Pediatric Bipolar Disorder: Advances in Treatment for Clinical Practice

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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
Can we wait?

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

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

Atypical Antipsychotics
n=1474

Traditional Mood Stabilizers
n=915

Other Anticonvulsants
n=244

Naturopathic Treatments
n=71

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

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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 \((5.51 [95\% \text{ confidence interval: } 0.51 \text{ to } 10.50])\) after adjustment for baseline YMRS score, age group, weight group, gender, and study site \((P = .03)\). Overall Clinical Global Impression–Improvement scores favored lithium \((n = 25; 47\% \text{ very much/much improved})\) compared with placebo \((n = 6; 21\% \text{ very much/much improved})\) at week 8/ET \((P = .03)\).

* A statistically significant increase in thyrotropin 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
Comorbid disorders

• Depression
  – Lithium, Lamotrigine, Lurasidone (or bupropion)
  – Avoid SSRI’s

• ADHD
  --Stimulant after mood stabilized

• Anxiety

Quetiapine **not** effective in Adolescent Bipolar Depression

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

* ***P<0.001 vs baseline*

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.

The Risk of Treatment-Emergent Mania With Methylphenidate in Bipolar Disorder

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American Journal of Psychiatry, 2017
• Bipolar disorder and ADHD commonly co-occur, where comorbid ADHD has been observed in up to 20% of patients with bipolar disorder
  – Evidence suggests that co-occurrence of these disorders is associated with a worse illness course than either disorder alone
• There is a high rate of nonresponse and residual functional impairment in comorbid ADHD and bipolar disorder
• Treatment for bipolar disorder may worsen ADHD symptoms, and clinicians have long worried that methylphenidate and other psychostimulants may also induce mania or even provoke psychosis
• Controlled studies and treatment guidelines are lacking regarding the efficacy and safety of psychostimulants with comorbid ADHD and bipolar disorder (especially in adults).
Objectives

The authors sought to determine the risk of treatment-emergent mania associated with methylphenidate, used in monotherapy or with a concomitant mood-stabilizing medication, in patients with bipolar disorder.
Methods

• Using linked Swedish national registries, the authors identified 2,307 adults with bipolar disorder who initiated therapy with methylphenidate between 2006 and 2014.

• The cohort was divided into two groups: those with and those without concomitant mood-stabilizing treatment.

• Treatment emergent mania defined as hospitalization for mania or a new dispensation of stabilizing medication.
Conclusions

• Methylphenidate may be associated with treatment-emergent mania in patients on methylphenidate monotherapy, but no evidence was found for a positive association between methylphenidate and treatment-emergent mania among bipolar patients who were concomitantly receiving a mood-stabilizing medication.

• On the basis of this finding, we recommend careful assessment to rule out bipolar disorder before initiating methylphenidate as a monotherapy.

• Concomitant therapy of ADHD is likely both safe and feasible in the context of ongoing preventive therapy.
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