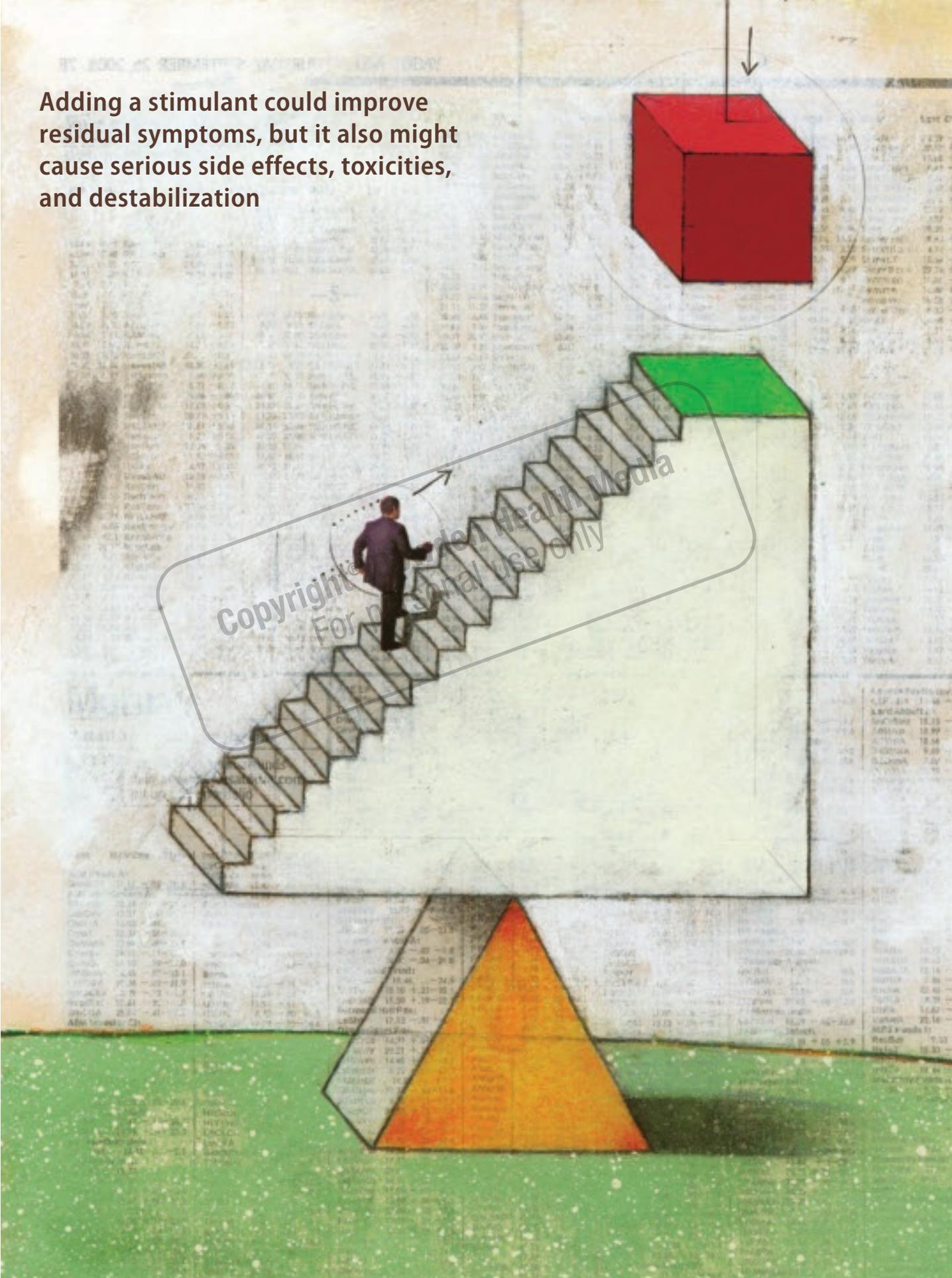


Adding a stimulant could improve residual symptoms, but it also might cause serious side effects, toxicities, and destabilization



Stimulants

for adult bipolar disorder?

Robert Gonzalez, MD

Fellow, Mood disorders clinical intervention training program (T32)
Department of psychiatry
University of Texas Southwestern Medical Center
Dallas, TX

Trisha Suppes, MD, PhD

Professor
Department of psychiatry and behavioral sciences
Stanford University Medical Center
and VA Palo Alto Health Care System
Palo Alto, CA

Patients with bipolar disorder show an unpredictable range of responses to stimulants, from virtually no ill effects to emerging manic-like symptoms.¹ Thus, although stimulants may be beneficial to some bipolar patients, there is a great deal of concern about using stimulants in this population. Even so, stimulants may be a rational adjunct for treating certain aspects of bipolar illness, particularly resistant depression, iatrogenic sedation, and comorbid attention-deficit/hyperactivity disorder (ADHD).

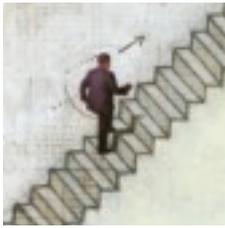
To help you decide if and when your patient might be a candidate for stimulant therapy, this article:

- reviews the evidence on stimulants' safety and tolerability for patients with bipolar disorder
- weighs potential benefits and risks of using stimulants in this population
- addresses stimulants' possible adverse effects on illness course and from interactions with other psychotropics
- discusses treatment options based on the limited evidence and our clinical experience.

Limited support

We are aware that using stimulants to treat patients with bipolar disorder is not an uncommon clinical practice, but supportive evidence is limited (*Table 1, page 38*). In searching the literature, we found only 2 randomized controlled studies—Frye et al² and

continued on page 38



Stimulants

Clinical Point

No stimulant, novel or traditional, is FDA-approved for adjunctive use in patients with bipolar disorder

Table 1

Clinical studies of stimulant use in patients with bipolar disorder

Stimulant(s) studied	Study design	Patients studied	Clinical outcomes
Traditional stimulants			
Adjunctive methylphenidate	Chart review, naturalistic ¹²	16 adults (5 with comorbid ADHD, 11 with bipolar depression)	Improvements in depression, overall functioning, and ability to concentrate; sleep disturbance, irritability/agitation reported
Adjunctive methylphenidate or racemic mixture of AMPH salts	Chart review of sedation and depressive symptoms ¹³	8 adults (BD II)	Improved clinical impression of bipolar illness; no manic switches, changes in cycling patterns, or substance abuse noted
Adjunctive methylphenidate	12-week open study, bipolar depression ¹⁴	12 adults (10 BD I, 2 BD II)	Significant clinical improvements in depressive symptoms; no change in manic symptoms; anxiety, agitation, and hypomania reported
Multiple stimulants	Chart review, history of stimulants and bipolar illness course ²⁵	34 hospitalized adolescents	Prior stimulant treatment associated with earlier age of illness onset
Adjunctive mixed amphetamine salts	Randomized, placebo-controlled; comorbid BD and ADHD ⁹	30 children with ADHD symptoms stabilized on divalproex sodium	Decrease in ADHD symptoms with adjunctive amphetamine treatment but not with divalproex sodium alone; 1 case of mania
Novel stimulant			
Adjunctive modafinil	Case series ¹⁵	Mixed sample of depressed adults (4 unipolar, 3 bipolar)	Significant improvement in depressive symptoms
Adjunctive modafinil	Randomized, double-blind, placebo-controlled ²	85 adults with bipolar depression	Treatment group showed greater response and remission of depressive symptoms compared with placebo group; no difference in development of manic symptoms

ADHD: attention-deficit/hyperactivity disorder; AMPH: amphetamine; BD: bipolar disorder; NOS: not otherwise specified

Scheffer et al³—that addressed this practice. (One author of this review [TS] participated as a coinvestigator with Frye et al.²) Other evidence that suggests a role for stimulants in bipolar disorder comes from case reports, retrospective case series, and open-label studies.⁴⁻¹¹

For this article, we recognize 2 broad stimulant categories:

- “traditional” stimulants (including amphetamine-based compounds such as dextroamphetamine, methylphenidate, dexmethylphenidate, and lisdexamfetamine) thought to affect the dopamine transporter, resulting in increased dopamine in nerve terminals

- the “novel” psychostimulant modafinil, thought to affect multiple neurotransmitter systems (dopamine, GABA, serotonin, histamine, and glutamate), although its mechanism of action is unclear.

The traditional stimulants are FDA-approved for ADHD, and some have an additional indication for narcolepsy. Modafinil is indicated for improving wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift-work sleep disorder. No stimulant is FDA-approved for adjunctive use in patients with bipolar disorder.

Depression and iatrogenic sedation

Small, uncontrolled trials have reported some benefit and tolerability in bipolar disorder patients when stimulants are used to treat residual depressive symptoms or iatrogenic sedation associated with mood stabilizers.

Traditional stimulants. A retrospective chart review of 16 patients treated with adjunctive methylphenidate noted improved functioning, as measured by the Global Assessment of Functioning scale. Some patients' depressive symptoms and concentration also appeared to improve, but how these parameters were assessed is not clear. Some patients tolerated stimulants well, whereas others experienced irritability, agitation, and sleep disturbances.¹²

Another retrospective chart review described 8 patients with iatrogenic sedation or depression who received adjunctive methylphenidate, mean 20 to 40 mg/d, or a racemic mixture of amphetamine salts, mean 20 to 40 mg/d. Overall bipolar symptoms decreased in severity, as measured by Clinical Global Impression (CGI) scores, but the authors did not directly measure sedation or depression. The stimulants were well-tolerated, with no evidence of stimulant-induced mania.¹³

In a 12-week open-label trial of methylphenidate in 14 patients with bipolar disorder, depressive symptoms improved as measured by the Hamilton Depression Rating Scale (HAM-D). Mean doses were 10 mg/d for the 3 patients who discontinued because of anxiety, agitation, or hypomania and 16.6 mg/d for those who completed the trial.¹⁴

Modafinil may have some efficacy in treating bipolar depression. In a case series of 7 depressed patients (4 unipolar and 3 bipolar), 5 patients showed a 50% decrease in HAM-D scores with adjunctive modafinil. Dosages ranged from 100 to 200 mg/d, although most patients took 200 mg/d. In this series, modafinil was added to a variety of treatments, including bupropion, nefazodone, paroxetine, venlafaxine, an unspecified tricyclic antidepressant (TCA), divalproex sodium, lamotrigine, lithium,

electroconvulsive therapy, olanzapine, and gabapentin.¹⁵

The only randomized, double-blind, placebo-controlled trial of adjunctive modafinil for bipolar depression enrolled 85 patients with moderate or more severe depression. In this 6-week trial by Frye et al,² 41 patients received modafinil, 100 to 200 mg/d (mean dose 174.2 mg/d), and 44 received placebo.

Response and remission rates—as measured by the clinician-rated Inventory of Depressive Symptoms—were significantly higher in patients treated with modafinil (44% and 39% respectively), compared with placebo (23% and 18%). Manic or hypomanic symptoms emerged in 6 patients during modafinil treatment and in 5 who received placebo. One patient in each group required hospitalization.

Bipolar disorder plus ADHD

An estimated 10% to 21% of bipolar patients meet criteria for ADHD,¹⁶⁻¹⁹ although at times the line differentiating these 2 disorders is unclear. Co-occurring ADHD worsens the course of bipolar illness,²⁰⁻²² and data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial suggest that only 2% of dual-diagnosis patients are receiving treatment specifically for ADHD symptoms.²³

Theoretically, overlapping symptoms such as talkativeness, distractibility, and physical activity remain relatively constant in ADHD but wax and wane with bipolar disorder's manic and depressive phases. Recent evidence suggests, however, that many bipolar patients experience prodromal symptoms that may resemble ADHD, including cognitive impairment, distractibility, and increased psychomotor activity.²⁴ In addition, medications used to treat bipolar disorder may impair cognitive function, making ADHD diagnosis difficult in this population.



Want to know more?

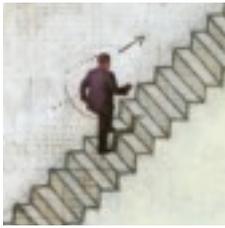
See this article at CurrentPsychiatry.com

ADHD: Only half the diagnosis in an adult with inattention?

June 2007

Clinical Point

Prodromal symptoms similar to ADHD may persist in patients with bipolar disorder



Stimulants

Clinical Point

Using adequate mood-stabilizer treatment may attenuate stimulants' undesirable effects in patients with bipolar disorder

Table 2

Possible stimulant side effects, signs of toxicity, and contraindications

Stimulant class	Possible side effects	Signs of toxicity/ overdose	Contraindications/ cautions
Traditional (amphetamine mixtures, dexamethylphenidate, dextroamphetamine, lisdexamfetamine, methylphenidate)*	Restlessness, insomnia, mood lability, anxiety	Agitation, confusion, tremor, tachycardia, hyperreflexia, hypertension, sweating, psychomotor agitation, seizure, arrhythmia, coma, psychosis	Cardiovascular disease, hypertension, hyperthyroidism, glaucoma, Tourette's syndrome/motor tics, history of seizure disorder, hypersensitivity to medication class
Novel (modafinil)	Restlessness, insomnia, mood lability, anxiety	Agitation, tremor, nausea, diarrhea, confusion	Cardiovascular disease, hepatic impairment, psychosis

*Amphetamines and dextroamphetamine (Adderall, Adderall XR); dexamethylphenidate (Focalin, Focalin XR), dextroamphetamine (Dexedrine, DextroStat); lisdexamfetamine (Vyvanse); methylphenidate (Concerta, Daytrana, Metadate CD, Methylin, Methylin ER, Ritalin, Ritalin LA, Ritalin SR)

We are not aware of any clinical trials that examined stimulants' safety and efficacy in adult bipolar patients with co-occurring ADHD. One of the only studies to examine stimulant treatment of ADHD symptoms in a bipolar population was a retrospective chart review of 34 adolescents hospitalized with bipolar mania. An earlier age of bipolar illness onset was reported in adolescents who had been exposed to stimulants, whether or not they also had ADHD.²⁵

One randomized trial. In a study by Schaffer et al³ of children with bipolar mania and ADHD, divalproex sodium produced an 80% response rate in manic symptoms but no significant decrease in ADHD symptoms.³ Forty responders then participated in a double-blind, placebo-controlled trial in which mixed amphetamine salts, 5 mg bid, was added for ADHD symptoms. In patients treated with divalproex sodium plus the stimulant, ADHD symptoms decreased significantly compared with the group receiving divalproex sodium plus placebo. Mania developed in 1 of 23 subjects treated with the combination therapy.

Possible adverse events

Some bipolar disorder patients tolerate stimulants well, whereas others experience serious side effects, toxicities, and illness destabilization (Table 2). Because

mood-stabilizer treatment may attenuate stimulants' undesirable effects in bipolar disorder patients,^{26,27} be sure to use adequate dosing of a mood stabilizer if you determine a stimulant trial is warranted in your patient.

Destabilization. Stimulants can have a direct negative effect on mood; they can cause restlessness, irritability, anxiety, and mood lability. Some bipolar patients may be more sensitive to these adverse effects than others. Particularly concerning is the possibility of switching to mania or worsening of manic symptoms.^{28,29} Other potential destabilizing effects include:

- changing cycling patterns, such as inducing rapid cycling
- sleep disturbance because stimulants promote wakefulness.

Substance abuse in bipolar disorder has been associated with increased treatment resistance, earlier age at illness onset, and an overall worse course of illness.^{30,31} Some reports have estimated substance abuse rates as high as 60% in bipolar populations.³² Particularly concerning is that up to 40% of patients with bipolar disorder may have a history of amphetamine abuse.³³

If you are considering stimulant treatment for a bipolar disorder patient in whom substance abuse is a concern, modafinil or lisdexamfetamine may have a lower abuse

Table 3

Possible stimulant interactions with other psychotropics

Stimulant class	Psychotropic medication	Possible adverse effects
Traditional (amphetamine mixtures, dexamethylphenidate, dextroamphetamine, lisdexamfetamine methylphenidate)*	MAOIs	Hypertensive crisis
	CBZ	Reduced methylphenidate levels; abruptly stopping CBZ increases methylphenidate's effect
	TCAs	Increased TCA concentration
	SSRIs, SNRIs	Possible decreased metabolism of antidepressants; potential for serotonin syndrome or NMS-like syndrome
	Typical and atypical antipsychotics	Each may interfere with the other's therapeutic action
Novel (modafinil)	CBZ	Decreased modafinil efficacy; decreased CBZ levels
	Triazolam	Decreased triazolam efficacy; increased effects of triazolam with modafinil discontinuation
	Fluoxetine, fluvoxamine	Decreased modafinil clearance
	Citalopram, escitalopram, sertraline	Prolonged elimination and increased levels of antidepressant
	MAOIs	Hypertensive crisis(?); not recommended
	Diazepam	Prolonged elimination and increased levels of diazepam
	TCAs	Prolonged elimination and increased levels of TCAs
	Clozapine	Increased clozapine concentration (case report)
	Aripiprazole	Decreased levels of aripiprazole

* Amphetamines and dextroamphetamine (Adderall, Adderall XR); dexamethylphenidate (Focalin, Focalin XR), dextroamphetamine (Dexedrine, DextroStat); lisdexamfetamine (Vyvanse); methylphenidate (Concerta, Daytrana, Metadate CD, Methylin, Methylin ER, Ritalin, Ritalin LA, Ritalin SR)
 CBZ: carbamazepine; MAOIs: monoamine oxidase inhibitors; NMS: neuroleptic malignant syndrome; SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants

Clinical Point

Modafinil or lisdexamfetamine may have a lower abuse potential compared with immediate-release psychostimulants

potential compared with immediate-release psychostimulants. Lisdexamfetamine is metabolized in the GI tract and does not produce high d-amphetamine blood levels or cause reinforcing effects if injected or snorted.³⁴

Drug-drug interactions

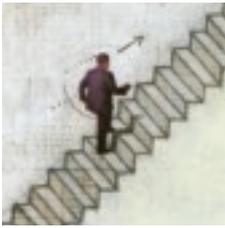
Polypharmacy is the rule in treating bipolar disorder, and stimulants can interact with many other psychotropics (Table 3).

Antidepressants. Never use traditional stimulants with monoamine oxidase inhibitors, as this combination may precipitate a hypertensive crisis. Coadministered stimulants also may decrease the metabolism of serotonergic agents—such as selective serotonin reuptake inhibitors (SSRIs) or sero-

tonin-norepinephrine reuptake inhibitors (SNRIs)—and cause side effects associated with increased serotonin neurotransmission, including serotonin syndrome.

Combining traditional stimulants with TCAs may increase TCA concentrations. When coadministered with bupropion, stimulants can increase the risk of seizures.

Carbamazepine, others. Certain psychotropics can affect stimulants' efficacy. For example, carbamazepine can decrease stimulant serum concentrations, possibly decreasing their therapeutic effect. Conversely, abruptly discontinuing carbamazepine may increase stimulants' plasma concentration and predispose patients to associated adverse effects. Antipsychotics and lithium may inhibit stimulants' stimulatory effects, although this balance may be



Stimulants

Clinical Point

Before adding a stimulant, optimize medications, assess the diagnosis, identify substance abuse, and treat medical comorbidity

Table 4

6 recommendations when using stimulants in bipolar disorder

Carefully assess patient's symptoms	Manic symptoms vs ADHD; medical conditions such as thyroid disorders, diabetes, or sleep apnea
Review possible iatrogenic causes of symptoms	Somnolence, decreased energy/fatigue, sedation, difficulty with concentration/focus
Engage patient in the therapeutic process	Discuss risks and benefits; monitor mood with life charts; enlist help of family, significant others when appropriate
Use caution in clinical scenarios that may herald adverse response to stimulants	Manic/hypomanic symptoms; sleep disturbances; psychosis; history of substance abuse
Administer stimulants with caution	Start low and go slow; always use stimulants in conjunction with a mood-stabilizing agent; be aware of possible interactions with patient's other medications; schedule more frequent visits when starting stimulants
Monitor for adverse events associated with stimulant administration	Manic symptoms, changes in cycling patterns, sleep disturbances, substance abuse

ADHD: attention-deficit/hyperactivity disorder

necessary to maintain mood stability and stimulant effects.

Modafinil is both an inducer and inhibitor of cytochrome P450 isoenzymes. Because it induces CYP3A4 and inhibits CYP2C19 and CYP2C9, modafinil interacts with many other psychopharmacologic agents:

- Its induction of CYP3A4 may increase the metabolism of commonly used medications such as carbamazepine, aripiprazole, and triazolam.
- Its inhibition of CYP2C19 may decrease the metabolism of many SSRIs, TCAs, diazepam, and clozapine, increasing these drugs' effects and adverse events.

Treatment considerations

Without evidence to support stimulants' safety and efficacy in patients with bipolar disorder, we cannot make specific recommendations. We would, however, like to offer some general recommendations if you decide to use stimulants when treating patients with bipolar disorder (*Table 4*).

Before adding a stimulant, optimize the patient's treatment regimen and carefully assess the side-effect profiles of his or her medications. Nearly every medication used to treat bipolar illness—including

divalproex sodium, lithium, quetiapine, olanzapine, and clozapine—may cause marked sedation, somnolence, and subjective feelings of decreased energy. Try switching to a medication with a lower incidence of these iatrogenic effects.

Carefully assess and—in many cases—reassess the patient's symptoms to clarify the diagnosis. As mentioned, ADHD and bipolar disorder share many symptoms, particularly in the manic phase of bipolar illness. Overlapping symptoms include decreased ability to concentrate and focus, distractibility, hyperactivity and psychomotor agitation, racing thoughts, and impulsivity.

Substance abuse can negatively impact bipolar illness and present as clinical scenarios in which stimulants are used (such as treatment-resistant depression, impulsivity, somnolence, or fatigue).

Treat medical conditions such as thyroid disease, diabetes, and sleep apnea, which may worsen depression, cause somnolence and sedation, and present with symptoms similar to those of ADHD.

When possible, use lifestyle techniques to help patients manage the course of bipolar illness. Encourage good sleep hygiene, exercise, stable social rhythms, and limited use of alcohol and caffeine (both of which can impair sleep quality, which affects illness stability).

The next step. When you have explored all medication options and ruled out all other causes for the patient's symptoms, stimulant treatment may be an appropriate next step. In these cases:

Engage the patient in decision-making. Carefully review target symptoms to be addressed by stimulant treatment, dosing, possible side effects and drug interactions, as well as safety concerns.

Encourage patients to participate in treatment, particularly in monitoring mood changes (as with life charts), symptoms associated with mood episodes, and emergence of side effects. When possible, involve family members in monitoring for adverse events.

Administration. Start stimulants only when bipolar illness is well-stabilized, especially regarding manic symptoms. We highly caution against using stimulants in patients with manic or hypomanic symptoms, including mixed states. We recommend not using stimulants in patients with:

- clinically significant insomnia or sleep fragmentation
- active suicidal ideation or psychotic symptoms, particularly if associated with manic symptoms.

The evidence does not clarify how well patients with bipolar disorder tolerate stimulants and what subtypes or phenotypes—bipolar I, bipolar II, not otherwise specified, rapid cycling, etc.—are associated with a better or worse clinical outcome. Therefore, when starting stimulants, use the minimum available dose of whatever stimulant you select and titrate slowly. Always use stimulants with a mood stabilizer, which may attenuate stimulants' undesirable effects on mood and behavior.^{26,27}

Schedule frequent office visits when prescribing stimulants. At least initially, see patients every other week to assess for the emergence of adverse events.

References

1. Silberman EK, Reus VI, Jimerson DC, et al. Heterogeneity of amphetamine response in depressed patients. *Am J Psychiatry* 1981;138(10):1302-7.
2. Frye MA, Grunze H, Suppes T, et al. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am J Psychiatry* 2007;164(8):1242-9.
3. 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

Related Resources

- The Texas Medication Algorithm Project. Texas Department of State Health Services. www.dshs.state.tx.us/mhprograms/tmapover.shtm.
- The Cochrane Collaboration. www.cochrane.org.

Drug Brand Names

Amphetamine and dextro-amphetamine • Adderall	Gabapentin • Neurontin
Aripiprazole • Abilify	Lamotrigine • Lamictal
Bupropion • Wellbutrin	Lisdexamfetamine • Vyvanse
Carbamazepine • Tegretol	Lithium • various
Citalopram • Celexa	Methylphenidate • Ritalin, Concerta, others
Clozapine • Clozaril	Modafinil • Provigil
Dexamethylphenidate • Focalin	Nefazodone • Serzone
Dextroamphetamine • Dexedrine, DextroStat	Olanzapine • Zyprexa
Diazepam • Valium	Paroxetine • Paxil
Divalproex sodium • Depakote	Quetiapine • Seroquel
Escitalopram • Lexapro	Sertraline • Zoloft
Fluoxetine • Prozac	Triazolam • Halcion
Fluvoxamine • Luvox	Valproic acid • Depakene
	Venlafaxine • Effexor

Disclosures

Dr. Gonzalez reports no financial relationship with any company whose products are mentioned in the article or with manufacturers of competing products. He is a recipient of a T32 Ruth L. Kirschstein National Research Service Awards training fellowship sponsored by the National Institutes of Health.

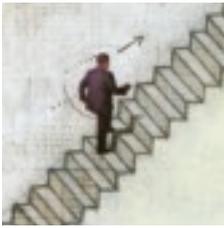
Dr. Suppes receives grants/research support from Abbott Laboratories, AstraZeneca, GlaxoSmithKline, JDS Pharmaceuticals, Janssen Pharmaceutica, National Institute of Mental Health, Novartis, Pfizer Inc., and the Stanley Medical Research Institute.

after mood stabilization with divalproex sodium. *Am J Psychiatry* 2005;162(1):58-64.

4. Meyers B. Treatment of imipramine-resistant depression and lithium-refractory mania through drug interactions. *Am J Psychiatry* 1978;135(11):1420-1.
5. Bannet J, Ebstein RP, Belmaker RH. Clinical aspects of the interaction of lithium and stimulants. *Br J Psychiatry* 1980;136:204.
6. Drimmer EJ, Gitlin MJ, Gwirtsman HE. Desipramine and methylphenidate combination treatment for depression: case report. *Am J Psychiatry* 1983;140(2):241-2.
7. Fernandes PP, Petty F. Modafinil for remitted bipolar depression with hypersomnia. *Ann Pharmacother* 2003;37(12):1807-9.
8. Berigan TR. Augmentation with modafinil to achieve remission in depression: a case report. *Prim Care Companion J Clin Psychiatry* 2001;3(1):32.
9. Berigan TR. Modafinil treatment of excessive daytime sedation and fatigue associated with topiramate. *Prim Care Companion J Clin Psychiatry* 2002;4(6):249-50.
10. Berigan T. Modafinil treatment of excessive sedation associated with divalproex sodium. *Can J Psychiatry* 2004;49(1):72-3.
11. Even C, Thuile J, Santos J, Bourgin P. Modafinil as an adjunctive treatment to sleep deprivation in depression. *J Psychiatry Neurosci* 2005;30(6):432-3.
12. Lydon E, El-Mallakh RS. Naturalistic long-term use of methylphenidate in bipolar disorder. *J Clin Psychopharmacol* 2006;26(5):516-8.
13. Carlson PJ, Merlock MC, Suppes T. Adjunctive stimulant use in patients with bipolar disorder: treatment of residual depression and sedation. *Bipolar Disord* 2004;6(5):416-20.
14. El-Mallakh RS. An open study of methylphenidate in bipolar depression. *Bipolar Disord* 2000;2(1):56-9.
15. Menza MA, Kaufman KR, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. *J Clin Psychiatry* 2000;61(5):378-81.

Clinical Point

When starting stimulants, use the minimum available dose of whatever stimulant you select and titrate slowly



Stimulants

Clinical Point

See patients every other week (at least initially) to assess for the emergence of stimulant-related adverse effects

- Wingo AP, Ghaemi SN. A systematic review of rates and diagnostic validity of comorbid adult attention-deficit/hyperactivity disorder and bipolar disorder. *J Clin Psychiatry* 2007;68(11):1776-84.
- Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry* 2006;163(4):716-23.
- Nierenberg AA, Miyahara S, Spencer T, et al. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. *Biol Psychiatry* 2005;57(11):1467-73.
- Tamam L, Tuğlu C, Karatas G, Ozcan S. Adult attention-deficit hyperactivity disorder in patients with bipolar I disorder in remission: preliminary study. *Psychiatry Clin Neurosci* 2006;60(4):480-5.
- Faraone SV, Biederman J, Mennin D, et al. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? *J Am Acad Child Adolesc Psychiatry* 1997;36(10):1378-87; discussion 1387-90.
- Faraone SV, Biederman J, Monuteaux MC. Attention deficit hyperactivity disorder with bipolar disorder in girls: further evidence for a familial subtype? *J Affect Disord* 2001;64(1):19-26.
- Faraone SV, Glatt SJ, Tsuang MT. The genetics of pediatric-onset bipolar disorder. *Biol Psychiatry* 2003;53(11):970-7.
- Simon NM, Otto MW, Weiss RD, et al. Pharmacotherapy for bipolar disorder and comorbid conditions: baseline data from STEP-BD. *J Clin Psychopharmacol* 2004;24(5):512-20.
- Calabrese JR. Overview of patient care issues and treatment in bipolar spectrum and bipolar II disorder. *J Clin Psychiatry* 2008;69(6):e18.
- 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(2):53-7.
- Van Kammen DP, Murphy DL. Attenuation of the euphoriant and activating effects of d- and l-amphetamine by lithium carbonate treatment. *Psychopharmacologia* 1975;44(3):215-24.
- Huey LY, Janowsky DS, Judd LL, et al. Effects of lithium carbonate on methylphenidate-induced mood, behavior, and cognitive processes. *Psychopharmacology (Berl)* 1981; 73(2):161-4.
- Gerner RH, Post RM, Bunney WE Jr. A dopaminergic mechanism in mania. *Am J Psychiatry* 1976;133(10):1177-80.
- Koehler-Troy C, Strober M, Malenbaum R. Methylphenidate-induced mania in a prepubertal child. *J Clin Psychiatry* 1986;47(11):566-7.
- Brady KT, Sonne SC. The relationship between substance abuse and bipolar disorder. *J Clin Psychiatry* 1995;56(suppl 3):19-24.
- Sonne SC, Brady KT. Substance abuse and bipolar comorbidity. *Psychiatr Clin North Am* 1999;22(3):609-27,ix.
- Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 1990;264(19):2511-8.
- Estroff TW, Dackis CA, Gold MS, Pottash AL. Drug abuse and bipolar disorders. *Int J Psychiatry Med* 1985-1986;15(1):37-40.
- Faraone SV. Lisdexamfetamine dimesylate: the first long-acting prodrug stimulant treatment for attention deficit/hyperactivity disorder. *Expert Opin Pharmacother* 2008;9(9): 1565-74.

Bottom Line

Stimulants may be appropriate in specific clinical scenarios when treating bipolar disorder, but adverse events or destabilization may occur. Before adding a stimulant to mood-stabilizing therapy, assess your patient's medications, diagnosis, sleep behavior, and caffeine and alcohol use. If you still consider stimulants an option, include the patient in this decision, titrate the stimulant slowly, and monitor frequently.



Committed to Veterans and to the Communities we serve

The John J. Pershing VA Medical Center in Poplar Bluff, MO seeks board-certified/board-eligible Psychiatrist for Poplar Bluff, MO and board-certified/board-eligible Psychiatrist for Paragould, AR community based outpatient clinic.

Benefits as follows

- Salary commensurate with qualifications
- Comprehensive benefits package includes health/life insurance, retirement, 401K
- Flexible spending accounts, long-term care coverage (self and family)
- 26 vacation days and 13 sick leave days may be earned each year
- Sign-on bonus and relocation expenses may be available
- Education Debt Reduction program subject to availability of funding
- Malpractice insurance covered by the Federal Tort Claims Act
- Full- and part-time positions available
- Flexible hours possible
- J-1 opportunities

CVs may be submitted to John J Pershing VA Medical Center, Attn: Human Resources (05), 1500 N. Westwood Blvd, Poplar Bluff, MO 63901. For more information please call Donna Reynolds at 573/778-4292. Position subject to physical and random drug screening. EOE