Severe Mood Dysregulation in Children and Adolescents
Research Findings Support Diagnostic Validity of Pediatric Bipolar Disorder

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Disclosure and Potential Conflicts

• In 2016-17, Janet Wozniak MD received no outside research support. She is author of the book, “Is Your Child Bipolar” published May 2008, Bantam Books.

• In 2016-17, her spouse received royalties from UpToDate and consultation fees from Advance Medical, FlexPharma, Merck, Otsuka and Gerson Lehman Group;
Bipolar I or II Disorder affected 2.9% of >10,000 adolescents, most with severe impairment.
<table>
<thead>
<tr>
<th>DSM-IV Disorder</th>
<th>Female</th>
<th>Male</th>
<th>13-14 y</th>
<th>15-16 y</th>
<th>17-18 y</th>
<th>Total</th>
<th>Adolescents with Severe Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mood disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depressive disorder or</td>
<td>15.9</td>
<td>7.7</td>
<td>8.4</td>
<td>12.6</td>
<td>15.4</td>
<td>11.7</td>
<td>8.7</td>
</tr>
<tr>
<td>dysthymia</td>
<td>1.3</td>
<td>0.8</td>
<td>1.3</td>
<td>1.3</td>
<td>1.4</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Bipolar I or II</strong></td>
<td>3.3</td>
<td>0.4</td>
<td>2.6</td>
<td>0.3</td>
<td>1.9</td>
<td>0.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Any mood disorder</td>
<td>18.3</td>
<td>1.4</td>
<td>10.5</td>
<td>1.1</td>
<td>10.5</td>
<td>1.3</td>
<td>14.3</td>
</tr>
<tr>
<td><strong>Anxiety disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>3.4</td>
<td>0.4</td>
<td>1.4</td>
<td>0.3</td>
<td>2.5</td>
<td>0.4</td>
<td>2.0</td>
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<tr>
<td>Generalized anxiety disorder</td>
<td>3.0</td>
<td>0.6</td>
<td>1.5</td>
<td>0.3</td>
<td>1.0</td>
<td>0.3</td>
<td>2.2</td>
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<tr>
<td>Social phobia</td>
<td>11.2</td>
<td>0.7</td>
<td>7.0</td>
<td>0.5</td>
<td>7.7</td>
<td>0.6</td>
<td>9.1</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>22.1</td>
<td>1.1</td>
<td>16.7</td>
<td>0.9</td>
<td>21.6</td>
<td>1.6</td>
<td>19.3</td>
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<tr>
<td>Panic disorder</td>
<td>2.6</td>
<td>0.3</td>
<td>2.0</td>
<td>0.3</td>
<td>1.8</td>
<td>0.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
<td>8.0</td>
<td>0.7</td>
<td>2.3</td>
<td>0.4</td>
<td>3.7</td>
<td>0.5</td>
<td>5.0</td>
</tr>
<tr>
<td>Separation anxiety disorder</td>
<td>9.0</td>
<td>0.6</td>
<td>6.3</td>
<td>0.5</td>
<td>7.8</td>
<td>0.6</td>
<td>7.6</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>38.0</td>
<td>1.4</td>
<td>26.1</td>
<td>0.8</td>
<td>31.4</td>
<td>1.9</td>
<td>31.9</td>
</tr>
<tr>
<td><strong>Behavior disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention deficit hyperactivity</td>
<td>4.2</td>
<td>0.5</td>
<td>13.0</td>
<td>1.0</td>
<td>8.8</td>
<td>0.9</td>
<td>8.7</td>
</tr>
<tr>
<td>disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oppositional defiant disorder</td>
<td>11.3</td>
<td>0.9</td>
<td>13.9</td>
<td>1.2</td>
<td>12.0</td>
<td>1.2</td>
<td>12.6</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>5.8</td>
<td>1.1</td>
<td>7.9</td>
<td>1.2</td>
<td>4.4</td>
<td>1.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Any behavior disorder</td>
<td>15.5</td>
<td>1.2</td>
<td>23.5</td>
<td>1.6</td>
<td>18.2</td>
<td>1.5</td>
<td>19.6</td>
</tr>
</tbody>
</table>

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.
“Common, transient, difficult to distinguish from ODD and CD”
Could the problem be that not all irritability is the same?

Our group has interpreted the K-SADS qualifier in the mania module of “super angry, grouchy, or cranky (or irritable) all of the time” to mean something different and more severe from the irritability in either the depression module (“mad or cranky most of the day nearly every day”) or the irritability in the oppositional defiant disorder (ODD) module (“Do you often lose your temper? Are you often angry or resentful? Is it easy to make you mad or annoy you”).
### Types of Irritability

#### Distribution of Irritability Ratings Among ADHD Probands

<table>
<thead>
<tr>
<th></th>
<th>All ADHD Subjects</th>
<th>Non-Mood Disordered</th>
<th>Unipolar Depression</th>
<th>Bipolar Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>274</td>
<td>144</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>ODD-type Irritability</td>
<td>209 (76)</td>
<td>97 (67)</td>
<td>85 (85)</td>
<td>27 (90)</td>
</tr>
<tr>
<td>Easily Annoyed</td>
<td>180 (66)</td>
<td>77 (54)</td>
<td>78 (78)</td>
<td>25 (83)</td>
</tr>
<tr>
<td>Loses Temper</td>
<td>159 (58)</td>
<td>66 (46)</td>
<td>67 (67)</td>
<td>26 (87)</td>
</tr>
<tr>
<td>Angry or Resentful</td>
<td>117 (43)</td>
<td>35 (24)</td>
<td>59 (59)</td>
<td>23 (77)</td>
</tr>
<tr>
<td>Mad / Cranky</td>
<td>103 (38)</td>
<td>24 (17)</td>
<td>55 (57)</td>
<td>24 (83)</td>
</tr>
<tr>
<td>Super Angry/Grouchy/</td>
<td>50 (18)</td>
<td>11 (8)</td>
<td>16 (16)</td>
<td>23 (77)</td>
</tr>
<tr>
<td>Cranky (Irritable)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mick et al (2005) Biological Psychiatry, 58 (7)
Irritability: 2009 COBY study findings
Pediatric-Onset Bipolar Disorder
Do children ‘look’ different?

Irritability and Fluctuating Mood States/Mixed States

Chronicity and Rapid Cycling

Developmental Distinctions in Symptoms
The most severe types of emotional dysregulation comes when mania and depression co-occur in the mixed states of bipolar disorder.

**Regular Kid** typical, some of the time

**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
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.’
MGH Study of Pediatric BPD

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  |  P = NS  |  P = NS  |  P = NS  |  P = NS
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)
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.

One of the reasons that diagnostic classification has fallen into disrepute among some psychiatrists is that diagnostic schemes have been largely based upon a priori principles rather than upon systematic studies. Such systematic studies are necessary, although they may be based upon different approaches. We have found that the approach described here facilitates the development of a valid classification in psychiatry. This paper illustrates its usefulness in schizophrenia.

The Five Phases

1. Clinical Description

In general, the first step is to describe the clinical picture of the disorder. This may be a single striking clinical feature or a combination of clinical features thought to be associated with one another. Race, sex, age at onset, precipitating factors, and other items may be used to define the clinical picture more precisely. The clinical picture thus does not include only symptoms.

2. Laboratory Studies
Is bipolar disorder different in girls?

Research report

Does sex moderate the clinical correlates of pediatric bipolar-I disorder? Results from a large controlled family-genetic study

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ABSTRACT

Background: Since little is known as to whether sex differences affect the clinical presentation of pediatric BP-I disorder, it is an area of high clinical, scientific and public health relevance.

Methods: Subjects are 239 BP-I probands (65 female probands, 174 male probands) and their 726 first-degree relatives, and 136 non-bipolar, non-ADHD control probands (37 female probands, 99 male probands) and their 411 first-degree relatives matched for age and sex. We modeled the psychiatric and
Is Pediatric Bipolar Disorder different in girls?

- Children referred to a family study of bipolar disorder
- N=239  females=65 (age 11.8)  males=174 (age 10.3)
- Age onset females 7.8±4.3 males 5.8±3.2
- Females has shorter duration mania and more episodes of depression
- Girls trended towards more panic (22% versus 11%) and substance abuse (14% vs 9%)
- Boys received more intensive academic services (42% versus 22%)

Wozniak, JAffecDis 2013
Similar rates in Males and Females with Pediatric Onset Bipolar Disorder

- Irritability 80%
- Mixed states 92%
- ADHD 77%
- Oppositional Defiant Disorder 90%
Mania Symptoms in Male and Female Probands

Increase in Activity:
Has your child shown an increased interest in sex or sexual matters?

Wozniak, JAffecDis 2013
Familial Risk of Bipolar Disorder in First Degree Relatives Stratified by Proband Sex

Overall Association: $\chi^2=45.6$, $p<0.0001$. BP-I-by-gender interaction: $z=-0.7$, $p=0.5$. Gender Effect: $z=0.5$, $p=0.6$; BP-I Effect: $z=3.7$, $p<0.001$

Wozniak, JAffecDis 2013
“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 5 Controlled Family Studies of Pediatric Bipolar Disorder

These odds ratios indicate a risk of bipolar I disorder to relatives of bipolar I probands that is 4-14 times greater than the risk to relatives of nonbipolar probands.

Figure 1. Meta-Analysis of Previous Family Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Bipolar I Probands, n</th>
<th>Age of Probands (y)</th>
<th>Relatives, n</th>
<th>OR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kutcher and Marton, 1991</td>
<td>23</td>
<td>17</td>
<td>81</td>
<td>14.26 (1.81–112.45)</td>
<td>3.21</td>
</tr>
<tr>
<td>Wozniak et al, 1995</td>
<td>16</td>
<td>≤12</td>
<td>46</td>
<td>4.56 (1.46–14.29)</td>
<td>10.49</td>
</tr>
<tr>
<td>Faraone et al, 1997</td>
<td>15</td>
<td>10.4</td>
<td>51</td>
<td>6.66 (2.49–17.78)</td>
<td>14.17</td>
</tr>
<tr>
<td>Geller et al, 2006</td>
<td>95</td>
<td>10.8</td>
<td>284</td>
<td>10.10 (5.10–19.97)</td>
<td>29.35</td>
</tr>
<tr>
<td>Wozniak et al, 2010</td>
<td>157</td>
<td>10.5</td>
<td>487</td>
<td>5.74 (3.26–10.11)</td>
<td>42.78</td>
</tr>
<tr>
<td>Overall (I² = 0.0%, P = .622)</td>
<td></td>
<td></td>
<td></td>
<td>6.96 (4.81–10.07)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Small dot indicates estimated odds ratio (OR), the size of the square surrounding the dot is proportional to the sample size, and the horizontal line indicates the 95% confidence interval (CI). Odds ratios greater than 1 indicate greater transmission of bipolar I disorder from relatives of bipolar I probands compared with control probands.

Weights are from random-effects analysis.

P < .001.

NO EVIDENCE OF HETEROGENEITY IN MAGNITUDE OF FAMILIAL TRANSMISSION

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

Proband n = 239
Relative n = 726

 bp-I  ADHD  Control

Proband n = 239  162  136
Relative n = 726  511  411

* p≤0.01 versus ADHD and controls

Wozniak J Clin Psych, 2012
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.
Persistence: Most bipolar adults in STEP-BD (N=983) reported onset in childhood or adolescence.

- About 65% of adults with onset < 18 years
- Almost a third with onset < 13 years
- 35% > 18 years
- 37% 13 to 18 years

Perlis, Miyahara, Marangell, Wisniewski, Ostacher, DelBello, Bowden, Sachs, Nierenberg, Biol Psych 2004;55:875-881
Conclusions: In grown-up subjects with child BP-I, the 44.4% frequency of manic episodes was 13 to 44 times higher than population prevalences, strongly supporting continuity.

Geller, et al, Arch Gen Psychiatry, 2008;65(10):1125-1133
Persistence of Pediatric Bipolar Disorder

Four-Year Longitudinal Course of Children and Adolescents With Bipolar Spectrum Disorders: The Course and Outcome of Bipolar Youth (COBY) Study

N=214
Bipolar I and N=169 Bipolar II and NOS, followed for 4 years with the Longitudinal Interview Follow Up Evaluation

Recurrences common
Symptomatic on average for 60% of the follow-up period
40% had symptoms during 75% of the followup period

25% of BPD II and 38% of BPD NOS converted to BPI

HIGH LEVEL OF PERSISTENCE OF PEDIATRIC BIPOLAR-I DISORDER FROM CHILDHOOD ONTO ADOLESCENT YEARS: A FOUR YEAR PROSPECTIVE

78 of 105 youth with Bipolar I disorder followed up after 3.6 years

• Baseline age 10.5 years, 76% male
• Age of onset bipolar disorder 4.9 years
• Duration of BPD at baseline 7.6 years

Wozniak et al, J Psychiatr Res, 2011
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 6.4%
Better, but Treated 9.0%

Only 5 (6.4%) subjects were better without treatment

Wozniak et al, J Psychiatr Res, 2011
Demographic characteristics of subjects with syndromatic or symptomatic remission, syndromatic persistence, and syndromatic persistence

<table>
<thead>
<tr>
<th></th>
<th>Syndromatic or Symptomatic Remission N = 13</th>
<th>Symptomatic Persistence N = 21</th>
<th>Syndromatic Persistence N = 34</th>
<th>Test Statistic</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Male)</td>
<td>10 (77)</td>
<td>14 (67)</td>
<td>27 (79)</td>
<td>$\chi^2_2 = 1.16$</td>
<td>0.56</td>
</tr>
<tr>
<td>Caucasian</td>
<td>13 (100)</td>
<td>20 (95)</td>
<td>33 (97)</td>
<td>Exact</td>
<td>1.00</td>
</tr>
<tr>
<td>Age at Baseline</td>
<td>11.5 ± 3.6</td>
<td>9.2 ± 3.5</td>
<td>9.3 ± 3.4</td>
<td>$\chi^2_2 = 5.07$</td>
<td>0.08</td>
</tr>
<tr>
<td>Age at Follow-Up</td>
<td>16.9 ± 4.2</td>
<td>14.5 ± 3.8</td>
<td>14.4 ± 3.6</td>
<td>$\chi^2_2 = 3.43$</td>
<td>0.18</td>
</tr>
<tr>
<td>SES</td>
<td>1.5 ± 1.0</td>
<td>2.0 ± 1.0</td>
<td>1.8 ± 1.0</td>
<td>$\chi^2_2 = 2.65$</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or N (%).

Wozniak, et al 2017
Persistence of DSM-IV BP-I in youth at the 5-year follow-up

Wozniak, et al 2017
If bipolar disorder exists in children, we need to worry about which children with depression have bipolar (versus unipolar) depression.
If bipolar disorder exists in children, we need to worry about which children with depression will ‘switch’
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

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

Rate per 100,000

Year 1900-2000

Bipolar adults with childhood and adolescent onset have more lifetime suicide attempts
Number of Subjects Participating in Pediatric Anti-Manic Trials

- Traditional Mood Stabilizers: n=915
- Atypical Antipsychotics: n=1474
- Other Anticonvulsants: n=244
- Naturopathic Treatments: n=71
Mean Change in YMRS from Baseline by Medication Class

<table>
<thead>
<tr>
<th>Traditional Mood Stabilizers</th>
<th>Other Anticonvulsants</th>
<th>Atypical Antipsychotics</th>
<th>Naturopathic Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>-10.99</td>
<td>-11.03</td>
<td>-16.8</td>
<td>-5.6</td>
</tr>
</tbody>
</table>
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
Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies


N=2769 11 studies

The weighted mean annual incidence of tardive dyskinesia for second-generation antipsychotics was 0% in the children, 0.8% (range=0.0%-1.5%) in the adults, 6.8% in the mixed adult and elderly population, and 5.3% (range=0.0%-13.4%) in the patients age 54 years and older, compared to 5.4% (range=4.1%-7.4%) in adults treated with haloperidol.

Results from 11 long-term studies support the idea that second-generation antipsychotics have a reduced risk for tardive dyskinesia, compared to first-generation antipsychotics. It would not appear premature for clinicians to consider these findings in making long-term treatment decisions.
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 therapeutic concentration was seen with lithium.
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
Inositol is a simple sugar isomer of glucose which is a precursor for a number of second messengers important in intracellular activity. Common in the human diet in higher amounts in beans, grains, nuts and many fruits. There is about 1 g in a healthy daily diet.

Inositol is key in the phosphatidyl inositol PI cycle part of the cell metabolism. This cycle is the second messenger system for numerous neurotransmitter receptors, including cholinergic muscarinic, alpha 1 noradrenergic, serotonin (5-HT2A and 5-HT2C) and dopaminergic D1 receptors.

Low inositol levels found in the CSF of depressed patients.

Lithium and antiepileptic mood stabilizing medications affect inositol uptake suggesting that stable inositol signaling may be crucial in mood stability.
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, MDa,b; Stephen V. Faraone, PhDc; James Chan, MAd; Laura Tarko, MPHa; Mariely Hernandez, MAg; Jacqueline Davis, BAg; K. Yvonne Woodworth, BAg; and Joseph Biederman, MDa,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.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 for new treatment options.
ANTI-MANIC RESPONSE TO TREATMENT

The combined treatment of omega-3s and inositol outperformed either treatment used alone for mania.
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</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>
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<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>
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<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).
Treat Comorbid disorders

• Depression
  – Lithium, lamotrigine, lurasidone, or bupropion
  – Avoid SSRI’s

• ADHD
  – Stimulant after mood stabilized

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
Future Research Questions

• Studies of young children < 12 years old and preschoolers
• Combination pharmacotherapy trials
• Pharmacotherapy of comorbid disorders
  – ADHD
  – Depression
  – OCD
• Psychosocial treatment