Pediatric Bipolar Disorder: Advances in Diagnosis and Research

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Mood Disorders affect 14.3% of Adolescents
Bipolar Disorder affects 2.9% of Adolescents

Objective: To present estimates of the lifetime prevalence of DSM-IV mental disorders with and without severe impairment, their comorbidity across broad classes of disorder, and their sociodemographic correlates.

Method: The National Comorbidity Survey-Adolescent Supplement NCS-A is a nationally representative face-to-face survey of 10,123 adolescents aged 13 to 18 years in the continental United States. DSM-IV mental disorders were assessed using a modified version of the fully structured World Health Organization Composite International Diagnostic Interview. Results: Anxiety disorders were the most common condition (31.9%), followed by behavior disorders (19.1%), mood disorders (14.3%), and substance use disorders (11.4%), with approximately 40% of participants with one class of disorder also meeting criteria for another class of lifetime disorder. The overall prevalence of disorders with severe impairment and/or distress was 22.2% (11.2% with mood disorders, 8.3% with anxiety disorders, and 9.6% behavior disorders). The median age of onset for disorder classes was 10.3 years for anxiety, 13.6 years for behavior, and 14.1 years for substance use disorders.

Conclusions: These findings provide the first prevalence data on a broad range of mental disorders in a nationally representative sample of U.S. adolescents. Approximately one in every four to five youth in the U.S. meets criteria for a mental disorder with severe impairment across their lifetime. The likelihood that common mental disorders in adults first emerge in childhood and adolescence highlights the need for a transition from the common focus on treatment of U.S. youth to that of prevention and early intervention. J. Am. Acad. Child Adolesc. Psychiatry, 2010;49(10):980–989. Key Words: epidemiology, adolescents, mental disorders, National Comorbidity Survey, correlates.
**SCOPE OF THE PROBLEM**

Meta-analysis of Epidemiologic Studies of Pediatric Bipolar Disorder

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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 negatively correlated with prevalence \((r = -0.04)\) and remained nonsignificant when controlling for study methodological differences.

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.

*J Clin Psychiatry* 2011;72(9):1250–1256
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Van Meter J Clin Psych 2011
DSM 5 Bipolar Disorders Changes – Pediatric vs Adult Priorities

Pediatrics:
Added DMDD, to ‘reduce the number of pediatric bipolar diagnoses’

Adult:
Added ‘energy’ to the requirements
Made it easier to diagnosis mixed states ‘to increase recognition of bipolar disorder and institute appropriate treatments’
The New Temper Tantrum Disorder
Will the new diagnostic manual for psychiatrists go too far in labeling kids dysfunctional?
By David Dobbs | Posted Friday, Dec. 7, 2012, at 1:12 PM ET
Disruptive Mood Dysregulation Disorder

DMDD Criteria

A. The disorder is characterized by severe recurrent temper outbursts that are grossly out of proportion in intensity or duration to the situation.
   1. The temper outbursts are manifest verbally and/or behaviorally, such as in the form of verbal rages or physical aggression towards people or property.
   2. The temper outbursts are inconsistent with developmental level.

B. Frequency: The temper outbursts occur, on average, three or more times per week.

C. Mood between temper outbursts:
   1. Nearly every day, most of the day, the mood between temper outbursts is persistently irritable or angry.
   2. The irritable or angry mood is observable by others (e.g., parents, teachers, peers).

D. Duration: Criteria A-C have been 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 of Criteria A-C.

E. Criterion A or C is present in at least two settings (at home, at school, or with peers) and must be severe in at least in one setting.

F. The diagnosis should not be made for the first time before age 6 or after age 18.

G. The onset of Criteria A through E is before age 10 years.
DMDD Exclusionary Criteria

H. There has never been a distinct period lasting more than one day during which abnormally elevated or expansive mood was present most of the day, and the abnormally elevated or expansive mood was accompanied by the onset, or worsening, of three of the “B” criteria of mania (i.e., grandiosity or inflated self-esteem, decreased need for sleep, pressured speech, flight of ideas, distractibility, increase in goal directed activity, or excessive involvement in activities with a high potential for painful consequences; see pp. XX). Abnormally elevated mood should be differentiated from developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation.

I. The behaviors do not occur exclusively during an episode of Major Depressive Disorder and are not better accounted for by another mental disorder (e.g., Autism Spectrum Disorder, Posttraumatic Stress Disorder, Separation Anxiety Disorder, Dysthymic Disorder). (Note: This diagnosis cannot co-exist with Oppositional Defiant Disorder or Bipolar Disorder, though it can co-exist with Attention Deficit/Hyperactivity Disorder, Conduct Disorder, and Substance Use Disorders. Individuals meeting criteria for both Disruptive Mood Dysregulation Disorder and Oppositional Defiant Disorder should only be given the diagnosis of Disruptive Mood Dysregulation Disorder. If an individual has ever experienced a manic or hypomanic episode, the diagnosis of Disruptive Mood Dysregulation Disorder should not be assigned.) The symptoms are not due to the effects of a drug or to a general medical or neurological condition.
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.

*J Clin Psychiatry* 2012;73(10):1342–1350

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DSM 5 Criteria

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
Criteria B symptoms of mania (DSM5)

Mania: developmental variability and overlap with ADHD symptoms complicates diagnosis of the combined condition across the life span, but especially in youth

High Energy in Criteria A may overlap with ‘hyperactivity’

Distractibility (OVERLAPS WITH ADHD)
Increased Energy (OVERLAPS WITH ADHD)
Grandiosity (CAN BE EXTREME OPPOSITIONAL DEFIENT DISORDER)
Flight of Ideas (CAN BE OBSERVED AND/OR EXPERIENCED)
Activities that are reckless (spending, sex) (GAUGE ACCORDING TO AGE)
Sleep (less, with energy) (NOT PHASE SHIFT)
Talkativeness (OVERLAPS WITH ADHD)
Bipolar disorder, while commonly encountered in the primary care setting, is often misdiagnosed or undiagnosed. In the *DSM-IV-TR*, patients could be diagnosed as being in a mixed state only if they had concurrent manic and depressive symptoms; while this occurs in some patients, many more experience subsyndromal mixed symptoms that would disqualify a “mixed state” diagnosis. The recently released *DSM-5* attempts to capture this large proportion of patients with subsyndromal mixed symptoms with the inclusion of the “mixed specifier.” The presence of such subsyndromal mixed symptoms has significant implications for both diagnosis and treatment. For those presenting with major depressive disorder with subsyndromal manic symptoms, clinicians must be vigilant for the development of full-blown bipolar disease. In treating this group, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors remain first-line therapy, but augmentation with other therapies is often required. If a diagnosis of bipolar disorder is confirmed and the patient is experiencing a depressive phase, traditional antidepressants should be avoided. For those presenting with mania and mixed depressive symptoms, treatment with a combination of atypical antipsychotics and mood stabilizers is best.
Manic/Hypomanic Episode with Mixed Features—at least 3

1. Prominent dysphoria or depressed mood as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
2. Diminished interest or pleasure in all, or almost all, activities (as indicated by either subjective account or observation made by others).
3. Psychomotor retardation nearly every day (observable by others, not merely subjective feelings of being slowed down).
4. Fatigue or loss of energy.
5. Feeling of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick).
6. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.\(^8\) (pp 149,150)

Hu, 2014
Major Depressive Episode with Mixed Features- at least 3

1. Elevated, expansive mood.
2. Inflated self-esteem or grandiosity.
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Increase in energy or goal-directed activity (socially, at work or school, or sexually).
6. Increased or excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
7. Decreased need for sleep (feeling rested despite sleeping less than usual, to be contrasted with insomnia). \( ^8(p150) \)

Hu, 2014
Mixed depression, in our research and experience as well as that of many others,\textsuperscript{9,10} is often characterised by markedly irritable mood and psychic or psychomotor agitation - the exact features excluded in DSM-5. This would be like proposing a new definition for migraine headaches, but excluding symptoms of pain in the head. Of course, one can have pain in the head from other conditions besides migraine, but why should this be a reason to exclude that symptom entirely?
Pediatric-Onset Bipolar Disorder

“Further evidence of unique developmental phenotypic correlates of pediatric bipolar disorder: findings from a large sample of clinically referred preadolescent children assessed over the last 7 years”

Biederman, Faraone, Wozniak, et al

Journal of Affective Disorders, 2004
Pediatric-Onset Bipolar Disorder

• Subjects: All consecutively referred children from aged 12 years and younger:

• 1991-1995 N=262
  – 16% (N=43) BPD
  – 79% (N=164) ADHD

• 1995-2002 N=768
  – 17% (N=129) BPD
  – 73% (N=562) ADHD
2002 MGH Study of Pediatric BPD

Age by Cohort

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Years (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD 1st Cohort</td>
<td>7.9</td>
</tr>
<tr>
<td>BPD 2nd Cohort</td>
<td>8.3</td>
</tr>
<tr>
<td>ADHD 2nd Cohort</td>
<td>8.2</td>
</tr>
</tbody>
</table>
2002 MGH Study of Pediatric BPD

Bipolar Symptoms by BPD Cohort

<table>
<thead>
<tr>
<th>Symptom</th>
<th>1st Cohort</th>
<th>2nd Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euphoria</td>
<td>33</td>
<td>17</td>
</tr>
<tr>
<td>Irritability</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Increased Energy</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>Flight of Ideas</td>
<td>63</td>
<td>72</td>
</tr>
</tbody>
</table>

P=NS
Bipolar Symptoms by BPD Cohort

- **Grandiose**
  - 1st Cohort: 64%
  - 2nd Cohort: 68%
  - *P=NS*

- **Decreased Sleep**
  - 1st Cohort: 54%
  - 2nd Cohort: 29%
  - *P=NS*

- **Pressured Speech**
  - 1st Cohort: 44%
  - 2nd Cohort: 81%
  - *P=NS*

- **Racing Thoughts**
  - 1st Cohort: 29%
  - 2nd Cohort: 78%
  - *P=NS*
Comorbid Disorders by Bipolar Cohort, Clinic Samples
Prior to 1995 and 1995-2002

Psychiatric Diagnoses

- Major Depression
- Psychosis
- ADHD
- Oppositional Defiant Disorder
- Conduct Disorder

P = NS

Bipolar 1st Cohort
Bipolar 2nd Cohort
56% Bipolar probands had multiple anxiety disorders

26% of ADHD (without bipolar disorder probands) had multiple anxiety disorders
Pediatric-Onset Bipolar Disorder: Very Poor Functioning

<table>
<thead>
<tr>
<th></th>
<th>BPD</th>
<th>ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>21%</td>
<td>2%</td>
</tr>
<tr>
<td>GAF</td>
<td>43</td>
<td>50</td>
</tr>
<tr>
<td>Learning disabilities-math</td>
<td>30%</td>
<td>24%</td>
</tr>
<tr>
<td>Learning disabilities-reading</td>
<td>42%</td>
<td>14%</td>
</tr>
</tbody>
</table>
Pediatric-Onset Bipolar Disorder
Do children ‘look’ different?

Irritability and Fluctuating Mood States/Mixed States
IRRITABILITY IS A COMMON FEATURE OF DEPRESSION AND BIPOLAR DISORDER

There is a misconception that depression is melancholy and bipolar disorder is only ‘highs’ and ‘lows’
Pediatric-Onset Bipolar Disorder: chronicity

• 83.3% (N=60) were rapid, ultra rapid or ultradian cycling (Geller, J Affec Dis, 1998)

• 50% (N=90) rapid cycling with almost no inter-episode recovery (Findling, Bipolar Disorder 2001)
Mania Episodicity (N = 92)

return to symptom free baseline rare

- 12% Rapid Cycling
  - > 4 episodes/yr
- 27% Ultra-Rapid
  - ≥ 20 episodes/yr
- 1% Ultradian
  - ≥ 300 episodes/yr
- 7% Episodic, ≥ 12 m
- 41% Single, ≥ 12 m
- 5% Episodic, < 12 m
- 7% Single, < 12 m

- Presentation varies: mixed, manic, depressed
- Mood switches: irritable, euphoric, melancholy
- Comorbidity evident
Persistence of Bipolar Disorder in youth at 4-year Follow-up (N=78)

- Most continue with Bipolar I disorder 73.1%
- Some symptoms of Mania 6.4%
- Not manic, but depressed 5.1%
- Better, but Treated 9.0%
- Better 6.4%

Only 5 (6.4%) subjects were better without treatment

Wozniak et al, J Psychiatr Res, 2011
Figure 1. Persistence of DSM-IV BP-I in youth at the 5-year follow-up.

- Syndromic or Symptomatic Remission
- Symptomatic Persistence
- Syndromic Persistence
- Euthymic 19%
- Full BP-I Disorder 50%
- Subthreshold BP-I Disorder 13%
- Full Major Depressive Disorder 13%
- Subthreshold Major Depressive Disorder 5%
Pediatric-Onset Bipolar Disorder

Wozniak & Biederman, et al., 1995

Presentation of Mania-Mixed Presentations Common

- Mixed
- Mania only
- Biphasic

N=36
N=6
N=1
There has been growing interest in the phenomenology and clinical implications of the opposing mixed state—that is, manic or hypomanic symptoms during a depressive episode. Mixed depression, variably defined, has been identified in 21%–76% of depressed patients (2, 3, 6–10) and has been associated with such adverse clinical outcomes as suicide attempt history (2, 3, 9), younger onset age (2, 6, 9), and longer episode duration (3, 9). The present study replicates the methodology of our previous work (5) and assesses the prevalence and correlations of depression with concurrent...
The most severe types of emotional dysregulation come when the abnormal moods of mania and depression co-occur in the mixed states of bipolar disorder.

**DEPRESSION**

Melancholy:
- Sad, no pleasure, down on self, suicidal, self-destructive

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

**MANIA**

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

IRRITABILITY:
- Swearing, disrespectful, threatening, wild, out of control with Explosions that are frequent, for 30-60+ minutes, destructive, aggressive
Heterogeneity of Irritability in Children

Mick et al, 2007
Irritability: 2009 COBY study findings

Irritability Without Elation in a Large Bipolar Youth Sample: Frequency and Clinical Description

JEFFREY HUNT, M.D., BORIS BIRMAHER, M.D., HENRIETTA LEONARD, M.D., MICHAEL STROBER, Ph.D., DAVID AXELSON, M.D., NEAL RYAN, M.D., MEI YANG, M.S., MARYKAY GILL, R.N., JENNIFER DYL, Ph.D., CHRISTIANNE ESPOSITO-SMYTHERS, Ph.D., LANCE SWENSON, Ph.D., BENJAMIN GOLSTEIN, M.D., Ph.D., TINA GOLSTEIN, Ph.D., ROBERT STOUT, Ph.D., AND MARTIN KELLER, M.D.

ABSTRACT

Objective: To determine whether some children with bipolar disorder (BP) manifest irritability without elation and whether these children differ on sociodemographic, phenotypic, and familial features from those who have elation and no irritability and from those who have both. Method: Three hundred sixty-one youths with BP recruited into the three-site Course and Outcome of Bipolar Illness in Youth study were assessed at baseline and for most severe past symptoms using standardized semistructured interviews. Bipolar disorder subtype was identified, and frequency and severity of manic symptoms were quantified. The subjects were required to have episodic mood disturbance to be diagnosed with BP. The sample was then reclassified and compared based on the most severe lifetime manic episode into three subgroups: elated only, irritable only, and both elated and irritable. Results: Irritable-only and elated-only subgroups constituted 10% and 15% of the sample, respectively. Except for the irritable-only subjects being significantly younger than the other two subgroups, there were no other between-group sociodemographic differences. There were no significant differences in the BP subtype, rate of psychiatric comorbidities, severity of illness, duration of illness, and family history of mania in first- or second-degree relatives and other psychiatric disorders in first-degree relatives, with the exception of depression and alcohol abuse occurring more frequently in the irritability-only subgroup. The elated-only group had higher scores on most DSM-IV maniacitation R items. Conclusions: The results of this study support the DSM-IV criteria for mania in youths. Irritable-only...
Familiality of Bipolar Disease, by Symptom

- **Euphoria**
- **Irritable**
- **Grandiosity**
- **Combined Euphoria and Grandiosity**
- **Decreased Need for Sleep**
- **More or Pressured Speech**
- **Flight of Ideas/Racing Thoughts**
- **Distractibility**
- **Increase in Activity/Increased Energy**
- **Poor Judgment**

* p<0.05  
** p<0.005

**With Symptom(s)**

**Without Symptom(s)**

Familiality (%)
What we learned about children with mania:

• Almost all of them had ADHD (especially when the onset of mania was prior to age 12)

• The major mood disorder chief complaint of the parents was severe irritability (rather than euphoria)

• The children had mostly mixed states (mania and depression overlapped in time)

• The children were seldom well due to mixed states, many cycles and comorbidity (chronicity)
Pediatric-Onset Bipolar Disorder

Is it consistent with Mania?

• Consistent presentation across samples
• Core symptoms of mania present
• High rates of Depression
• High rates of Psychosis
• Poor global functioning
Pediatric-Onset Bipolar Disorder

Is it consistent with ADHD?

• Consistent presentation across samples

• Core symptoms of mania present

• High prevalence of non-mood comorbid disorders associated with ADHD
  1. Conduct disorder
  2. Oppositional defiant Disorder
The lifetime impact of attention-deficit hyperactivity disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions

- N=34,000 adults age 18+ 2.5% Adult ADHD
- 34% with ADHD had bipolar disorder versus 6% without ADHD

Bernardi, Psychol Med 2012

The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication

- N=3199 ages 18-44 4.4% Adult ADHD
- 19% with ADHD had bipolar disorder versus 3% without ADHD

Kessler, Am J Psych 2006
Persistence: Most bipolar adults in STEP-BD (N=983) reported onset in childhood or adolescence

- About 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
Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants

9.5% lifetime prevalence comorbid ADHD

BPD+ADHD Adult patients:
• had earlier onset BPD by 5 years
• had shorter periods of wellness
• were more frequently depressed
• had more comorbidity (anxiety and substance use)

Nierenberg, BiolPsych, 2005
Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants

9.5% lifetime prevalence comorbid ADHD

BPD+ADHD Adult patients:
• were more likely to be male
• were more likely to have Bipolar I
• had lower GAF
• had more days irritable and more days elated

Nierenberg, BiolPsych, 2005
Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants

9.5% lifetime prevalence comorbid ADHD

BPD+ADHD Adult patients:
- more suicide attempts
- more violence
- more legal problems

Nierenberg, BiolPsych, 2005
“Family studies have consistently found a higher rate of bipolar disorder among the relatives of early onset bipolar disorder patients than in relatives of later-onset cases, which supports the notion of a larger genetic contribution to the early-onset cases.”

Faraone, Glatt, Tsuang *The Genetics of Pediatric Onset Bipolar Disorder* Biol Psych 2003
Meta-Analysis of Controlled Family Studies of Pediatric Bipolar Disorder: Familiality in BP-I Probands vs Controls

<table>
<thead>
<tr>
<th>Study</th>
<th>BP-I probands (N)</th>
<th>Familiality</th>
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<tbody>
<tr>
<td>Kutcher 1991</td>
<td>N=23</td>
<td>15%</td>
</tr>
<tr>
<td>Wozniak 1995</td>
<td>N=16</td>
<td>13%</td>
</tr>
<tr>
<td>Faraone 1997</td>
<td>N=15</td>
<td>16%</td>
</tr>
<tr>
<td>Geller 2006</td>
<td>N=95</td>
<td>28%</td>
</tr>
<tr>
<td>Wozniak 2010</td>
<td>N=157</td>
<td>18%</td>
</tr>
</tbody>
</table>

Wozniak J Clin Psych, 2012
Familial risk of bipolar I disorder in first-degree relatives of BP-I, ADHD and Control Probands

*<p<0.01 versus ADHD and controls

Proband n = 239
Relative n = 726

Delimitation from ADHD

Wozniak J Clin Psych, 2012
Figure 1. Rates of full BP-I disorder and major depressive disorder among relatives of control, ADHD, subthreshold BP-I, and full BP-I probands. A. Full BP-I disorder. B. Major depressive disorder.

\[ a \text{ Compared to relatives of control probands. } b \text{ Compared to relatives of ADHD probands. } ^*P<0.05, ^{**}P<0.005, ^{***}P<0.001 \]

A. Full BP-I Disorder

<table>
<thead>
<tr>
<th></th>
<th>Relatives of Control Probands</th>
<th>Relatives of ADHD Probands</th>
<th>Relatives of Subthreshold BP-I Probands</th>
<th>Relatives of Full BP-I Probands</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with Full BP-I Disorder</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>25</td>
</tr>
</tbody>
</table>

B. Major Depressive Disorder

<table>
<thead>
<tr>
<th></th>
<th>Relatives of Control Probands</th>
<th>Relatives of ADHD Probands</th>
<th>Relatives of Subthreshold BP-I Probands</th>
<th>Relatives of Full BP-I Probands</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with Major Depressive Disorder</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>25</td>
</tr>
</tbody>
</table>

† Smaller sample sizes for relatives of ADHD probands (n = 506) and relatives of full BP-I probands (n = 685).
Archival Report

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

Kimm J.E. van Hulzen, Claus J. Scholz, Barbara Franke, Stephan Rioke, Marieke Klein.

RESULTS: We found a significant single nucleotide polymorphism-based genetic correlation between ADHD and BPD in the full and age-restricted samples ($r_{G\text{full}} = .64, p = 3.13 \times 10^{-14}$; $r_{G\text{restricted}} = .71, p = 4.09 \times 10^{-16}$). The

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.

Additional nominally significant regions identified contained 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.

RESULTS: We found a significant single nucleotide polymorphism-based genetic correlation between ADHD and BPD in the full and age-restricted samples ($r_{G\text{full}} = .64, p = 3.13 \times 10^{-14}$; $r_{G\text{restricted}} = .71, p = 4.09 \times 10^{-16}$). The

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
Conclusion

• By providing information that is 1 step removed from a diagnosis in an affected child, family study methodology remains a key feature for the validation of complex psychiatric disorders such as pediatric bipolar disorder.

• By documenting the high familiality of pediatric bipolar disorder, our study provides strong support for the validity of pediatric bipolar disorder.

• Early onset bipolar disorder (with high rates of ADHD) may be caused by a different genetics than later onset forms of the disorder.
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 in 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
Why is appropriate diagnosis important? Because it leads to the best evidence based treatment

Treatment Risk versus Benefit includes the risk of not treating Bipolar Disorder with attendant:

- Suicide attempts and completed suicide
- Substance Abuse and Addiction
- Reckless Behavior with Arrest
- Other consequences of hypersexuality and dangerous impulsivity
ultradian cycling, and fewer days euthymic (all $P<.05$).  

**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. Both childhood onset and treatment delay were associated with a persistently more adverse course of illness rated prospectively in adults. These data should help foster efforts to ensure earlier and more effective treatment of bipolar illness in children and adolescents. It is hoped that appropriate early intervention would result in a more benign illness and a better prognosis in adulthood.

*J Clin Psychiatry* 2010;71(7):864–872

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ADHD is associated with

• Family conflict, poor relationships
• Injuries and trauma
• Impaired driving
• Substance use disorders
• Low educational achievement
• Poor work performance
• High health care costs
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
20TH-CENTURY - CHANGES IN YOUTH SUICIDE RATES
— UNITED STATES, AGES 15–24 —

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

Year 1900-2000

Rate per 100,000

BOYS
5X AS MANY
COMPLETED
SUICIDES

GIRLS
3X AS MANY
ATTEMPTS

Everyday I think why am I still here?
Number of Subjects Participating in Pediatric Anti-Manic Trials

Mean Change in YMRS from Baseline by Medication Class

<table>
<thead>
<tr>
<th>Medication Class</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>
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 4304 subjects (including 1750 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.

Weight Gain in 8-week Open Label Trials of Second Generation Antipsychotic Monotherapy in 116 Children with Bipolar Disorder

Biederman et al (2007), AACAP; Boston
Lithium, Divalproex Sodium, and Carbamazepine in Bipolar Disorder

Kowatch et al. JAACAP 39, 713-720, 2000

**Results**

- The response rates were
  - 53% for divalproex sodium
  - 38% for lithium
  - 38% for carbamazepine
- All 3 mood stabilizers were well tolerated with no serious adverse effects
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, Brieana M. Rowles, MA, Jacqui Lingler, BS, Karen Martz, MS, Ravinder 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 = 28) for up to 8 weeks. The a priori primary efficacy measure was change from baseline to the end of study (week 8/ET) in the Young Mania Rating Scale (YMRS) score, based on last-observation-carried-forward analysis.

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/ET (P = .03).

A statistically significant increase in thyrotropin concentration was seen with lithium.

Findling Pediatrics 2015
Pediatric Bipolar Disorder: Progress in Treatments

• A prospective open-label trial of lamotrigine monotherapy in children and adolescents with bipolar disorder. J.CNS Neurosci Ther. 2010

• A prospective open-label trial of extended-release carbamazepine monotherapy in children with bipolar disorder. JCAP 2010
One of the concerns about increasing the diagnosis of bipolar disorder is that it will lead to exposure to medications with unknown effects on the developing brain.

Intervening with supplementation during critical periods may enhance brain development.

Thus an agent with minimal effect on the adult brain could play a major role in the developing brain.
This study was highly publicized in the major news media and suggest that 2 months of supplementation can have positive effects after one year on psychotic symptoms.
Our own study shows that omega-3s can treat bipolar disorder in children. This result is about 50% what we see with atypical antipsychotic medications, but without the serious or annoying side effects.
Change in Young Mania Rating Scale (YMRS) Scores in subjects treated with omega-3 fatty acid monotherapy in an open study over 8 Weeks

YMRS, Young Mania Rating Scale. LOCF, Last Observation Carried Forward *p<0.05 versus baseline

Wozniak, European Neuropsychopharmacology, 2007
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,*}

\textbf{Abstract}

\textbf{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 need.
ANTI-MANIC RESPONSE TO TREATMENT

The combined treatment of omega-3s and inositol outperformed either treatment used alone for mania.

Wozniak, J Clinical Psychiatry 2015
ANTI-DEPRESSANT RESPONSE TO TREATMENT

The combined treatment with both omega-3s and inositol outperformed either agent used alone in bipolar spectrum youth.

Wozniak J Clinical Psychiatry 2015
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.

DONATE
Demographic characteristics for subjects who were exposed to the study treatment (≥2 weeks) (N=13)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exposed Subjects N=13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>9.7 ± 4.2</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>7 (54%)</td>
</tr>
<tr>
<td>Socioeconomic Status</td>
<td>1.8 ± 1.1</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>9 (69%)</td>
</tr>
<tr>
<td>Unknown or Not Reported</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

Data are reported as mean ± standard deviation or n (%).
Change in Young Mania Rating Scale, Hamilton Depression Rating Scale, Brief Psychiatric Rating Scale, and ADHD Rating Scale total scores from baseline to end point

<table>
<thead>
<tr>
<th>Rating Scale</th>
<th>N</th>
<th>Baseline</th>
<th>End Point</th>
<th>Change</th>
<th>Test Statistic</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young Mania Rating Scale</td>
<td>13</td>
<td>25.4 ± 5.6</td>
<td>20.4 ± 4.9</td>
<td>-5.0 ± 5.7</td>
<td>z=-2.42</td>
<td>0.02</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale</td>
<td>13</td>
<td>18.2 ± 5.7</td>
<td>14.7 ± 8.5</td>
<td>-3.5 ± 7.0</td>
<td>z=-1.79</td>
<td>0.07</td>
</tr>
<tr>
<td>Brief Psychiatric Rating Scale†</td>
<td>10</td>
<td>48.1 ± 9.5</td>
<td>43.4 ± 12.7</td>
<td>-4.7 ± 8.8</td>
<td>z=-1.43</td>
<td>0.15</td>
</tr>
<tr>
<td>ADHD Rating Scale†</td>
<td>11</td>
<td>35.5 ± 14.9</td>
<td>34.1 ± 11.2</td>
<td>-1.4 ± 7.7</td>
<td>z=-0.87</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation.
† One subject missing baseline scores for the BPRS and 2 subjects did not make it to week 6 and do not have end point scores (BPRS & ADHD-RS).
Comorbid disorders

• Depression
  – Lithium, Lamotrigine, Lurasidone (or bupropion)
  – Avoid SSRI’s
• ADHD
  – Stimulant after mood stabilized

Quetiapine **not** effective in Adolescent Bipolar Depression

**Mean (SD) change in CDRS-R scores from baseline to endpoint**

DelBello et al., 2009
In this placebo-controlled study, monotherapy with lurasidone, in the dose range of 20-80 mg/day, significantly reduced depressive symptoms in children and adolescents with bipolar depression. Lurasidone was well-tolerated, with minimal effects on weight and metabolic parameters.
Figure 2 Least squares mean change from baseline in primary (Children’s Depression Rating Scale, Revised [CDRS-R]) and key secondary (Clinical Global Impression-Bipolar-Severity [CGI-BP-S]) efficacy measures (mixed model for repeated measures analysis of intent-to-treat population). Note: A) CDRS-R total score; B) CGI-BP-S score. LS = least squares.
Lurasidone in Children and Adolescents with Bipolar I Depression: Efficacy and Safety

Open Label Lamotrigine and Lithium Effective in Adolescent Bipolar Depression

Chang et al JAmAcadChildAdolPsyc 2006
N=20
Adjunctive or monotherapy lamotrigine
63% responders (at least 50% decrease in CDRS)
84% much or very much improved CGI-I

Patel et al JAmAcadChildAdolPsyc 2006
N=27
Monotherapy Lithium
48% responders (at least 50% decrease in CDRS)
Euthymic youths with bipolar disorder and ADHD may benefit from short-term concomitant treatment with methylphenidate

A 4-week double-blind, placebo-controlled trial in youths ages 5 to 17 years with bipolar disorder and ADHD, were currently receiving a stable dose of at least one thymoleptic, and while euthymic continued to have clinically significant symptoms of ADHD.

Patients received 1 week each of placebo, methylphenidate 5 mg twice daily, methylphenidate 10 mg twice daily, and methylphenidate 15 mg twice daily using a crossover design. Subjects were randomly assigned to receive one of six possible dosing orders. The primary outcome measure was the total score on the parent-completed ADHD Rating Scale-IV.

**RESULTS**

Lower scores during best dose treatment compared to the week of placebo treatment were found on the ADHD Rating Scale-IV (p < .05), suggesting a therapeutic benefit. A large effect size (Cohen's d = 0.90) was found for methylphenidate. Treatment was generally well tolerated. Rating Scale-IV.

Pediatric Bipolar Disorder Treatment Summary

• Atypical antipsychotic agents outperform traditional mood stabilizers and other anticonvulsants
• Emerging evidence to support combination pharmacotherapy or natural treatments
• Highly comorbid, so combined therapies routine
• Depression difficult to treat
International Society for Bipolar Disorders (ISBD) Review --Future Directions

Goldstein, Birmaher, Carlson, DelBello, Findling, Fristad, Kowatch, Miklowitz, Nery, Perez-Algorta, Van Meter, Hilligers, Correll, Wozniak, Kim, Chang, Zeni & Youngstrom, in revision, Bipolar Disorders

1. **New epidemiologic studies are needed**
2. **Explore international differences in prevalence, phenomenology, course, treatment and biology of BPSD**
3. **Increase use of evidence-based assessment**
4. **Explore utility of neurocognitive, neuroimaging, Internet-based, smartphone delivery methods**
5. **Improve biological interventions**
6. **Improve psychotherapies**
7. **Increase understanding of brain structure/function**
8. **Increase understanding of biomarkers/mechanism**