

How to reduce mania risk when prescribing stimulants

Evidence-based hierarchy helps
when bipolar and ADHD symptoms overlap



© Susan Johann / Corbis

Steven L. Dubovsky, MD

Professor and chair
Department of psychiatry
State University of New York
at Buffalo

Adjoint professor of psychiatry
and medicine
University of Colorado School
of Medicine, Denver

Stimulants are most effective for childhood attention-deficit/hyperactivity disorder (ADHD),¹ but they may induce mania or trigger a treatment-resistant course in children with comorbid bipolar disorder. To help you safely manage these complicated symptoms, this article offers a treatment algorithm and tips to:

- differentiate bipolar and ADHD symptoms
- identify patients at risk for stimulant-induced mania

- choose medications by a hierarchy that may reduce the risk of mood destabilization.

ADHD AND/OR BIPOLAR DISORDER?

Some 70% to 90% of bipolar children and at least 30% to 40% of bipolar adolescents also have ADHD.² This high comorbidity (*Box 1*)³⁻⁸ might mean that:

- one disorder predisposes to the other
- one is a precursor of the other

- they share common vulnerabilities or causes
- their symptoms overlap so much that patients with one disorder appear to meet criteria for the other.

Some experts contend that bipolar disorder and ADHD usually can be differentiated. Bipolar children score higher than those with ADHD on measures of anxiety/depression, aggression, and attention problems on the Child Behavior Checklist.⁹ Others believe ADHD symptoms that occur with bipolar disorder are a dimension of bipolar illness rather than a separate disorder.¹⁰

For every DSM-IV-TR diagnostic criterion for ADHD, a corresponding diagnostic criterion or common feature of bipolar disorder can be identified (*Table 1, page 38*). Mania and hypomania are obviously associated with hyperactivity and impulsivity, and tangential thinking and distractibility interfere with attention in many patients with bipolar disorder.

Though most ADHD symptoms can occur in bipolar patients, some features of bipolar illness are not characteristic of ADHD (*Table 2, page 47*). Children with ADHD can become hyper-focused on video games and television, for example, but they usually do not become engrossed in long, complicated books or preoccupied with other people, as can occur in bipolar disorder.

A TREATMENT HIERARCHY

Whether a bipolar patient's attention problems are features of the primary condition or caused by comorbid ADHD may be unclear, but the treatment implications are important. All antidepressants can induce mania/hypomania and increase the risk of mixed states and mood cycling. Because stimulants have antidepressant properties and because some antidepressants are used to treat ADHD, a systematic approach is necessary when treating inattention in juvenile bipolar disorder.

Box 1

Bipolar disorder and ADHD: High comorbidity, greater impairment

Bipolar mood symptoms emerge before age 20 in about 25% of persons with bipolar disorder (BP).³ Early-onset BP may be more severe than the adult-onset form, with more-affected family members and greater comorbidity with other disorders, especially ADHD.⁴

In one study, 91% of children with BP also met criteria for ADHD, and 19% of patients with ADHD also received a diagnosis of BP.⁵ Among 31 children ages 2 to 5 with BP, 80% met criteria for concurrent ADHD.⁶

Of 40 children age <5 presenting consecutively to a mental health clinic, 11 (28%) met criteria for mania, which was usually associated with euphoria.⁷ These 11 children also met criteria for ADHD.

A comparison study⁸ of children (mean age 12) found greater impairment, suicidality, irritability, and sadness in 43 with ADHD plus bipolar depression than in:

- 109 with ADHD plus major depressive disorder
- 128 without depression or mania.

Family prevalence of bipolar disorder and major depression was highest in the bipolar-ADHD group, which also had the highest rates of comorbid conduct disorder, oppositional defiant disorder, alcohol abuse, and agoraphobia. Average age of bipolar diagnosis was 6.3 years.

A treatment hierarchy developed by the American Academy of Child and Adolescent Psychiatry Workgroup on Bipolar Disorder recommends beginning psychosocial approaches, such as training parents in behavior management techniques, and:

- treating bipolar disorder first in children who clearly have both ADHD and bipolar disorder
- adding ADHD treatment if ADHD symptoms persist and impair functioning.²

continued



WHO'S AT RISK FOR MOOD DESTABILIZATION?

No data address differences between bipolar patients whose mood disorders deteriorate with stimulant use and those who remain stable. However, risk factors for mood destabilization that have been reported with antidepressants likely also apply to stimulants (Table 3, page 48) because stimulants' adverse effects in bipolar disorder are probably related to their antidepressant properties.

For example, depressed patients who report that an antidepressant worked within hours to days may have bipolar disorder and be at risk for mood destabilization leading to treatment resistance.¹¹ Antidepressant-induced mania also may be more likely:

- when depression is mixed with hypomanic symptoms such as racing thoughts, excessive talkativeness, aggression, irritability, distractibility, and increased drive¹²
- in patients with a history of antidepressant-induced mania, family history of bipolar disorder, or multiple antidepressant trials.¹³

Similarly, patients who report feeling better immediately after starting a stimulant—especially if they have evidence of elation, increased irritability, more aggression or impulsivity, decreased sleep, or related symptoms—may be developing stimulant-induced hypomania.

ANTIDEPRESSANT-INDUCED MANIA

Most studies of antidepressant-induced mania have examined outright mania, but hypomania and subsyndromal hypomanic syndromes also may cause significant morbidity and may worsen

Table 1

How ADHD, bipolar symptoms overlap in three domains

ADHD	Bipolar disorder
Inattention	
Fails to pay attention	Racing and tangential thoughts
Difficulty sustaining attention	Attention driven by racing thoughts, affective themes, and psychosis
Does not follow through	Direction of activity shifts with shifting mood
Difficulty organizing tasks	Disorganization, psychosis, excessive energy
Easily distracted	Distractibility
Hyperactivity	
Fidgets or squirms	Increased energy and activity
Runs about or climbs excessively	Hyperactivity, thrill-seeking
Difficulty engaging quietly in leisure activities	Increased energy, boredom
Often on the go	Increased energy, hyperactivity
Talks excessively	Rapid, pressured speech
Impulsivity	
Blurts out answers	Rapid, pressured, impulsive speech
Difficulty awaiting turn	Hyperactivity, increased energy, impatience, grandiosity
Interrupts or intrudes on others	Grandiosity, impatience, pressured speech, increased mental content

bipolar disorder's course. A change in polarity may worsen a patient's prognosis, but how do we know that antidepressants (or stimulants) caused it?

One suggested criterion is that mania or hypomania develops within 8 weeks of starting an antidepressant for the first time. A chart review of 51 bipolar patients who had extensive

continued on page 47

continued from page 38

life charting found that 82% developed mania while taking an antidepressant—35% of them within 8 weeks.¹⁴ The authors attributed 50% of the risk of a first manic episode and/or cycle acceleration to antidepressants and 50% to spontaneous mood swings. They also noted that:

- an initial manic episode appeared to sensitize patients to subsequent manic episodes and rapid cycling
- mood stabilizers did not seem to prevent these outcomes.

A meta-analysis of 12 randomized, controlled, 4- to 12-week trials among 1,088 patients found antidepressants no more likely than placebo to induce mania in the short term.¹⁵ These trials did not, however, consider less-severe forms of overstimulation and were not designed to determine mania risk in bipolar depressed patients.

Post-manic cycling. Rapid and ultradian cycling and other forms of deterioration are more likely to occur after a manic or hypomanic episode than after a depressive episode.¹⁶

A longitudinal study¹⁷ indicated that antidepressant use did not predictably predate rapid cycling when depression was controlled. The authors, however, looked at the correlation between taking an antidepressant at study entry and rapid cycling over 1 year but did not examine whether antidepressants were started or stopped during the study.¹⁸ Rapid cycling prevalence declined from 19% to 5% during the study, but they did not determine whether withdrawing antidepressants was associated with this change.

In an earlier prospective study, rapid cycling was more severe while patients were taking antidepressants—despite the use of mood stabilizers—and cycling duration decreased when antidepressants were withdrawn.¹⁹

Rapid and ultradian cycling are more common after manic rather than depressive episodes

Table 2

Bipolar features not seen in ADHD

- Depression
- Elation
- Suicidal thoughts
- Murderous rage
- Psychosis
- Grandiosity
- Decreased/increased sleep
- Hypersexuality
- Affective family history

TCAs vs. newer agents. Tricyclic antidepressants (TCAs) are perceived as more likely to induce mania than are selective serotonin reuptake inhibitors (SSRIs) or bupropion. Comparing TCAs' and newer antidepressants' switch rates is difficult, however. Most antidepressant trials were designed to show efficacy and safety in unipolar, not bipolar, depression. Moreover, as exclusion criteria have improved with greater awareness of bipolar illness' polymorphic manifestations, recent studies likely have enrolled fewer bipolar patients—who are most at risk to develop a manic switch—than did earlier TCA trials.

Bupropion, which has been used to treat ADHD, has been thought to have a low risk of inducing mania. In open observation, however, >50% of 11 patients with a history of developing mania with other antidepressants also had a manic switch on bupropion, even though they were taking mood stabilizers.²⁰

Analysis of 155 antidepressant trials in 41 depressed patients found mania risk to be similar with bupropion, SSRIs, TCAs, monoamine oxidase inhibitors (MAOIs), and other newer anti-



Table 3

Risk factors that may increase risk of stimulant-induced mania

- Family history of bipolar disorder
- Early onset of the mood disorder
- Comorbid substance use disorder
- History of rapid cycling or antidepressant-induced mania with other medications
- Multiple antidepressant trials

Source: Reference 25

depressants.²¹ Mania risk doubled when patients were not also taking mood stabilizers.

Going without mood stabilizers. Reports have emerged of patients with bipolar depression taking antidepressants such as fluoxetine and venlafaxine without a mood stabilizer for extended periods, without high rates of mania or mood cycling.²²⁻²⁴ These reports suggest that some bipolar depressed patients can tolerate antidepressants without a mood stabilizer, although we have no way to identify such patients in advance.

Cycle acceleration and treatment resistance may follow antidepressant-induced mania.²⁵ In DSM-IV field trials, antidepressants appeared to have triggered rapid cycling in some 20% of bipolar patients.²⁶ Mood stabilizers were not particularly effective in patients with treatment-resistant ultradian cycling, but withdrawing antidepressants improved outcome.²⁷

STIMULANT-INDUCED MANIA

Compared with antidepressants, less information is available about stimulant-induced mania and rapid cycling.

Some carefully selected bipolar patients may tolerate ongoing stimulant treatment. For example, in 2 years of open experience with 5 bipolar type I and 3 bipolar type II adults, adding methyl-

phenidate or amphetamine for residual depression or sedation was moderately helpful and did not lead to manic switching or drug misuse.²⁸

On the other hand, affective symptoms worsened in nearly two-thirds of 31 children ages 2 to 5 when treated with stimulants or antidepressants without mood stabilizers. Most of the children also had ADHD, and valproate usually helped.⁶

In 40 patients, mean age 10, who entered the open-label phase of an 8-week trial of divalproex for manic and ADHD symptoms:

- Young Mania Rating Scale (YMRS) scores declined by $\geq 50\%$ in 32 (80%) by week 8, a greater initial response than usually reported in pediatric bipolar disorder with comorbid ADHD.
- ADHD symptoms, measured by Clinical Global Impressions (CGI) scores, did not change significantly.²⁹

Thirty divalproex responders then received mixed amphetamine salts, 10 mg/d, or placebo plus divalproex, crossing over to the other treatment in a 4-week, double-blind trial. ADHD symptoms improved twice as much with the stimulant as with placebo, as measured by CGI scores, whereas YMRS scores did not differ significantly. Among 23 patients who continued the stimulant and divalproex for 12 more weeks, 45% required an increase in stimulant dosage and 1 relapsed into mania.

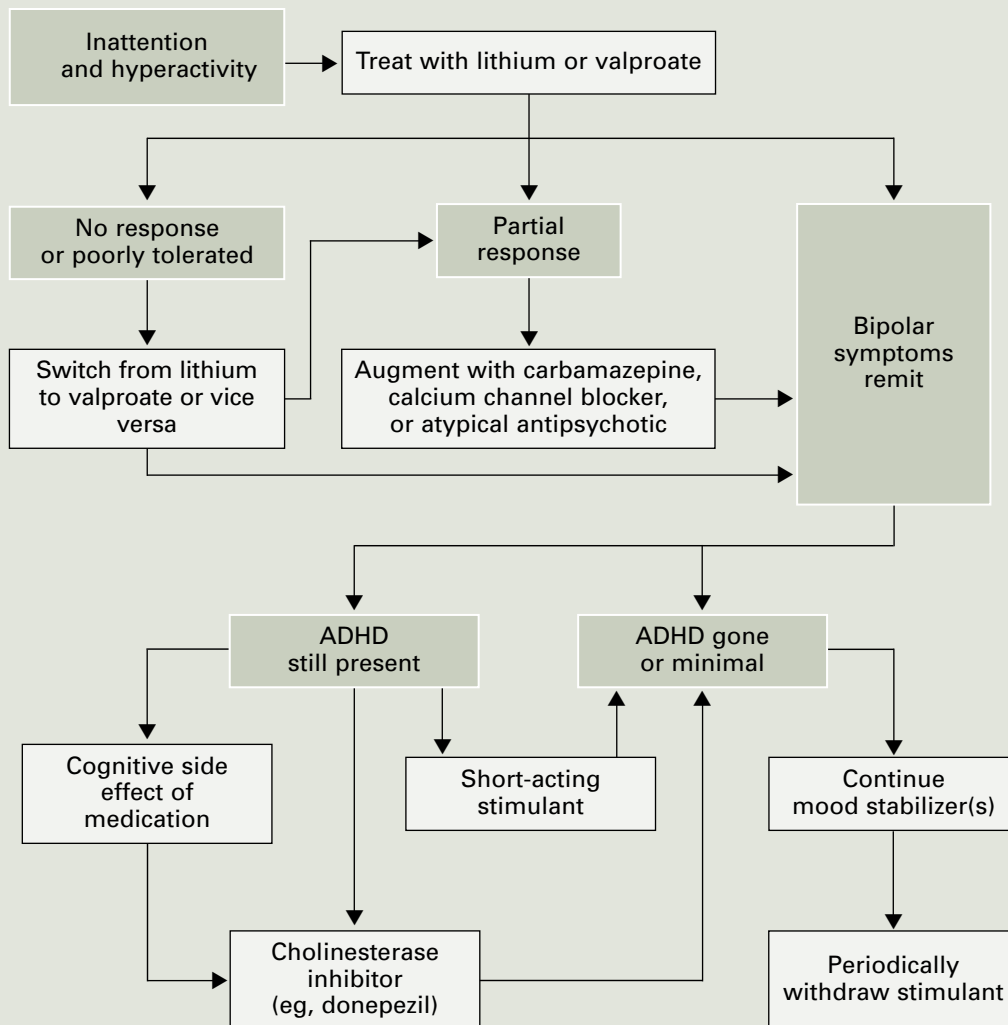
In this study, ADHD symptoms did not respond to mania treatment but did improve when a stimulant was added. This suggests either that patients had two disorders or that not all bipolar features remit at the same time. The trial's low stimulant dosage and short duration provide insufficient evidence to support using stimulants over long periods in bipolar children.

LONG-TERM STIMULANT EFFECTS

Without long-term observations, some investigators have inferred stimulants' impact on bipolar

Algorithm

Reducing mania risk: Using stimulants in children with bipolar disorder



disorder. A poll of pediatric psychiatrists in the Netherlands, for example, found bipolar disorder in 39 children ages <13 (0.001%) in the previous year, compared with a prevalence of at least 1% in the United States.³ The authors concluded:

- Bipolar disorder emerges at younger ages in the United States than in the Netherlands.
- One reason may be that U.S. psychiatrists

have a lower threshold for treating pediatric depression and hyperactivity with antidepressants and stimulants than Dutch psychiatrists do, evoking more-obvious bipolar symptoms at an earlier age.

Observations of 30 U.S. children with a manic episode and ADHD suggested that stimulants can induce manic symptoms:

continued



- Mean age of ADHD onset was 5.5 years.
- Mean age of starting stimulants was 6.9 years.
- Mean age of hypomanic or manic symptom onset was 7.1 years.³⁰

Similarly, in a survey of 34 adolescent manic inpatients, those who had taken stimulants had earlier mania onset (mean age 10.7) than did those who had not taken stimulants (mean age 13.9). Exposure to two stimulants was associated with earlier onset than exposure to one, but comorbid ADHD alone did not affect age of bipolar disorder onset.³¹

The same group¹⁰ reviewed charts of 80 consecutively hospitalized adolescents with a manic or mixed bipolar episode and found stimulant exposure was associated with relatively worse inpatient course, longer length of stay, more emergency medications, and more seclusion and restraint orders. Comorbid ADHD, mixed versus manic episode, and prior antidepressant exposure did not worsen the inpatient course.

A chart review by El-Mallakh et al³² found bipolar disorder was diagnosed at mean age 10.7 in 49 children exposed to antidepressants or stimulants, compared with mean age 12.7 in 44 unexposed children. The exposed group appeared to have tolerated stimulants longer than antidepressants before mania or hypomania emerged.³³

In contrast, a retrospective review by Carlson et al³⁴ of data from a longitudinal study of 75 boys with “hyperkinetic reaction of childhood” found that methylphenidate treatment did not appear more common in boys later diagnosed with bipolar disorder than in those without a bipolar diagnosis. This study had obvious methodologic limitations, lacking a hypothesis and focusing on a population with “minimal brain dysfunction.”

In a reanalysis of data from a 1-month methylphenidate titration trial, Galanter et al³⁵

examined whether some 300 children ages 5 to 12 experienced manic symptoms, using the Diagnostic Interview Schedule for Children or the Child Behavior Checklist. At least during this brief trial, patients with and without manic symptoms showed no differences in response rates or adverse effects with stimulant therapy.

DRUG TREATMENT HIERARCHY

Mood stabilizers. Evidence supports starting all bipolar children with a mood stabilizer such as lithium or valproate (*Algorithm, page 49*). A few patients may tolerate stimulants without mood stabilizers, but the risk is high of inducing mania and precipitating a more complex and treatment-resistant disorder.

Carbamazepine can be effective, but it makes some youths aggressive or disorganized. Antipsychotics have not been tested in controlled trials in bipolar children and are not considered first-line treatments, especially as mood stabilizers. They can be effective for childhood mania, but outpatients needing ADHD treatment usually do not have severe manic syndromes.

Combination therapy. Like many adults, bipolar children often require combinations of mood stabilizers. Kowatch et al³⁶ found that 16 of 20 acutely ill bipolar children (mean age 11) responded to a combination of mood stabilizers after not responding to 8 weeks of a single mood stabilizer. Because bipolar disorder with comorbid ADHD suggests a complex pathophysiology, patients with both disorders may be more likely to require mood-stabilizer combinations than those with bipolar disorder alone.

The goal in treating bipolar disorder is to eliminate symptoms as completely as possible. In bipolar children with comorbid ADHD, be cer-

Start all bipolar children with a mood stabilizer such as lithium or valproate, then treat ADHD

continued on page 53

continued from page 50

tain that subtle hypomanic symptoms—irritability, decreased sleep, hypersensitivity to interactions, psychosis—have remitted, as they could account for continued inattention. Persistent mood lability may indicate incomplete treatment of the mood disorder, which can increase sensitivity to destabilization by a stimulant.

If a child remains inattentive after the mood disorder is controlled, consider whether medications for the mood disorder are to blame. If medications are working well but causing cognitive side effects, a cholinesterase inhibitor may help.

Adding stimulants. If attention problems persist, consider cautiously adding a stimulant. Informed consent includes telling patients and families about the risks of mood destabilization with stimulants, even when used with mood stabilizers.

Increase stimulant dosage very slowly, and monitor the patient closely for emerging mood instability or subtle evidence of dysphoric hypomania. Address hypersensitivity to sounds, increased irritability, or other signs of activation with more-aggressive mood stabilization before assuming that these are ADHD symptoms that require a higher stimulant dosage.

Sustained-release stimulant preparations are probably second-line choices in patients with concomitant bipolar disorder. With long-acting stimulants, any worsening of the mood disorder will take longer to wear off. Antidepressants such as bupropion are potential alternatives to stimulants but are as likely to induce hypomania and mood cycling and may not be as effective.

Compared with stimulants, atomoxetine has a less-potent antidepressant effect and may be somewhat safer, but it is not as effective for ADHD and is longer-acting. Thus, atomoxetine could be a first-line alternative for comorbid ADHD, with stimulants being added if it is not effective. Clonidine can reduce hyperactivity but does not stabilize mood or improve attention.

When an antidepressant has brought bipolar

depression into remission, discontinue it slowly to reduce the risk of rebound while continuing mood stabilizers to prevent recurrence. Because ADHD is not cyclical like bipolar depression, inattention returns for many patients when stimulants are withdrawn.

We do not yet know whether the risk of mood destabilization increases with long-term stimulant use, but discontinuation-induced refractoriness has not been reported with stimulants as it has with mood stabilizers and antidepressants. Thus, trying to withdraw stimulants once ADHD symptoms have remitted is prudent, while supplementing the regimen with behavioral treatments. If managing ADHD symptoms requires continued stimulant treatment, monitor the patient closely for mood destabilization.

References

1. Greenhill LL, Pliszka S, Dulcan MK, et al; AACAP Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. *J Am Acad Child Adolesc Psychiatry* 2002;41(suppl 2):26S-49S.
2. Kowatch RA, Fristad M, Birmaher B, et al. Treatment guidelines for children and adolescents with bipolar disorder: child psychiatric workgroup on bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2005;44:213-35.
3. Reichart CG, Nolen W. Earlier onset of bipolar disorder in children by antidepressants or stimulants? An hypothesis. *J Affect Disord* 2004;78:81-4.
4. Faraone SV, Glatt SJ, Tsuang MT. The genetics of pediatric-onset bipolar disorder. *Biol Psychiatry* 2003;53:970-7.
5. Geller B, Zimmerman B, Williams MB, et al. Bipolar disorder at prospective follow-up of adults who had prepubertal major depressive disorder. *Am J Psychiatry* 2001;158:125-7.

Determining whether the mood disorder or comorbid ADHD is causing inattention in bipolar children can be very difficult. Stabilize mood as much as possible before treating ADHD to reduce mania risk. Then, if inattention persists, adding intermittent short-acting stimulant therapy is less likely to destabilize mood.

BottomLine

continued



Related resources

- ▶ American Academy of Child and Adolescent Psychiatry. Facts for families: Bipolar disorder in children and teens. www.aacap.org/publications/factsFam/bipolar.htm.
- ▶ National Institute of Mental Health. Database on ADHD. www.nimh.nih.gov/publicat/adhd.cfm.

DRUG BRAND NAMES

Amphetamine salts • Adderall
 Atomoxetine • Strattera
 Bupropion • Wellbutrin
 Carbamazepine • Tegretol, others
 Clonidine • Catapres
 Dexamethylphenidate • Focalin
 Fluoxetine • Prozac
 Lithium • Lithobid, others
 Methylphenidate • Concerta,
 Ritalin, others
 Valproate • Depakene, Depakote
 Venlafaxine • Effexor

DISCLOSURES

Dr. Dubovsky receives research support from UCB Pharma, Forest Laboratories, and Solvay Pharmaceuticals, and is a speaker for Janssen Pharmaceutica and Forest Laboratories.

- Scheffer RE, Niskala Apps JA. The diagnosis of preschool bipolar disorder presenting with mania: open pharmacological treatment. *J Affect Disord*. 2004;82(suppl 1):S25-S34.
- Dilsaver SC, Akiskal HS. Preschool-onset mania: incidence, phenomenology and family history. *J Affect Disord* 2004;82(suppl 1):S35-S43.
- Wozniak J, Spencer T, Biederman J, et al. The clinical characteristics of unipolar vs. bipolar major depression in ADHD youth. *J Affect Disord* 2004;82(suppl 1):S59-S69.
- Mick E, Biederman J, Pandina G, Faraone SV. A preliminary meta-analysis of the Child Behavior Checklist in pediatric bipolar disorder. *Biol Psychiatry* 2003;53:1021-7.
- Soutullo CA, DelBello MP, Ochsner JE, et al. Severity of bipolarity in hospitalized manic adolescents with history of stimulant or antidepressant treatment. *J Affect Disord* 2002;70:323-7.
- Piver A. Ultrarapid response to an antidepressant: A clue to bipolarity? *Can J Psychiatry* 2003;48:427-8.
- Bottlender R, Sato T, Kleindienst N, et al. Mixed depressive features predict maniform switch during treatment of depression in bipolar I disorder. *J Affect Disord* 2004;78:149-52.
- Goldberg J, Truman CJ. Antidepressant-induced mania: an overview of current controversies. *Bipolar Disord* 2003;5:407-20.
- Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced mania and cycle acceleration: a controversy revisited. *Am J Psychiatry* 1995;152(8):1130-8.
- Gijsman HJ, Geddes J, Rendell J, et al. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry* 2004;161:1537-47.
- Post RM, Roy-Byrne PP, Uhde TW. Graphic representation of the life course of illness in patients with affective disorder. *Am J Psychiatry* 1988;145:844-8.
- Coryell W, Endicott J, Keller M. Rapidly cycling affective disorder: demographics, diagnosis, family history and course. *Arch Gen Psychiatry* 1992;49:126-31.
- Wehr TA. Can antidepressants induce rapid cycling? *Arch Gen Psychiatry* 1993;50(6):495-6.
- Wehr TA, Sack DA, Rosenthal NE, Cowdry RW. Rapid cycling affective disorder: contributing factors and treatment responses in 51 patients. *Am J Psychiatry* 1988;145:179-84.
- Fogelson DL, Bystritsky A, Pasnau R. Bupropion in the treatment of bipolar disorders: the same old story. *J Clin Psychiatry* 1992; 53:443-6.
- Goldberg J, Ernst CL. Features associated with the delayed initiation of mood stabilizers at illness onset in bipolar disorder. *J Clin Psychiatry* 2002;63:985-91.
- Amsterdam JD, Shults J, Brunswick DJ, Hundert M. Short-term fluoxetine monotherapy for bipolar type II or bipolar NOS major depression—low manic switch rate. *Bipolar Disord* 2004;6:75-81.
- Simpson SG, DePaulo JR. Fluoxetine treatment of bipolar II depression. *J Clin Psychopharmacol* 1991;11:52-4.
- Amsterdam JD, Garcia-Espana F. Venlafaxine monotherapy in women with bipolar II and unipolar major depression. *J Affect Disord* 2000;59:225-9.
- Goldberg J. When do antidepressants worsen the course of bipolar disorder? *J Psychiatr Pract* 2003;9:181-94.
- Bauer M, Calabrese JR, Dunner DL. Multisite data reanalysis of the validity of rapid cycling as a course modifier for bipolar disorder in DSM-IV. *Am J Psychiatry* 1994;151:506-15.
- Prien RF, Kupfer DJ, Mansky PA. Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders: Report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. *Arch Gen Psychiatry* 1984;41:1096-1104.
- Carlson PJ, Merlock MC, Suppes T. Adjunctive stimulant use in patients with bipolar disorder: treatment of residual depression and sedation. *Bipolar Disord* 2004;6:416-20.
- Scheffer RE, Kowatch RA, Carmody T, Rush AJ. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. *Am J Psychiatry* 2005;162:58-64.
- Kowatch RA, Suppes T, Carmody T, et al. Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2000;39:713-20.
- DelBello MP, Soutullo CA, Hendricks W, et al. Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. *Bipolar Disord* 2001;3:53-7.
- El-Mallakh RS, Cicero D, Holman J, Robertson J. Antidepressant exposure in children diagnosed with bipolar disorder. *Bipolar Disord* 2001;3(suppl 1):35-9.
- Cicero D, El-Mallakh RS, Holman J, Robertson J. Antidepressant exposure in bipolar children. *Psychiatry* 2003;66:317-22.
- Carlson G, Loney J, Salisbury H, et al. Stimulant treatment in young boys with symptoms suggesting childhood mania: A report from a longitudinal study. *J Child Adolesc Psychopharmacol* 2000; 10:175-84.
- Galanter CA, Carlson GA, Jensen PS, et al. Response to methylphenidate in children with attention deficit hyperactivity disorder and manic symptoms in the multimodal treatment study of children with attention deficit hyperactivity disorder titration trial. *J Child Adolesc Psychopharmacol* 2003;13:123-36.
- Kowatch RA, Sethuraman G, Hume JH, Kromelis M, Weinberg WA. Combination pharmacotherapy in children and adolescents with bipolar disorder. *Biol Psychiatry*. 2003;53:978-84.