Pharmacological Approaches to Pediatric Mania

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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, FlexPharma, Merck, Otsuka and Gerson Lehman Group

- **Spouse research support**: RLS Foundation
Pediatric Bipolar Disorder: Advances in Treatment for Clinical Practice

Janet Wozniak, MD
Director, Pediatric Bipolar Disorder Research Program
Associate Professor of Psychiatry
Harvard Medical School
Massachusetts General Hospital

Increasing numbers of treatment trials

- Traditional Mood Stabilizers: n=915
- Atypical Antipsychotics: n=1474
- Other Anticonvulsants: n=244
- Naturopathic Treatments: n=71
**Overview:** Pediatric Bipolar disorder is a highly morbid condition that usually requires pharmacologic treatment due to severity of illness. SGA’s are the first line of treatment and comorbid conditions usually must be addressed.

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

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

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

**Natural Treatments:** Complementary and alternative treatments hold promise for safe treatment and prevention.
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)
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

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 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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Not treating is not an option due to the severity of symptoms associated with early onset bipolar disorder.
20TH-CENTURY - RISING RATE OF SUICIDE IN YOUTH
UNITED STATES, AGES 15–24

Bipolar adults with pediatric onset have more lifetime suicide attempts

Year 1900-2000

BOYS
5X AS MANY COMPLETED SUICIDES

GIRLS
3X AS MANY ATTEMPTS
The algorithm for pediatric bipolar disorder pharmacologic treatment is general

Stage I – 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

Kowatch JAACAP 2005
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

- Atypical Antipsychotics: n=1474
- Traditional Mood Stabilizers: n=915
- Other Anticonvulsants: n=244
- Naturopathic Treatments: n=71
The mean decrease in YMRS in pediatric studies is much greater for the SGAs than for other agents.

SGA=second generation antipsychotic

Liu JAACAP 2011

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
Response Rates (50%+ decrease in YMRS) Open Label Trials

YMRS=Young Mania Rating Scale

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Liu JAACAP 2011;50(8):749-762
Response Rates (50%+ decrease in YMRS) Open Label Trials

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| Subtotal                   |               |

| Naturopathic Treatments    |               |
| Wozniak et al. (2007)      | Omega-3       |
| Subtotal                   |               |

| Overall                    |               |

- **aripiprazole 70%**
- **risperidone 52%**
- **olanzapine 51%**
- **quetiapine 45%**
Response Rates (50%+ decrease in YMRS) Open Label Trials

- Aripiprazole 70%
- Risperidone 52%
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- Quetiapine 45%
- Ziprasidone 33%
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Liu JAACAP 2011;50(8):749-762
Response Rates (50%+ decrease in YMRS) Open Label Trials

- Aripiprazole 70%
- Risperidone 52%
- Olanzapine 51%
- Quetiapine 45%
- Ziprasidone 33%

- Valproic acid 22%
- Omega-3 35%

Liu JAACAP 2011;50(8):749-762
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 45 trials (involving 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.
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

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

- N=2769
- 11 studies
- 1+year

Correll AmJPsych 2004
Unfortunate weight gain noted in 8-week open label trials of SGA monotherapy in children with bipolar disorder

SGA=second generation antipsychotic

Parallel trials
Total N=116

Biederman 2007 AACAP Boston

www.mghcme.org
Weight gain associated with SGA medications in children and adolescents: Data from 34 studies

SGA=second generation antipsychotic

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

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

SGA = second generation antipsychotic

**RESPONSE RATES FAIR**

- **Divalproex sodium**: 53%
- **Lithium**: 38%
- **Carbamazepine**: 38%

Trials notable for:
- High drop out rates
- Need for rescue medications

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, 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.

**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.

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

greater reduction of manic symptoms
more rapid onset of effect

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

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

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

Comparable risk of psychiatric hospital admission 186 days

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

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

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

SGA=second generation antipsychotic

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
Depression
- Lithium, Lamotrigine, Lurasidone
- Avoid SSRIs

Anxiety
- Avoid SSRIs

ADHD
- Employ stimulant after mood stabilized

Comorbidity must be addressed in addition to mania

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

4-week double-blind placebo-controlled trial for ages 5-17 years old with bipolar disorder and ADHD.

Anti-manic medication is administered to euthymic patients with clinically significant symptoms of ADHD.

1 week each of placebo methylphenidate at 5 mg BID, 10 mg BID, and 15 mg BID.

Crossover design randomly assigns one of six possible dosing orders.

Therapeutic benefit is measured by lower ADHD Rating Scale scores during the best dose treatment vs placebo.

Findling 2007
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

Findling 2007
Amphetamine Salts provided therapeutic benefit versus placebo in a double-blind crossover trial of pediatric bipolar disorder and ADHD.
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

p<0.001
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

Viktorin 2017
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.
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.

STUDY OF A NATURAL TREATMENT FOR YOUNG PEOPLE WITH BIPOLAR DISORDER
This positive result for omega-3 fatty acids is about 50% what we see with antipsychotics, but without the side effects.
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).

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**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<sup>a</sup><sup>,b</sup>; Stephen V. Faraone, PhD<sup>c</sup>; James Chan, MA<sup>a</sup>; Laura Tarko, MPH<sup>a</sup>; Mariely Hernandez, MA<sup>a</sup>; Jacqueline Davis, BA<sup>a</sup>; K. Yvonne Woodworth, BA<sup>a</sup>; and Joseph Biederman, MD<sup>a</sup><sup>,b</sup><sup>,</sup><sup>*</sup>

**Abstract**

**Objective:** We conducted a 12-week, double-blind, randomized, placebo-controlled, parallel-group study of high eicosapentaenoic acid 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. 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 frequent 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 efficacy while limiting potentially harmful side effects.

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**Advances in safe biologic treatments will encourage early identification**
The combined treatment of omega-3s and inositol outperformed either treatment used alone for mania.

Wozniak, J Clinical Psychiatry 2015
The combined treatment of omega-3s and inositol outperformed either agent used alone for depression.
Recruitment for clinical trials is difficult due to the burden of many in-person visits.

The next generation of clinical trials can use technology to improve recruitment and access to care.

**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 telespsychiatry 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 visits 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 telespsychiatry. Cost savings are difficult to precisely determine and depend on the scope of the cost and benefit measured.

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

**Keywords:** technology, telemental health, telespsychiatry, 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.
**Overview:** Pediatric Bipolar disorder is a highly morbid condition that usually requires pharmacologic treatment due to severity of illness. SGAs are the first line of treatment and comorbid conditions usually must be addressed.

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

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

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

**Natural Treatments:** Complementary and alternative treatments hold promise for safe treatment and prevention.

What questions would you like to ask?