Pediatric Bipolar Disorder and ASD

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Massachusetts General Hospital
Disclosures

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

<table>
<thead>
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<th>Royalties (Spouse):</th>
<th>Cambridge University Press, UptoDate</th>
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<tr>
<td>Consultation Fees (Spouse):</td>
<td>Advance Medical, FlexPharma, Merck</td>
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<tr>
<td>Research Support (Spouse):</td>
<td>UCB Pharma, NeuroMetrix</td>
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Scope of the Problem: Population Studies of Bipolar Disorder and Related Disorders in Youth

Not USA: 1.9%*
- 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%

USA: 1.7%*
- from Van Meter et al., JCP, in press
## SCOPE OF THE PROBLEM

Merikangas, et al, National Comorbidity Survey Replication-Adolescent Supplement

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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
Clinical Presentation
DSM Mania Diagnosis

• Period of abnormally and persistently elevated, expansive or irritable mood and increased energy or activity (DSM5 addition) lasting 1 week or requiring hospitalization

• 3 of the following criteria (4 if irritable)
  – Grandiosity
  – Less sleep
  – Pressured speech
  – Flight of ideas
  – Distractibility
  – Goal-directed activity
  – Excessive pleasurable activity
The most severe types of emotional dysregulation come when mania and depression co-occur in the mixed states of bipolar disorder.

**Regular Kid!** typical

**Melancholy**: sad, no pleasure, down on self, suicidal, self-destructive

**Euphoric**: Giddy, goofy, silly, high, “on drugs,” laughing fits

**Irritability** of Depression: angry, grouchy, cranky, whiney, complaining, difficult to please, short-tempered

**Manic level SEVERE**

**IRRITABILITY**:
swearing, disrespectful, threatening, wild, out of control with **Explosions** that are frequent, for 30-60+ minutes, destructive, aggressive
Euphoria and Irritability in BPD Probands

- Euphoric
- Irritable

Diagram showing the overlap between Euphoric and Irritable conditions.
A DAY IN THE LIFE OF A BIPOLAR CHILD IS A ROLLER COASTER OF MOODS

• 10 year old Laura was cranky and miserable all day refusing her mother’s suggestions for fun activities.

• After a phone from a friend she was talking a ‘mile a minute’ with excitement over a school party, exaggerating her popularity.

• She demanded her mother buy her a new cell phone to use to text about the party and, when her mother refused, required a physical hold for over 60 minutes after she exploded in anger.

• Before bed, she sobbed and sobbed and told her mother ‘How can you love me? I cause you so much trouble. You should just kill me.’
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.

Heterogeneity of Irritability

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

16% of children 6-12 years of age in a clinic sample (N=262) met full criteria for mania

Mania-Like Symptoms Suggestive of Childhood-Onset Bipolar Disorder in Clinically Referred Children

JANET WOZNIAK, M.D., JOSEPH BIEDERMAN, M.D., KATHLEEN KIELY, B.A., J. STUART ABLON, B.A., STEPHEN V. FARAONE, PH.D., ELIZABETH MUNDY, B.A., AND DOUGLAS MENNIN, B.A.

ABSTRACT

Objective: To examine the prevalence, characteristics, and correlates of mania among referred children aged 12 or younger. Many case reports challenge the widely accepted belief that childhood-onset mania is rare. Sources of diagnostic confusion include the variable developmental expression of mania and its symptomatic overlap with attention-deficit hyperactivity disorder (ADHD). Method: The authors compared 43 children aged 12 years or younger who satisfied criteria for mania, 164 ADHD children without mania, and 84 non-ADHD control children. Results: The clinical picture was fully compatible with the DSM-III-R diagnosis of mania in 16% (n = 43) of referred children. All but one of the children meeting criteria for mania also met criteria for ADHD. Compared with ADHD children without mania, manic children had significantly higher rates of major depression, psychosis, multiple anxiety disorders, conduct disorder, and oppositional defiant disorder as well as evidence of significantly more impaired psychosocial functioning. In addition, 21% (n = 9) of manic children had had at least one previous psychiatric hospitalization. Conclusions: Mania may be relatively common among psychiatrically referred children. The clinical picture of childhood-onset mania is very severe and frequently comorbid with ADHD and other psychiatric disorders. Because of the high comorbidity with ADHD, more work is needed to clarify whether these children have ADHD, bipolar disorder, or both. J. Am. Acad. Child Adolesc. Psychiatry, 1995, 34, 7:867–876. Key Words: bipolar disorder, attention-deficit hyperactivity disorder, comorbidity, children.
2002 MGH Study of Pediatric BPD

Diagnostic Overlap of BPD and ADHD [Second Cohort]

ADHD
N=450

BPD
N=112
N=17

MGH Study of Pediatric BPD

BPD Illness Age of Onset

BPD 1st Cohort: 4.4 years (mean)
BPD 2nd Cohort: 4.8 years (mean)

BPD Illness Duration

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

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%

Mania in Children With Pervasive Developmental Disorder Revisited

JANET WOZNIAK, M.D., JOSEPH BIEDERMAN, M.D., STEPHEN V. FARAOE, PH.D., JEAN FRAZIER, M.D., JANE KIM, B.A., RACHAEL MILLSTEIN, B.A., JONATHAN GERSHON, B.A., AYANNA THORNELL, B.A., KRISTINE CHA, M.D., AND JAMES B. SNYDER, M.D.

ABSTRACT

Objective: Although a small literature of case reports suggests that mania co-occurs with pervasive developmental disorder (PDD), little is known about this overlap. The authors systematically investigated the overlap between mania and PDD in a consecutive sample of referred youths, examining its prevalence and correlates. It was hypothesized that children with PDD plus manic features have both disorders. Method: Subjects were consecutively referred children meeting diagnostic criteria on structured interview for PDD without mania (n = 52), the comorbid condition PDD+mania (n = 14), and mania without PDD (n = 114). All subjects were evaluated using a comprehensive diagnostic battery that included assessment of psychopathology (structured diagnostic interview and Child Behavior Checklist), cognition, and functioning. Results: Of the 727 referred children, 52 met criteria for PDD, 114 met criteria for mania, and 14 for both. The 14 children with both PDD+mania represented 21% of the PDD subjects and 11% of all manic subjects. Clinical characteristics of PDD were similar in PDD subjects with and without mania, and manic features were similar in manic children with and without PDD. Conclusions: Children with PDD and mania may suffer from two disorders. Comorbid mania among patients with PDD may be more common than previously thought. Identification of the comorbid

ACCOMPANYING EDITORIAL BY AUTISM EXPERT Peter Tanguay, MD

“I suggest that the authors have mistaken the manifestations of difficult temperament in young children with autism for mania......Those of us who deal with children with PDD know that 10% to 20% of them also have a difficult temperament.”

The Heavy Burden of Psychiatric Comorbidity in Youth with Autism Spectrum Disorders: A Large Comparative Study of a Psychiatrically Referred Population

Gagan Joshi · Carter Petty · Janet Wozniak · Aude Henin · Ronna Fried · Maribel Galdo · Meghan Kotarski · Sarah Walls · Joseph Biederman

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Abstract The objective of the study was to systematically examine patterns of psychiatric comorbidity in referred youth with autism spectrum disorders (ASD) including autistic disorder and pervasive developmental disorder not otherwise specified. Consecutively referred children and adolescents to a pediatric psychopharmacology program were assessed with structured diagnostic interview and measures of psychosocial functioning. high levels of psychiatric comorbidity and dysfunction comparable to the referred population of youth without ASD. These findings emphasize the heavy burden of psychiatric comorbidity afflicting youth with ASD and may be important targets for intervention.

Keywords Autism spectrum disorders · Psychiatric comorbidity · Children and adolescents
Diagnoses in Psychiatrically Referred Youth with and without ASD
N=2323

Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

Autism Complicates the Course of Bipolar Disorder

**School Functioning**

- **Extra help**: A*** A*** A*** AB*** C**
- **Special class**: A*** A*** A*** AB***
- **Repeated grade**: A*** AB* B**

**Hospitalization**

- **Controls**: A*** AB***
- **ADHD**: A*** AB***
- **BPD-I**: A*** AB***
- **BPD-I+ASD**: A*** AB***

Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001
A = vs. Control; B = vs. ADHD; C = vs. BPD

Symptoms of Mania in BPD Youth with and without Autism

Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

Summary of Clinical Presentation

• Frequently irritable
• Frequently non-episodic
• Frequently chronic
• Frequently mixed
• Highly comorbid with ADHD, ODD, CD, anxiety and ASD
Is Pediatric BPD Familial?
Familial Risk of BP-I Disorder in First Degree Relatives

P <0.01 vs. ADHD and Controls

Proband n= 157, 162, 136
Relative n= 508, 511, 411

Wozniak et al. Psychol Medicine 2011
Bipolar Disorder in First-Degree Relatives

A family history of bipolar disorder is present in bipolar youth with and without autism

Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001
A = vs. Control; B = vs. ADHD

Does Pediatric BPD have a unique course?
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
Does Pediatric BPD have a unique pharmacological response?
“The unfortunate reality is that current medications help too few people to get better and very few people to get well.”
- Thomas Insel
NIMH Director

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-5).

One of the draft’s most talked-about features is a new diagnostic category for children: disruptive dysregulation disorder with dysphoria (TTDD). The addition has been praised to save at a verdict on one of the most common problems in child psychiatry: the dramatic increase in the number of children with a diagnosis of bipolar disorder among children. The answer appears to be the creation of a new category: disruptive dysregulation disorder. Will the DD5 diagnostic criteria make it easier for providers to identify disruptive dysregulation disorder? In the mid-20th century, a small but influential group of child psychiatrists began to notice more children with disruptive dysregulation disorder. Despite the frequency of disruptive behavior, most children with disruptive dysregulation disorder do not have disruptive episodes of mood but instead have chronic and very severe irritability. The label was meant to encode the problem of childhood disruptive behavior, and the DSM-V diagnostic criteria are a necessary step forward. It is difficult to say how many children with disruptive dysregulation disorder will fit under the new diagnostic criteria. NEJM 362;20. May 20, 2010.
1989 to 2010: FDA-Approved Medications for PBD

- 1989-2007 Lithium
- 2007 Risperidone
- 2008 Aripiprazole
- 2009 Olanzapine
- 2009 Quetiapine
Many FDA Approved Treatments for Children and Adolescents with Emotional Dysregulation

- Lithium: manic or mixed states, patients aged 13-17 years
- Risperidone: manic or mixed states, age 10-17 years
- Aripiprazole: manic or mixed states, age 10-17 years
- Olanzapine: manic or mixed states, age 13-17 years
- Quetiapine: monotherapy or adjunct to lithium or divalproex sodium, manic states, age 10-17 years
- Saphris manic or mixed episodes assoc with BPD I, age 10-17
- Fluoxetine: depression and OCD age 8+
- Escitalopram: depression age 12+
- Sertraline, fluvoxamine, anfranil: pediatric OCD
- Aripiprazole: irritability associated with autistic disorder ages 6-17
- Risperidone: irritability associated with autism ages 5-16
Pharmacologic Treatments for Pediatric Bipolar Disorder: A Review and Meta-Analysis


Objective: A growing body of literature has documented pediatric bipolar disorder to be a severely impairing form of psychopathology. However, concerns remain as to the inadequacy of the extant literature on its pharmacotherapy. Furthermore, treatment studies have not been systematically reviewed for treatment effects on core and associated symptoms. Thus, a systematic evaluation and synthesis of the available literature on the efficacy of antimanic pharmacotherapy for pediatric bipolar disorder on symptoms of mania, depression, and attention-deficit/hyperactivity disorder was undertaken. Method: A systematic search was conducted through PubMed from 1989 through 2010 for open-label and randomized controlled trials published in English on the pharmacotherapy of pediatric mania. Results: There have been 46 open-label (n = 29) and randomized (n = 17) clinical trials of antimanic agents in pediatric bipolar disorder encompassing 2,666 subjects that evaluated a range of therapeutic agents, including traditional mood stabilizers, other anticonvulsants, second-generation antipsychotics, and naturopathic compounds. This literature has documented that the available armamentarium has different levels of efficacy in the treatment of pediatric mania. Because all psychotropic classes are associated with important adverse effects, a careful risk-benefit analysis is warranted when initiating pharmacologic treatment with any of these compounds. In the limited data available, the effects of antimanic agents on depression and symptoms of attention-deficit/hyperactivity disorder have been, in general, modest. Few studies have evaluated the effects of antimanic agents in children younger than 10 years. Conclusions: A substantial body of scientific literature has evaluated the safety and efficacy of various medicines and drug classes in the treatment of mania in pediatric bipolar disorder. More work is needed to assess the safety and efficacy of psychotropic drugs in children younger than 10 years, to further evaluate the efficacy of naturopathic compounds, and to further evaluate the effects of antimanic treatments for the management of depression and attention-deficit/hyperactivity disorder. J. Am. Acad. Child Adolesc. Psychiatry, 2011;50(8):749–762. Key Words: pediatric bipolar disorder, psychopharmacology, mania, depression, attention-deficit/hyperactivity disorder.
Studies of Pediatric Mania
Psychopharmacology 1989 - 2010

• 40 Published Studies
  – 28 Open Label
  – 12 RCT

• 2704 Subjects participated across studies

![Graph showing the number of studies by year, with bars for Open Label and RCT studies.]

- 1989-1999: Open Label 2, RCT 1
- 2000-2005: Open Label 13, RCT 3
- 2005-2010: Open Label 13, RCT 8
Mean Change in YMRS from Baseline by Medication Class

- Traditional Mood Stabilizers: -10.99
- Other Anticonvulsants: -11.03
- Atypical Antipsychotics: -16.8
- Naturopathic Treatments: -5.6
Bipolar Youth with Autism Included in Clinical Trials of SGAs for Bipolar Youth
N=151

Rating Scales in BPD Youth with and without Autism
N=151

Anti-Manic Response of Bipolar Youth to SGA Monotherapy: No difference with and without ASD

N=151

STUDY OF A NATURAL TREATMENT FOR YOUNG PEOPLE WITH BIPOLAR DISORDER

Every gift matters. Please support Mass General’s initiative to study NAC in bipolar children.

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NAC STUDY
A Randomized Clinical Trial of High Eicosapentaenoic Acid Omega-3 Fatty Acids and Inositol as Monotherapy and in Combination in the Treatment of Pediatric Bipolar Spectrum Disorders:
A Pilot Study

Janet Wozniak, MD\textsuperscript{a,b}; Stephen V. Faraone, PhD\textsuperscript{c}; James Chan, MA\textsuperscript{a}; Laura Tarko, MPH\textsuperscript{a}; Mariely Hernandez, MA\textsuperscript{a}; Jacqueline Davis, BA\textsuperscript{a}; K. Yvonne Woodworth, BA\textsuperscript{a}; and Joseph Biederman, MD\textsuperscript{a,b,*}

ABSTRACT

Objective: We conducted a 12-week, randomized, double-blind, controlled clinical trial to evaluate the effectiveness and tolerability of high eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) omega-3 fatty acids and inositol as monotherapy and in combination in children with bipolar spectrum disorders.

Pediatric bipolar disorder is increasingly recognized across the world as a prevalent and highly morbid disorder.\textsuperscript{1–3} While several medications have received US Food and Drug Administration (FDA) approval for the treatment of pediatric bipolar disorder, their use is associated with significant and serious adverse effects, including weight gain, dyslipidemias, glycemic dyscontrol and risk for diabetes, and risk for tardive dyskinesia. This state of affairs supports the search for alternative safe and effective treatment to address the urgent...
HIGH EPA OMEGA-3 FATTY ACIDS AND INSOSITOL IN PEDIATRIC BPD STUDY: ANIDEPRESSANT RESPONSE

Wozniak et al, JCP in press

- CGI MDD Improvement ≤2
- 30% HAM-D Improvement
- 50% HAM-D Improvement
- 30% CDRS Improvement
- 50% CDRS Improvement

Inositol (n=7)  | Omega-3 FA (n=7)  | Omega-3 FA + Inositol (n=10)
HIGH EPA OMEGA-3 FATTY ACIDS AND INSOSITOL IN PEDIATRIC BPD STUDY: OTHER RESPONSES

Wozniak et al, JCP in press

Percent of Subjects

CGI ADHD Improvement ≤2
CGI Anxiety Improvement ≤2
CGI ODD Improvement ≤2
30% BPRS Improvement

Inositol (n=7)  Omega-3 FA (n=7)  Omega-3 FA + Inositol (n=10)

BPRS SMD (Omega-3 FA vs. Inositol)=0.77
BPRS SMD (Omega-3 FA + Inositol vs. Inositol)=0.60
CGI Anxiety SMD (Omega-3 FA + Inositol vs. Inositol)=0.55
CGI ODD SMD (Omega-3 FA + Inositol vs. Omega-3 FA)=0.45

OR=5.83
OR=3.11
OR=2.50
OR=8.08
OR=6.00
OR=2.40
OR=0.67
OR=3.46
OR=1.25
OR=3.46
OR=6.82
OR=1.25
PBD Mania Trials: Summary

• Significant increase in clinical trials of anti-manic agents over the past 10 years
• Atypical antipsychotic agents outperform traditional mood stabilizers and other anticonvulsants
SUMMARY: Pediatric BP Disorder

• 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
SUMMARY: BP and ASD

• A clinically significant subgroup of individuals with ASD suffer from BP disorder
• Symptom of mania and familiality of BP disorder are similar in BP youth with and without ASD
• No differences in anti-manic response or tolerability to SGAs in BP disorder youth with or without ASD