiatric hospital admission 186 days

Patients who initiated on SGA were less likely to discontinue the treatment

Patients who initiated on SGA were less likely to receive treatment augmentation

Retrospective Medicaid claims study of pediatric bipolar disorder patients who initiated a new treatment episode for bipolar disorder on either an SGA or mood stabilizer, followed for 12 months

Chen 2014
Comorbidity must be addressed in the management of pediatric BP disorder

- Depression
  - Lithium,
  - Lamotrigine,
  - Lurasidone
  - Avoid SSRIs

- Anxiety
  - Avoid SSRIs

- ADHD
  - Employ stimulant after mood stabilized

Joshi
2009
Antidepressants have a high risk for manic switching......

ANTI-DEPRESSANTS

- Pharmacologically induced hypomania was a predictor of a bipolar course.
- Antidepressant induced mood change was seen more in BP MDD.
- Rate of switching was higher in subjects with history of receiving antidepressants especially in children.

Strober; Shon; Martin
Pharmacologic management of pediatric BP depression is very difficult

- Use antidepressants at all?
  - Lamotrigine?
  - Lithium?
  - Lurasidone?
- Mood stabilizer only?
- Antidepressant only?
  - FDA approved meds for bipolar depression?
- Antidepressant + mood stabilizer?
Quetiapine was not effective in adolescent BP depression, although the placebo response was very high.

Similar negative outcome with (N=193) quetiapine XR 150-300mg

DelBello 2009; Findling 2014
Lurasidone significantly reduced depressive symptoms in youth with BP Depression.

- Placebo-controlled study
- Monotherapy with lurasidone
- Dose range of 20-80 mg/day,

DelBello JAACAP 2017
Lurasidone significantly reduced depressive symptoms in youth with BP Depression.

- placebo-controlled study
- monotherapy with lurasidone
- dose range of 20-80 mg/day,

minimal effects on weight and metabolic parameters

DelBello JAACAP 2017
SGAs have antidepressant qualities

- FDA (2008) approved the use of aripiprazole in combination with antidepressant medication for the treatment of major depression in adults.
- RCT demonstrated increased antidepressant effect from the addition of risperidone to antidepressant monotherapy.
- Two reports with olanzapine N=18 adult patients found that 14 had positive response.

Zarate 1998; Rothschild 1999; Mahmoud 2007
Euthymic youths with bipolar disorder and ADHD may benefit from concomitant treatment with stimulants.

4-week double-blind placebo-controlled ages 5-17 Bipolar disorder and ADHD

Anti-manic medication Euthymic Clinically significant symptoms of ADHD

placebo methylphenidate 5 mg BID
10 mg BID
15 mg BID

Crossover design randomly assigned to one of six possible

Therapeutic benefit
Lower ADHD Rating Scale scores during best dose treatment vs placebo

Findling 2007
Treatment for bipolar disorder involves antipsychotic medications with side effects, fueling reluctance to diagnose.

Traditional antidepressants should be avoided ... treatment with a combination of atypical antipsychotics and mood stabilizers is best.
**Overview:** Pediatric Bipolar disorder is a highly morbid condition that usually requires pharmacologic treatment due to severity of illness. SGA’s are the first line of treatment and comorbid conditions usually must be addressed.

**Severity:** Pediatric Bipolar Disorder is associated with suicidality, substance addiction and conduct disorder.

**Treatment:** Pharmacologic treatment is generally required and SGAs are the first line of treatment.

**Comorbid Conditions:** ADHD and depression and anxiety can be treated by sequencing appropriate treatments after the mania is stabilized.

What questions would you like to ask?
Summary

• Pediatric BP is a prevalent and highly morbid disorder
• Strong evidence for validity
• High rates of comorbidity with MDD, ADHD, ODD and Anxiety disorders
• SGAs are the most effective treatments for mania
• Antidepressants should be avoided
Questions?