Pediatric Bipolar Disorder and Mood Disorders

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

For Janet Wozniak MD

*Research support*: PCORI


*Spouse royalties*: UpToDate

*Spouse consultation fees*: Advance Medical, Gerson Lehman Group, Springer Healthcare

*Spouse research support*: Merck, RLS Foundation
Pediatric bipolar disorder

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Director, Pediatric Bipolar Disorder Research Program
Associate Professor of Psychiatry
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Rising Rates of Pediatric Bipolar Disorder

![Graph showing rising rates of bipolar disorder in children and adults from 1994 to present.](image_url)
**Overview:** Pediatric Bipolar disorder is a highly morbid, valid condition that affects a significant minority of young children and is often comorbid with ADHD.

**Diagnosis:** Pediatric Bipolar Disorder is now in the differential diagnosis for moody children, can be reliably diagnosed and is often mixed and irritable and comorbid with ADHD.

**Persistence and Familiality:** Pediatric onset of bipolar disorder is familial and persists over time.

**Treatment:** Pharmacologic treatment is generally required, SGAs are the first line of treatment and comorbid conditions can be treated and complementary treatments hold promise.

**Biomarkers:** We have progress towards objective identification with rating scale and biomarkers.
Bipolar disorder is now considered in the differential diagnosis of youngsters with mood symptoms. Consecutively referred children < 12 years:

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

MGH clinical studies using structured interview diagnoses (KSADS) led a paradigm shift. Wozniak, 1995; Biederman, 2004
The symptoms of mania are the same in children and adults with presentations appropriate to developmental stage

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

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

Diagnostic and Statistical Manual (DSM-5)
What we learned about children with mania:

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

**MIXED**
- The children had mostly mixed states (mania and depression overlapped in time)

**CHRONIC**
- The children were seldom well due to mixed states, many cycles and comorbidity (chronicity)

Wozniak, 1995; Biederman, 2004
What we learned about children with mania:

<table>
<thead>
<tr>
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<td>ADHD</td>
<td>Almost all of them had ADHD (especially when the onset of mania was prior to age 12)</td>
</tr>
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</table>

Wozniak, 1995; Biederman, 2004
Despite a substantial bi-directional overlap, bipolar disorder is a different more impairing condition from ADHD alone.

<table>
<thead>
<tr>
<th></th>
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<tr>
<td>Depression</td>
<td>86%</td>
<td>38%</td>
</tr>
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<td>16%</td>
<td>0</td>
</tr>
<tr>
<td>Defiance (ODD)</td>
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<tr>
<td>Functioning</td>
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<td>fair</td>
</tr>
<tr>
<td>Learning Disability</td>
<td>42%</td>
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Most young children with bipolar disorder also have comorbid ADHD.

Wozniak, 1995; Biederman, 2004
Despite a substantial bi-directional overlap, bipolar disorder is a different more impairing condition from ADHD alone.

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Most children with bipolar disorder also have comorbid ADHD.

Wozniak, 1995; Biederman, 2004
Pediatric bipolar disorder often co-occurs and overlaps with ADHD, but requires mood symptoms to diagnose.

There are overlapping symptoms between ADHD and BPD:

- **Distractibility** very severe in bipolar disorder
- **Hyperactivity** vs. increased energy/activity in bipolar disorder
- **Talkativeness** vs. pressured speech in bipolar disorder
- **Bipolar disorder requires severe mood symptoms** euphoria/irritability/melancholy

Biederman JAACAP 1996
ADHD+bipolar disorder occurs in adults: Adults with ADHD have higher rates of bipolar disorder than adults without ADHD

The National Epidemiologic Survey on Alcohol and Related Conditions

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

The National Comorbidity Survey Replication

N=3199 adults
4.4% ADHD
19% with ADHD had bipolar disorder versus 3% without ADHD

In study of 10,000+ US adolescents, 2.9% were bipolar and in a meta-analysis of international studies, the rate of pediatric bipolar disorder was 1.8%.

Despite the rise in rate, pediatric bipolar disorder affects a minority of youth and ADHD is more common (8.7%).

Merikangas 2010: Van Meter J Clin Psych 2011
A new disorder was created called Disruptive Mood Dysregulation Disorder to ‘decrease the # bipolar diagnoses’
DMDD is “common, transient, difficult to distinguish from ODD and CD

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

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

Conclusions: In this clinical sample, DMDD could not be delimit 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.

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

Exclusionary:
Euphoria for 1+ day with 3/7 B criteria
During MDD episode
History of (hypo)mania
A framework for the validation of psychiatric disorders can be applied to pediatric bipolar disorder

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

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

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

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

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

This work was supported in part by Public Health Service grants MH-13002 and MH-57081 from the National Institute of Mental Health.

Amer. J. Psychiat. 126:7, January 1970

1. Unique Clinical characteristics
2. Familiality
3. Course (persistence)
4. Unique Pharmacological Responsivity
5. Laboratory Studies
The symptoms of mania are the same in two cohorts of pre-adolescent age (<12 years) youth with bipolar disorder.

- **1991-1995**
  - N=43
  - Age at presentation: 8 years
  - Age of onset: 4.5 years
  - Duration of illness: >3 years

- **1995-2002**
  - N=129

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

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

Wozniak, 1995; Biederman, 2004
Irritability lasting “7 days or longer most of the day most every day” is more common than euphoria in BPD Youth.

Wozniak, 1995; Biederman, 2004
The type of irritability observed in manic children is very severe, persistent and often violent.

- Outbursts often include threatening or attacking behavior towards others: kicking, hitting, biting, spitting, swearing, disrespectful, wild, out of control, destructive *explosions*.

- Outbursts are frequent often daily and long lasting, 30-60+ minutes.
All forms of irritability are not the same but can co-exist and overlap, creating a ‘never well’ condition.
Mixed presentations are common

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

Wozniak, 1995; Biederman, 2004
Pediatric bipolar disorder is familial, a feature of a valid diagnosis

Familial risk of bipolar I disorder is greatest in first-degree relatives of pediatric BP-I probands versus ADHD and control probands

Wozniak J Clin Psych 2012

Bipolar I probands
239 probands
726 relatives

ADHD
162 probands
511 relatives

Neither
136 probands
411 relatives

*p<0.01 versus ADHD and controls
Pediatric bipolar disorder is familial, a feature of a valid diagnosis

Familial risk of bipolar I disorder is greatest in first-degree relatives of pediatric BP-I probands versus ADHD and control probands

Pediatric probands with subthreshold bipolar disorder have rates of familiality similar to full syndrome probands

<table>
<thead>
<tr>
<th>Bipolar disorder in first-degree relatives</th>
<th>Morbid risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar I probands</td>
<td>14</td>
</tr>
<tr>
<td>ADHD</td>
<td>6</td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
</tr>
</tbody>
</table>

- 239 probands
- 162 probands
- 136 probands

- 726 relatives
- 511 relatives
- 411 relatives

*P < 0.01 versus ADHD and controls

Wozniak J Clin Psych 2012
Pediatric bipolar disorder is highly persistent in our 4-year MGH longitudinal study and few improved without treatment.

N=78
Baseline age 10 years
76% male
Age of onset Bipolar Disorder 5 years

73% continue with Bipolar I

persistent

non-persistent (improved)
6% euthymic
9% euthymic, treated
5% depressed
6% symptoms of mania
Pediatric bipolar disorder is highly persistent in our 4-year MGH longitudinal study and few improved without treatment

N=78, Baseline age 10 years, 76% male, Age of onset 5 years

73% continue with Bipolar I

Non-persistent (improved)
- 6% euthymic
- 9% euthymic, treated
- 5% depressed
- 6% symptoms of mania

Consistent with longitudinal studies by Geller (WashU) and Birmaher (COBY)

Wozniak JPsychiatrRes 2011; Geller ArchGenPsychiatry 2008; Birmaher AmJPsychiatry 2009
BP-I disorder continues to persist at 5 year follow-up

**EUTHYMIC-Remission of syndrome and symptoms**

**PERSISTENT-full BP-I**

Partial remission-ST mania and full/ST MDD
Most bipolar adults in STEP-BD (N=983) reported onset in childhood or adolescence demonstrating continuity

Age of onset of bipolar disorder for bipolar adults

- > 18 years: 35%
- < 13 years: 28%
- 13 to 18 years: 37%

9.5% lifetime prevalence comorbid ADHD

BPD+ADHD Adult patients:
- had earlier onset BPD by 5 years
- had shorter periods of wellness (chronic)
- had more comorbidity (anxiety and substance)
- were more likely to be male
- were more likely to have Bipolar I
- had more days irritable and more days elated
- had lower GAF
- more suicide attempts
- more violence
- more legal problems (conduct disorder)

Perlis  Biol Psych 2004; Nierenberg 2005
We have many FDA approved treatments for youth with emotional dysregulation

Lithium: manic or mixed states, patients age 13-17
Risperidone: manic or mixed states, age 10-17
Aripiprazole: manic or mixed states, age 10-17
Olanzapine: manic or mixed states, age 13-17
Quetiapine: monotherapy or adjunct to lithium or divalproex sodium, manic states, age 10-17
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 age 6-17
Risperidone: irritability associated with autism age 5-16
The risk-benefit analysis of treatment must include the risks associated with not treating Bipolar Disorder.
Delaying treatment could lead to worse outcomes

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 respectively 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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The algorithm for pediatric bipolar disorder pharmacologic treatment is general

Stage 1 – monotherapy +/- augmentation

Stage 2 – switch monotherapy agent

Stage 3 – combination mood stabilizer + SGA
  (Or switch monotherapy agent)

Stage 4 – combination
  1 mood stabilizer + SGA
  2 mood stabilizers + SGA

Stage 5 – alternate monotherapy

Stage 6 – ECT vs. Clozapine

SGA=second generation antipsychotic
Pediatric bipolar disorder is difficult to treat

50% of adults and adolescents with mania require augmentation with another agent/combination therapy

Kowatch 2003, 2005
Many subjects have participated in pediatric anti-manic trials.
The mean decrease in YMRS in pediatric studies is much greater for the SGAs than for other agents.

SGAs are more effective than placebo in available trials:
- Perform well in open label – 80+%
- Mean response rate of ~60% drug vs. 20-30% placebo
- Mean decrease in YMRS ranged from 14.2 to 18.5 in medication group vs. 8.2 to 9.99 for placebo
- Relatively rapid response, relatively well tolerated

SGA = second generation antipsychotic

Liu JAACAP 2011
### Response Rates (50%+ decrease in YMRS) Open Label Trials

**YMRS=Young Mania Rating Scale**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>70%</td>
</tr>
<tr>
<td>Risperidone</td>
<td>52%</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>51%</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>45%</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>33%</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>22%</td>
</tr>
<tr>
<td>Omega-3</td>
<td>35%</td>
</tr>
</tbody>
</table>
SGAs are a robust treatment for adults with bipolar disorder

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

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

Data Synthesis: Data from 12 placebo-controlled monotherapy and 6 placebo-controlled adjunctive therapy trials involving a total of 4,249 patients (including 1,750 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.
Tardive dyskinesia is dreaded, but low risk (although data limited by small sample sizes, low doses and limited durations)

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

- 0% children
- 0.8% adult
- 6.8% adult and elderly

- N=2769
- 11 studies
- 1+year

There is a lower risk for tardive dyskinesia associated with SGAs versus first generation antipsychotics.
Unfortunate weight gain noted in 8-week open label trials of SGA monotherapy in children with bipolar disorder.

SGA = second generation antipsychotic

![Line graph showing weight change over 8 weeks for olanzapine, quetiapine, risperidone, aripiprazole, and ziprasidone.](image)

Biederman 2007 AACAP Boston

Parallel trials
Total N=116
Weight gain associated with SGA medications in children and adolescents: Data from 34 studies

- Olanzapine (n=353): 3.8 to 16.2 kg
- Clozapine (n=97): 0.9 to 9.5 kg
- Risperidone (n=571): 1.9 to 7.2 kg
- Quetiapine (n=133): 2.3 to 6.1 kg
- Aripiprazole (n=451): 0 to 4.4 kg

SGA = second generation antipsychotic

Correll JChildAdolescPsychopharm 2011
Lithium, divalproex sodium, carbamazepine can be used for pediatric bipolar disorder but are not as effective as SGAs.

**Response Rates Fair**

<table>
<thead>
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<td>Lithium</td>
<td>38%</td>
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<tr>
<td>Carbamazepine</td>
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Trials notable for:
- high drop out rates
- need for rescue medications

SGA = second generation antipsychotic

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

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

Robert L. Findling, MD, MBA; Adelaide Robb, MD; Nora K. McNamara, MD; Mani N. Pavuluri, MD, PhD; Vivian Kafantaris, MD; Russell Scheffer, MD; Jean A. Frazier, MD; Moira Rynn, MD; Melissa DelBello, MD; Robert A. Kowatch, MD, PhD; Brianna M. Rowles, MA; Jacquie Lingler, BS; Karen Martz, MS; Ravinder Anand, PhD; Traci E. Clemona, 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 in YMRS score.

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 serum lithium concentration was seen with lithium.

47% lithium vs 21% placebo “much/very much improved”
SGAs perform better than valproate for pediatric bipolar disorder

SGA=second generation antipsychotic

3 double blind RCTs
1 chart review

valproate versus second generation antipsychotics

more rapid onset of effect

greater reduction of manic symptoms

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

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

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

Comparative risk of psychiatric hospital admission
186 days

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

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

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

Chen 2014
Newer mood stabilizers hold promise for the treatment of mania in children with bipolar disorder

Prospective open-label trial of lamotrigine monotherapy

Prospective open-label trial of extended-release carbamazepine monotherapy

Joshi 2010
Comorbidity must be addressed in addition to mania

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

- **Anxiety**
  - Avoid SSRIs

- **ADHD**
  - Employ stimulant after mood stabilized

Joshi 2009
Euthymic youths with bipolar disorder and ADHD may benefit from concomitant treatment with methylphenidate

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

- Anti-manic medication
  - Euthymic
  - Clinically significant symptoms of ADHD

- 1 week each of placebo methylphenidate
  - 5 mg BID
  - 10 mg BID
  - 15 mg BID

- Crossover design randomly assigned to one of six possible dosing orders

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

Fully mood stabilized, low dose stimulant, short term
Amphetamine Salts provided therapeutic benefit versus placebo in a double-blind crossover trial of pediatric bipolar disorder and ADHD

 Fully mood stabilized, low dose stimulant, short term

Scheffer 2005
Treatment of ADHD in patients with bipolar disorder is feasible in the context of anti-manic treatment

Determine the risk of treatment-emergent mania associated with methylphenidate in patients with bipolar disorder

Swedish national registries 2006-14
N=2,307
Adults with bipolar disorder who initiated therapy with methylphenidate

TWO GROUPS
Those WITH concomitant mood-stabilizing treatment
Those WITHOUT concomitant mood-stabilizing treatment

Treatment emergent mania:
Hospitalization
New mood stabilizing medication

No association between methylphenidate and treatment-emergent mania among bipolar patients who were concomitantly receiving a mood-stabilizing medication

Rule out bipolar disorder before initiating methylphenidate as a monotherapy

Viktorin 2017
Treatment for bipolar disorder involves antipsychotic medications with side effects, fueling reluctance to diagnose.

Traditional antidepressants should be avoided ... treatment with a combination of atypical antipsychotics and mood stabilizers is best.

Mixed Specifier for Bipolar Mania and Depression: Highlights of DSM-5 Changes and Implications for Diagnosis and Treatment in Primary Care

Jia Hu, MD, Rodrigo Mansur, MD, and Roger S. McIntyre, MD

Abstract

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 removes this specification, allowing patients who have either mania or depression with some symptoms of the opposite mood to be diagnosed as having a mixed state.

Clinical Points

- 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.
N-acetylcysteine currently in testing for pediatric bipolar disorder is a safe alternative.

Complementary and alternative treatments may be especially useful for the earliest symptoms and the youngest children.
This positive result for omega-3 fatty acids is about 50% what we see with antipsychotics, but without the side effects.

Omega-3 fatty acid monotherapy for pediatric bipolar disorder: A prospective open-label trial

Janet Wozniak, Joseph Biederman, Eric Michel, James Waxmonsky, Liisa Hantsoo, Catherine Berretti, Joanne E. Gruette-Brown, Michael Laposa

Received 9 June 2006; received in revised form 21 November 2006; accepted 29 N

Keywords
Pediatric; Mania; Bipolar disorder; Treatment; (Omega-3) fatty acid; Children

Abstract
Background: To test the effectiveness and safety of the treatment of pediatric bipolar disorder (BDP). Method: Subjects (N=10) were ambulations of both diagnosis of BDP and Young Mania Rating Scale (YMRS). In open-label trial with omega-3 fatty acids (DHA and EPA) versus placebo. Results: Subjects experienced a statistically significant YMRS score (baseline YMRS=26.9 ± 10.1) and events were few and mild. Red blood cell membrane

Keywords
Wozniak, European Neuropsychopharmacology, 2007
A novel study design of very young children allows all to receive treatment, but randomized and treated blindly.

**Funding/support:** This study was supported by a generous philanthropic donation from Kent and Elizabeth Dauten (Chicago, Illinois).
The combined treatment of omega-3s and inositol outperformed either treatment used alone for mania
The combined treatment of omega-3s and inositol outperformed either agent used alone for depression.
The next generation of clinical trials can use technology to improve recruitment and access to care

Recruitment for clinical trials is difficult due to the burden of many in-person visits

Practical Issues in Delivery of Clinician-to-Patient Telemental Health in an Academic Medical Center


Background: In the age of online communication, psychiatric care can now be provided via videoconferencing technologies. While virtual visits as a part of telepsychiatry and telemental health provide a highly efficient and beneficial modality of care, the implementation of virtual visits requires attention to quality and safety issues. As practitioners continue to utilize this technology, issues of clinician licensing, treatment outcomes of virtual versus in-person visits, and cost offset require ongoing study.

Results: The technological, legal, and regulatory issues vary from state to state and over time. The emerging research addressing diverse populations and disorders provides strong evidence for the effectiveness of telepsychiatry. Cost savings are difficult to precisely determine and depend on the scope of the cost and benefit measured.

Conclusion: Establishing a telepsychiatry program requires a comprehensive approach with up-to-date legal and technological considerations.

Keywords: technology, telemedicine, standards, telemental health, telepsychiatry, videoconferencing

Abrams...Wozniak, Harvard Review of Psych, 2017
Recruitment for clinical trials is difficult due to the burden of many rating scales and clinical interviews. The next generation of clinical trials can take advantage of advances in evidence-based assessments to improve identification and participation in research.
Unique Markers/ Biomarkers external to clinician diagnosis?
Given disputes in diagnosis, the MGH group has published extensively on the utility of the CBCL in assisting with the identification of bipolar disorder in youth.

Certain CBCL scores are associated with a diagnosis of pediatric bipolar disorder.
The Child Behavior Checklist is a parent completed rating scale that is easy to administer and score. Parents score choosing from Likert scale responses:

- 0 = not true
- 1 = somewhat or sometimes true
- 2 = very true or often true

The 120 statements are grouped into 8 subscales or syndrome scales:

1. Acts too young for his/her age
2. Drinks alcohol without parents approval
3. Argues a lot
4. Fails to finish things he/she starts
5. ……..

There is a list of items that describe children and youths. For each item that describes your child now or within the past months, please circle the 2 if the item is very true or often true of your child. Circle the 1 if the item is somewhat or sometimes true of your child. Circle the 0 if the item is not true of your child.

Below is a list of items that describe children and youths. For each item that describes your child now or within the past months, please circle the 2 if the item is very true or often true of your child. Circle the 1 if the item is somewhat or sometimes true of your child. Circle the 0 if the item is not true of your child.

Parents should answer all items as well as you can, even if some items do not seem to apply to your child.
The CBCL can be a useful screening tool for pediatric bipolar disorder with highest scores found on Aggression, Anxious/depressed and Attention scales.

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

Biederman JAACAP 1995

Child Behavior Checklist T-Scores

* p<0.01 Bipolar vs. ADHD
ROC analyses demonstrates usefulness of CBCL in identifying bipolar youth from controls and ADHD.

**BP-I probands & Controls**
- CBCL Scores $\geq$210:
  - Sensitivity: 57%
  - Specificity: 99.2%
  - Positive Predictive Value: 99%
  - Negative Predictive Value: 66%
  - Area Under the Curve: 99%

**BP-I probands & ADHD probands**
- CBCL Scores $\geq$210:
  - Sensitivity: 57%
  - Specificity: 92%
  - Positive Predictive Value: 92%
  - Negative Predictive Value: 56%
  - Area Under the Curve: 85%
Increased emotional dysregulation is associated with elevated glutamate in the anterior cingulate cortex in pediatric bipolar disorder.

Glutamatergic dysregulation in the ACC may represent a useful biomarker of emotional dysregulation in youth worthy of further investigation.

The CBCL is a useful tool for providing a continuous measure of emotional dysregulation for correlation with biomarkers.

Proton magnetic resonance spectroscopy (H-MRS) is an imaging technique that can quantify biochemical compounds in the brain.

Moore 2006; Wozniak 2011
Elevated glutamate in the anterior cingulate cortex

Glutamatergic dysregulation in the ACC may represent a useful biomarker of emotional dysregulation in youth worthy of further investigation.

The CBCL is a useful tool for providing a continuous measure of emotional dysregulation for correlation with biomarkers.
Greater severity emotional dysregulation is associated with more impaired matter abnormalities in the cingulum bundle (increased diffusivity)

**Diffusion tensor imaging (DTI)** is a magnetic resonance imaging technique measuring the diffusion of water in tissue in order to produce neural tract images.

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

- Findings indicate that greater severity the emotional dysregulation as indexed through the CBCL-ED profile is associated with more impaired matter abnormalities in the cingulum bundle areas as indexed through mean diffusivity and axial diffusivity values.

Uchida 2018
Converging evidence from GWAS supports the notion that bipolar + ADHD is an early onset genetic subtype.

Early onset bipolar disorder (with high rates of ADHD) may be caused by a different genetics than later onset forms of the disorder.
Overview: Pediatric Bipolar disorder is a highly morbid, valid condition that affects a significant minority of young children and is often comorbid with ADHD

Diagnosis: Pediatric Bipolar Disorder is now in the differential diagnosis for moody children, can be reliably diagnosed and is often mixed and irritable and comorbid with ADHD

Persistence and Familiality: Pediatric onset of bipolar disorder is familial and persists over time.

Treatment: Pharmacologic treatment is generally required, SGAs are the first line of treatment and complementary treatments hold promise

Biomarkers: We have progress towards objective identification with rating scale and biomarkers