

What's the best treatment for comorbid ADHD/bipolar mania?

How to stabilize mood without worsening ADHD symptoms



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Comorbid attention-deficit/hyperactivity disorder (ADHD) is nearly universal in youths with bipolar disorder (BPD),¹ and comorbid mania has been noted in 16% of children with ADHD.² Choosing medication for these complex patients is difficult because psychostimulants may worsen mania and mood stabilizers may not resolve ADHD symptoms. Yet, very little information exists on combining psychostimulants with mood stabilizers or atypical antipsychotics.

This article offers evidence to help you decide:

- which to treat first—ADHD or BPD
- how to individualize combination therapy.

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CHALLENGES OF COMORBIDITY

Differential diagnosis. ADHD and bipolar disorder (BPD) symptoms overlap, and experts disagree on which symptoms indicate co-existing ADHD and BPD. Multiple daily mood swings and irritability are commonly found in prepubertal BPD.³ Recent reviews address differential diagnosis and specific assessment tools;³⁻⁵ after careful evaluation, then focus on treatment.

Treating comorbid ADHD and BPD usually requires more than one medication, and use of multiple drugs in children and adolescents is becoming increasingly common.^{6,7}

PSYCHOSTIMULANTS AND MOOD STABILIZERS

Small, uncontrolled studies of children and adolescents with comorbid ADHD and BPD have shown that treatment with a mood stabilizer and a psychostimulant can control both sets of symptoms. For example:

- Lithium (serum levels 0.7 to 1.1 mEq/L) plus methylphenidate (10 to 20 mg/d) improved attention and hyperactivity symptoms more effectively than either agent alone in 7 children (6 boys, 1 girl) ages 6 to 10 hospitalized with disruptive behavioral disorders and BPD or major depression.⁸
- A retrospective analysis of 38 children (ages 3 to 16; 84% male) with BPD found that ADHD symptoms were 7.5 times more likely to improve if mood was stabilized before rather than after ADHD treatment with tricyclic antidepressants.⁹

The efficacy of combining a mood stabilizer and psychostimulant has been confirmed by only one controlled study—a randomized, placebo-controlled trial of mixed amphetamine salts in divalproex-treated patients.¹⁰ Forty patients (ages 6 to 17; 83% male) with BPD and ADHD received open-label divalproex (median dosage 750 mg/d) for 8 weeks. Thirty patients whose manic symptoms were significantly reduced entered a 4-week, dou-

ble-blind, crossover trial of mixed amphetamine salts, 10 mg/d, or placebo.

Following this double-blind phase, 23 patients received open-label divalproex plus mixed amphetamine salts for 12 weeks. The Young Mania Rating Scale and Clinical Global Impression-Improvement scale were used to assess manic and ADHD symptoms during all three study phases.

Manic symptoms in patients treated with divalproex monotherapy improved significantly, but ADHD symptoms did not. ADHD symptoms improved more with divalproex plus mixed amphetamine salts than with divalproex plus placebo. One patient experienced manic symptom exacerbation with combination therapy.

Treating comorbid ADHD and bipolar disorder usually requires more than one medication

PSYCHOSTIMULANTS AND ANTIPSYCHOTICS

Combinations of psychostimulants and atypical antipsychotics are commonly used in children and adolescents with comorbid psychiatric and behavioral disorders, such as ADHD and disruptive behavioral disorders (oppositional defiant disorder, conduct disorder). In 78 children ages 5 to 12 (83% male) with comorbid ADHD and a disruptive behavioral disorder, disruptive behavior and hyperactivity improved significantly with risperidone alone or with a psychostimulant.¹¹

Combined psychostimulant/atypical antipsychotic therapy may help youths with comorbid ADHD and Tourette syndrome. Methylphenidate can reduce ADHD symptoms without exacerbating tics,¹² and risperidone can treat tic disorders, even in patients with comorbid ADHD.^{13,14} No controlled trials have examined psychostimulant and atypical antipsychotic combinations in these patients, however.

Atypical antipsychotics have been shown to be effective in treating adult BPD, and limited data suggest the same to be true in pediatric patients.

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Table 1

Atypical antipsychotic studies in pediatric bipolar disorder

Drug and mean dosage	Study design	Sample characteristics	Efficacy measures	Results
Olanzapine ¹⁵ 9.6±4.3 mg/d	8-week, open-label monotherapy	23 patients, mean age 10±3 yrs, 57% male	≥30% decrease on YMRS	Response rate 61%
Quetiapine ¹⁶ 432 mg/d	6-week, randomized, placebo-controlled, adjunctive (+DVP)	30 patients, mean age 14±2 yrs, 53% male	≥50% decrease on YMRS	Response rates: DVP + placebo 53% DVP + quetiapine 87%
Risperidone ¹⁷ 1.7±1.3 mg/d	Retrospective, adjunctive	28 patients, mean age 10±4 yrs, 97% male	≤2 on CGI-I	Response rate 82%

CGI-I: Clinical Global Impressions-Improvement scale
DVP: divalproex
YMRS: Young Mania Rating Scale

Olanzapine, quetiapine, and risperidone have been shown to reduce manic symptoms in children and adolescents (*Table 1*).¹⁵⁻¹⁷ Atypical antipsychotics, however, have been associated with metabolic side effects, including weight gain, hyperglycemia, hyperlipidemia, and hyperprolactinemia.

To date, no study has systematically evaluated combination psychostimulant and atypical antipsychotic treatment in comorbid ADHD and BPD. In the olanzapine and risperidone studies,^{15,17} concomitant psychostimulant use was permitted and did not affect manic symptom response.

WHICH COMBINATION?

Which combination treatment—psychostimulant plus mood stabilizer, psychostimulant plus atypical antipsychotic, or psychostimulant plus both mood stabilizer and atypical antipsychotic—is most appropriate for a child or adolescent with comorbid ADHD and BPD? Recommended treatment strategies are based on studies of pediatric and adult BPD and expert consensus.^{18,19}

Consider the type of bipolar episode (*Table 2, page 34*).

For initial treatment of youths with BPD manic or mixed without psychosis, recent guidelines by Kowatch et al suggest using mood-stabilizer or atypical antipsychotic monotherapy. Youths who are more severely ill or present with psychosis may respond more favorably to a mood stabilizer plus an atypical antipsychotic.^{16,19}

Individual patient traits will also determine whether a mood stabilizer or atypical antipsychotic is used and which agent within either medication class is chosen. For example:

- If the patient is aggressive, risperidone may reduce aggression and manic symptoms. Among the atypicals, risperidone has the most evidence suggesting efficacy for aggressive behaviors in youths across psychiatric conditions.²⁰
- If an atypical antipsychotic is warranted and the patient’s weight is an issue, ziprasidone or aripiprazole would be preferred. These agents are considered weight-neutral compared with other atypicals.²⁰

Other factors to consider include medication side effects, interactions, adherence, and cost.

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Table 2

Mood stabilizer, atypical antipsychotic, or both with ADHD therapy?

Type of bipolar episode	Recommended psychotropics
Manic or mixed episode with psychosis	Mood stabilizer + atypical antipsychotic
Manic or mixed episode without psychosis	Mood stabilizer or atypical antipsychotic monotherapy first <ul style="list-style-type: none"> • if no response, switch to the other monotherapy • if partial response, augment one with the other
Prominent irritability without psychosis	Atypical antipsychotic

Source: Adapted from references 18 and 19

WHICH TO TREAT FIRST?

If the child or adolescent with comorbid ADHD and BPD has acute manic symptoms, available data and expert opinion recommend starting treatment with a mood stabilizer or atypical antipsychotic.^{9,19,21} If ADHD symptoms persist after mood stabilization, a psychostimulant trial is warranted.

In practice, however, youngsters usually present with ADHD symptoms first. Psychostimulant treatment is initiated, ADHD symptoms are controlled, and the child’s academic and social functioning improve. Bipolar symptoms emerge later, often heralded by a depressive or mixed episode. Is it necessary to discontinue the psychostimulant and risk worsening ADHD symptoms before starting a mood stabilizer or atypical antipsychotic?

Clinical lore and one case report suggest that psychostimulants may destabilize mood.^{22,23} A 10-year-old boy with severe hyperactivity and family history of BPD experienced manic symptoms—rapid and pressured speech, grandiose delusions of identity, and tangentiality of thought processes—during methylphenidate treatment.²²

Conversely, an analysis²⁴ of children ages 7 to 10 from the National Institute of Mental Health Multimodal Treatment Study of Children with ADHD contradicts these assumptions. Although a

clinical diagnosis of BPD was not assigned, 29 children (83% male) met the Diagnostic Interview Schedule for Children proxy for mania, 32 (88% male) met the Child Behavior Checklist proxy, and 7 met both proxies for mania.

The first month of methylphenidate treatment did not increase irritability, mood symptoms, or mania in the 54 children with ADHD and manic symptoms, compared with children with ADHD alone. The authors concluded that clinicians should not categorically avoid using stimulants in children with ADHD and some manic symptoms.

In a study by Pavuluri et al¹⁸ of pediatric bipolar type I disorder, 17 patients (mean age 11±4 years) received mood stabilizers—following a drug therapy algorithm that included risperidone—and typically received a psychostimulant after mood stabilization. This group was compared with 17 patients receiving “treatment as usual.”

The usual-treatment group remained on psychostimulant therapy after BPD intervention with a mood stabilizer and was less likely to receive an atypical antipsychotic. The algorithm treatment group showed better outcomes overall, specifically for mania and aggression.

Clearly, more studies are needed to determine the optimum treatment sequence with psychos-

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Table 3

Using atypical antipsychotics to treat comorbid ADHD/bipolar disorder

Drug	Target dosage (mg/d)	Side effects	Useful in...
Aripiprazole	10 to 15	Nausea, vomiting	Comorbid disruptive behavioral disorders, maintenance stabilization
Olanzapine	10 to 20	Weight gain, hyperlipidemia, hyperglycemia, sedation	Maintenance stabilization
Quetiapine	400 to 600	Weight gain, sedation	Mixed states, bipolar depression
Risperidone	1 to 2	Weight gain, hyperprolactinemia, extrapyramidal symptoms	Comorbid disruptive behavioral disorders, including aggression
Ziprasidone	80 to 120	Cardiac abnormalities, akathisia	Mixed states, bipolar depression

timulants and mood stabilizers in youths with comorbid ADHD and BPD. With either approach, routinely monitor patients treated with psychostimulants for emerging or worsening bipolar symptoms.

LESSONS FROM CLINICAL EXPERIENCE

Nonstimulants. Using psychostimulants is appropriate for ADHD in patients with stable bipolar symptoms. Evidence for using nonstimulants such as clonidine, guanfacine, or atomoxetine is less clear.

In a naturalistic study of 153 children and adolescent outpatients treated with atomoxetine, 51 (33%) experienced irritability, aggression, mania, or hypomania. Of these patients, 31 (61%) had a family history of a mood disorder, and 41 (80%) had a personal history of mood symptoms. Although these findings suggest that atomoxetine may be associated with mood exacerbation and hypomania, additional data are needed to determine whether atomoxetine may be used for ADHD symptoms in youths with comorbid BPD.

Atypical antipsychotics. Mood stabilization—particularly with atypical antipsychotics—often can address comorbid disruptive behaviors and aggressive symptoms. Combinations of atypical antipsychotics with psychostimulants are largely devoid of drug-drug interactions and metabolic interference, making them uncomplicated to use.

Though published studies of pediatric BPD have focused on three atypical antipsychotics—olanzapine, quetiapine, and risperidone—any agent in this class can be used in this population, with the choice often depending on how side effects are likely to affect individual patients.

Pharmacologic attributes may also determine which atypical antipsychotic is used. For example, ziprasidone’s serotonergic profile—with serotonin-1A receptor agonism and serotonin-1D antagonism—may make it useful for patients with mixed states and bipolar depression. Aripiprazole offers potential synergism of dopamine agonism with psychostimulant therapy, which could be useful for treating both disruptive behaviors and ADHD.

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Related resources

- ▶ Child and Adolescent Bipolar Foundation. www.bpkids.org
- ▶ Children and Adults with Attention-Deficit Hyperactivity Disorder (CHADD). www.chadd.org
- ▶ Findling RF, Kowatch RA, Post RM. *Pediatric bipolar disorders: a handbook for clinicians*. London: Martin Dunitz Press, 2002.

DRUG BRAND NAMES

Atomoxetine • Strattera	Quetiapine • Seroquel
Aripiprazole • Abilify	Risperidone • Risperdal
Divalproex • Depakote	Ziprasidone • Geodon
Olanzapine • Zyprexa	

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When bipolar disorder occurs in youths with ADHD, proceed cautiously with psychostimulants to avoid manic decompensation or suboptimal ADHD treatment. Removing psychostimulant therapy may not be necessary, although this is controversial. Adding an atypical antipsychotic appears to be the most common remedy.

BottomLine