Dispelling misconceptions leads to rationale-based steps for treating bipolar depression.
Antidepressants in bipolar disorder

7 myths and realities

Few topics are as controversial as the role of antidepressants for patients with bipolar disorder. Although depression usually is the predominant, most enduring mood state in bipolar disorder, clinicians often face uncertainty about using antidepressants because of concerns about safety and efficacy. Whether and when to use antidepressants for bipolar depression hinges on complex parameters that preclude any single, simple rule.

Rather than asking if antidepressants are useful or detrimental for depressed patients with bipolar disorder, a more practical question might be: Under what circumstances are antidepressants likely to be beneficial, deleterious, or ineffective for an individual patient? Because “real world” patients often have idiosyncrasies that defy practice guidelines’ generic treatment recommendations, clinicians who practice in the proverbial trenches need strategies to tailor treatments to each patient that are informed—but not dictated—by evidence-based research.

Early suspicions
Concerns that antidepressants might precipitate mania were first described with tricyclic antidepressant (TCA) use in Europe in the 1960s. After bupropion and selective serotonin reuptake inhibitors (SSRIs) emerged, some clinicians believed they posed a lesser risk for this phenomenon compared with TCAs or monoamine oxidase inhibitors (MAOIs).

Antidepressants’ potential to induce short-term mania/hypomania following acute exposure has been weighed against the longer-term risk for worsening illness course by increasing frequency of subsequent
Bipolar depression episodes (so-called cycle acceleration). In the 1980s, some researchers suggested that rapid cycling might—at least in some instances—represent an iatrogenic phenomenon caused by long-term antidepressant use. These issues remain controversial, but more than 20 years of research suggest that antidepressants induce mania or accelerate cycling in a smaller minority of bipolar disorder patients than was once thought.

Table 1 and Table 2 (page 44) summarize findings from randomized controlled studies that have examined antidepressants’ efficacy for acute bipolar depression. Except for a study of fluoxetine plus olanzapine, no large-scale placebo-controlled trial has demonstrated superior antidepressant response to a mood stabilizer plus antidepressant compared with a mood stabilizer alone.

MYTH 1
Antidepressant-induced mania is a highly prevalent, widespread problem.

Reality: Although some might argue that the precise relative risk of antidepressant-induced mania or hypomania is unknown (eg, considering intervening factors such as the natural illness course), recent literature suggests that the emergence of mania or hypomania can be reasonably attributed to antidepressant use in no more than 10% to 25% of patients with bipolar disorder. Part of the difficulty in estimating the true prevalence of antidepressant-induced mania involves variability and inconsistency in defining mania induction.

A recent consensus statement proposed a graduated series of definitions for treatment-emergent affective switch:7

• “Definite” switch involves fulfilling DSM-IV syndromic criteria for a manic, hypomanic, or mixed episode for at least 2 days, within 8 weeks of antidepressant introduction.

• “Likely” switches call for at least 2 DSM-IV mania or hypomania symptoms plus a Young Mania Rating Scale (YMRS) score >12, occurring for at least 2 days, within 12 weeks of antidepressant introduction.

• “Possible” switches require a “clear change” in mood or energy with a YMRS score >8, persisting ≥4 hours over 2 days, occurring within 12 weeks of antidepressant initiation.

Adverse effects such as agitation typically diminish or remit with dosage reductions or drug cessation, whereas true antidepressant-induced polarity switches persist even after the medication is discontinued. Moreover, it is often difficult—if not impossible—to know with certainty when a polarity switch results from treatment effects vs the natural illness course. In my experience, true manic or hypomanic syndromes soon after antidepressant exposure are less common than heterogeneous, nonspecific symptoms such as agitation, anxiety, insomnia, or worsening depression (ie, lack of efficacy).

MYTH 2
Antidepressant response rates are lower in bipolar depression.

Reality: It is difficult to draw broad conclusions about antidepressant response rates in unipolar vs bipolar depression because:

• few direct comparisons have been reported

• all relevant studies are retrospective

• small sample sizes in most studies may not have satisfactorily controlled for factors that could predispose to mood destabilization (Table 3, page 46).

A retrospective review of bipolar (n=41) and unipolar (n=37) depressed patients by Ghaemi et al8 found no significant difference in acute nonresponse rates between the groups. Similarly, Bottlender et al9 found no differences in treatment response when comparing naturalistic antidepressant outcomes for 50 unipolar and 50 bipolar patients matched for age, sex, and illness duration. Comparable antidepressant response outcomes also were reported in a retrospective study of 2,032 unipolar and bipolar inpatients conducted by Möller et al,10 and between unipolar (n=31) vs bipolar II (n=17) depressed patients receiving venlafaxine monotherapy for 6 weeks.11

Antidepressant response may depend on factors such as episode chronicity or the number of failed medication trials within a
given episode, regardless of illness polarity. This was suggested by the remarkably low response rates after 2 failed initial antidepressant treatments in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) unipolar depression trials. In my experience, antidepressant efficacy is more often a function of factors in addition to polarity, including:

- illness severity
- chronicity
- psychiatric, medical, or substance use comorbidity
- psychosocial skills, such as the capacity to tolerate distress, utilize effective coping techniques, and maintain appropriate relationships with others.

**MYTH 3**

**Most antidepressants have been systematically studied for treatment of depression in bipolar disorder.**

**Reality:** Only paroxetine, bupropion, and imipramine have been studied in randomized, large-scale, adequately powered placebo-controlled trials. Studies of other antidepressants suffer from small sample sizes (inadequate statistical power), lack of placebo controls, or failure to control for possible confounding factors, such as lack of stratification for bipolar I vs II subtype or presence vs absence of rapid cycling.

One large randomized trial showed comparable antidepressant efficacy with a mood stabilizer plus adjunctive venlafaxine (43%)
Bipolar depression

Clinical Point
Using a medication that has been studied specifically for bipolar depression is preferable to using one that has not

Antidepressants for bipolar depression: MAOIs, TCAs, and bupropion*

<table>
<thead>
<tr>
<th>Acute efficacy</th>
<th>Reported switch risk</th>
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<tbody>
<tr>
<td>Tranlycypromine (MAOI)</td>
<td></td>
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<tr>
<td>81% response (monotherapy) in bipolar I (n=24) or bipolar II (n=32) patients over 16 weeksa</td>
<td>21%</td>
</tr>
<tr>
<td>75% response among imipramine nonresponders (n=12)b</td>
<td>17%</td>
</tr>
<tr>
<td>Moclobemide (MAOI)</td>
<td></td>
</tr>
<tr>
<td>46% response over 8 weeks in 156 bipolar patients (some, but not all, took concomitant mood stabilizers), not significantly different from imipramine comparatorc</td>
<td>4%</td>
</tr>
<tr>
<td>Imipramine (TCA)</td>
<td></td>
</tr>
<tr>
<td>57% response rate after 3 weeks in a 6-week double-blind randomized comparison with fluoxetine or placebod</td>
<td>Not reported</td>
</tr>
<tr>
<td>48% response (monotherapy) in bipolar I (n=24) or bipolar II (N=32) patients over 16 weeks2</td>
<td>24%</td>
</tr>
<tr>
<td>53% response over 8 weeks in 156 bipolar patients (some, but not all, took concomitant mood stabilizers), not significantly different from moclobemide comparatorc</td>
<td>11%</td>
</tr>
<tr>
<td>41% (coadministered with therapeutically dosed lithium)e</td>
<td>8%</td>
</tr>
<tr>
<td>Desipramine (TCA)</td>
<td></td>
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<tr>
<td>50% (5/10) response rate (coadministered with a mood stabilizer over 8 weeks)f</td>
<td>50%</td>
</tr>
<tr>
<td>Bupropion</td>
<td></td>
</tr>
<tr>
<td>55% response (5/9) (coadministered with a mood stabilizer over 8 weeks)f</td>
<td>11%</td>
</tr>
<tr>
<td>33% response rate (coadministered with mood stabilizers over 10 weeks)g</td>
<td>20%</td>
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</table>

*aNo data are available for isocarboxazid, mirtazapine, nefazodone, phenelzine, or selegiline transdermal MAOI: monoamine oxidase inhibitor; TCA: tricyclic antidepressant

Source: For reference citations, see this article at CurrentPsychiatry.com

vs sertraline (55%) vs bupropion (49%) over 10 weeks,14 but the lack of a mood stabilizer monotherapy comparison group limits the ability to anticipate whether adjunctive antidepressants increase response or remission rates more than mood stabilizers alone. Adjunctive imipramine,15 paroxetine,12,13,15 and bupropion15 yield no greater improvement in depressive symptoms than is seen with optimally dosed mood stabilizers alone.

Mirtazapine, a serotonergic/noradrenergic antidepressant that is sometimes prescribed off-label as a sleep aid, has not been systematically studied for safety or efficacy in bipolar depression. In case reports, mirtazapine has induced mania in patients with unipolar depression.16-18 Using mirtazapine to counteract insomnia may be safer in patients with unipolar depression than in those with bipolar disorder. Because poor sleep is a core feature of mania, be certain to differentiate complaints that reflect simple insomnia from a loss of need for sleep:

- daytime fatigue is more common in insomnia than loss of need for sleep
- nocturnal hyperactivity is more often associated with loss of need for sleep.

Using an antidepressant to treat sleep problems that may derive from emerging mania or hypomania runs counter to basic pharmacodynamic principles and may pose greater risk than benefit.

Generally, using a medication that has been studied for treating a specific clinical entity such as bipolar depression is preferable to using one that has not. Avoid medications that have multiple negative placebo-controlled trials—such as paroxetine—unless you have evidence of efficacy in an individual patient.

**MYTH 4**
Risk for inducing mania is higher with noradrenergic antidepressants.

**Reality:** This popular belief arose from a unifying hypothesis offered by Sachs et al1.
and Leverich et al\textsuperscript{14} to explain higher rates of mania following treatment with desipramine than bupropion,\textsuperscript{1} SSRIs compared with TCAs,\textsuperscript{2} or venlafaxine compared with bupropion or sertraline.\textsuperscript{14} However, while plausible, this hypothesis does not fully account for the putative noradrenergic properties of bupropion—presumably via increased presynaptic norepinephrine outflow, rather than noradrenergic reuptake inhibition\textsuperscript{19}—which reportedly has a lower risk of switching than desipramine\textsuperscript{1} or venlafaxine.\textsuperscript{14}

The risk for venlafaxine monotherapy to induce mania or hypomania in patients with bipolar II depression has been reported to be nonexistent\textsuperscript{11} or no higher than seen with lithium.\textsuperscript{20} Also, some noradrenergic agents, such as duloxetine, have not been shown to induce mania in major depression,\textsuperscript{21} although duloxetine’s potential to destabilize mood is unknown because of the absence of data in bipolar disorder. Finally, although large-scale clinical trials have not examined the safety and efficacy of the noradrenergic reuptake inhibitor atomoxetine, several case reports have suggested its potential for inducing mania or hypomania.\textsuperscript{22,23}

Likely, all-or-none admonitions against using noradrenergic antidepressants are oversimplifications.

**MYTH 5**

**Coadministering an antimanic mood stabilizer reliably prevents antidepressant-induced mania.**

**Reality:** Most practice guidelines advise administering antimanic mood stabilizers before initiating an antidepressant. Clinicians widely interpret this recommendation as reinforcing the assumption that a mood stabilizer will diminish mania risk when introducing an antidepressant. (Less often, clinicians interpret it as meaning that a mood stabilizer itself may provide antidepressant efficacy.) In fact, whether (and which) antimanic agents mitigate the risk for antidepressant-induced mania has received little empirical study. The largest dataset on this topic—the randomized controlled data from Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)\textsuperscript{22}—found that the risk for treatment-emergent manic switch with paroxetine or bupropion was almost identical (about 10%) with or without an FDA-approved antimanic agent.

In a retrospective study, Henry et al\textsuperscript{6} found that cotherapy with lithium but not divalproex or carbamazepine protects against antidepressant-induced mania, and that switch rates to mania were the same whether or not an antidepressant was taken with an anticonvulsant. In a naturalistic retrospective study (n=158), Bottlender et al\textsuperscript{24} revealed that mood stabilizers (lithium, carbamazepine, or divalproex) prevented switches from depression to mania during treatment with TCAs but not SSRIs or MAOIs.

I favor incorporating lithium or other antimanic agents in the regimens of patients with bipolar depression not primarily to guard against antidepressant-induced mania but more for pharmacodynamic synergy—complementary mechanisms of action that collectively may produce more substantial antidepressant effects—especially when the patient’s illness course has included manic or hypomanic features in the preceding year.

**MYTH 6**

**Antidepressants cause or worsen rapid cycling.**

**Reality:** Wehr et al\textsuperscript{25} reported that antidepressants may accelerate cycling frequency (ie, inter-episode durations become shorter) in a small subgroup (N=10) of patients. By contrast, use of TCAs was not more likely in the weeks preceding shifts from depression to mania or hypomania in a 14-year follow-up study of bipolar rapid cycling from the NIMH Collaborative Depression Study.\textsuperscript{26} In fact, rapid-cycling patients spent more weeks depressed when taking lithium without a TCA than with 1.

Findings from STEP-BD indicate that prospectively observed rapid cycling, as defined by DSM-IV criteria, is relatively rare, although subjects taking antidepressants often had multiple episodes per year.\textsuperscript{27} These naturalistic data could suggest that antidepressant use leads to more depressive episodes, or that more depressive episodes lead to more antidepressant use. Causal relationships cannot be inferred from the
Bipolar depression

Clinical Point
I believe that, in general, antidepressants are unlikely to improve a truly rapid-cycling illness course.

Nonrandomized study design. Nevertheless, antidepressant use was not associated with reduced depressive episodes over 1 year.

I believe that, in general, antidepressants are unlikely to improve a truly rapid-cycling illness course. In this scenario, a more “panoramic” understanding of the need to treat multiple relapses and polarity changes over time likely warrants using multiple anticycling agents. Rapid cycling is treated over the course of 1 year, rather than 1 episode.

MYTH 7
Antidepressants should never be used without a mood stabilizer for bipolar depression.

Reality: This admonition is widely cited as a general recommendation from modern practice guidelines; however, it mainly pertains to depression treatment in patients with bipolar I disorder, for whom most controlled trial data exist. For example, relative- ly high rates of treatment-emergent mania have been reported with TCA or MAOI monotherapy in bipolar I disorder patients (Table 2, page 44). Yet for bipolar II disorder, controlled trials demonstrate superior outcomes with venlafaxine monotherapy compared with lithium monotherapy, with no increase in mood destabilization. 20

Neither the safety nor the efficacy of antidepressants with vs without mood stabilizers has been studied systematically in cyclothymic or mood disorder patients who may fall within the so-called bipolar spectrum but have never met DSM-IV criteria for a lifetime manic or hypomanic episode (ie, bipolar disorder not otherwise specified). Extrapolation from findings based on bipolar I disorder patients may not be valid for all bipolar subtypes.

Clinical strategies
In constructing a rationale-based approach to bipolar depression, consider these steps:

Step 1: Assess candidacy for antidepressant use. A number of key features can help you delineate the current illness state and context in which depressive symptoms arise—features that may influence you patient’s vulnerability to mood destabilization, and therefore are pertinent for gauging the likelihood that antidepressants may help or harm (Table 4).

Step 2: Consider mood stabilizers with antidepressant properties. Determine whether your patient is taking any mood stabilizers that possess robust antidepres-

<table>
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<th>Table 3</th>
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<td><strong>What increases risk of antidepressant-induced mania?</strong></td>
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<tr>
<td><strong>Factor</strong></td>
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<tr>
<td>History of antidepressant-induced mania or hypomania</td>
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<tr>
<td>Recent mania preceding current depressive episode</td>
</tr>
<tr>
<td>Bipolar I vs bipolar II subtype</td>
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<tr>
<td>Comorbid alcohol or substance use disorder</td>
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<td>Noradrenergic vs serotonergic antidepressants</td>
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<td>Concurrent mania symptoms during a depressive episode</td>
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<td>Hyperthymic temperamental traits</td>
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SNRIs: serotonin/norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants

Source: For reference citations, see this article at CurrentPsychiatry.com
sant properties, or whether it may be beneficial to introduce one of these agents before initiating adjunctive antidepressants. Mood stabilizers with antidepressant efficacy are compelling options for patients presenting with any of the features listed in the right-hand column of Table 4, as well as those with:

- psychotic features
- marked agitation
- multiple prior antidepressant nonresponses
- high depression recurrence rates regardless of episode duration (ie, cyclicity, irrespective of ≥4 discrete episodes per year).

Prospective mood charting may help to establish the latter, in which case recurrence (rather than polarity) may cause waxing and waning depressed mood states.

Psychotropic agents or combinations that have shown to be effective for bipolar depression (supported by at least 1 randomized controlled trial) without destabilizing mood include quetiapine, olanzapine, olanzapine-fluoxetine combination, lamotrigine, and lithium plus lamotrigine. Those with some—but less robustly demonstrated—antidepressant action include lithium, divalproex, carbamazepine, or an antipsychotic rather than prescribing antidepressant monotherapy. There is greater diversity of opinion about the safety of antidepressant monotherapy for bipolar II depression.

- Consider using antidepressants that have at least 1 positive randomized controlled trial in bipolar disorder and low risk for mood destabilization (buproprion,[12,14] sertraline,[14] fluoxetine,[4,5] tranylcypromine,[3,28] or venlafaxine in bipolar II depression[20]) before using those with reported increased risk for inducing mania or hypomania (TCAs[1,2] or venlafaxine in bipolar I depression[19]), multiple negative controlled trials (paroxetine,[12,13]), or no controlled data in bipolar depression (citalopram, escitalopram, fluvoxamine, mirtazapine, duloxetine, desvenlafaxine, nefazodone, and selegiline transdermal). Combinations of antidepressants have not been adequately studied in bipolar depression.

- The optimal duration of antidepressant therapy is unknown. However, longer-term treatment may be worthwhile in patients who show robust acute antidepressant response and experience infrequent mania or

### Table 4

<table>
<thead>
<tr>
<th>Favors antidepressant use</th>
<th>Discourages antidepressant use</th>
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<tr>
<td>Bipolar II disorder</td>
<td>Bipolar I disorder&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Depressed (non-mixed) states</td>
<td>Mixed manic and depressive features&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Absence of rapid cycling</td>
<td>Presence of rapid cycling&lt;sup&gt;d,e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Absence of recent mania or hypomania (preceding 2 to 3 months)</td>
<td>Mania or hypomania in past 2 to 3 months&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Absence of comorbid alcohol or substance use disorder</td>
<td>Presence of comorbid alcohol or substance use disorder&lt;sup&gt;g,h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prior favorable antidepressant response</td>
<td>Suboptimal responses to prior antidepressants</td>
</tr>
<tr>
<td>No history of antidepressant-induced mania or hypomania</td>
<td>History of antidepressant-induced mania or hypomania&lt;sup&gt;i&lt;/sup&gt;</td>
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*Source:* For reference citations, see this article at CurrentPsychiatry.com

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**Step 3: Use antidepressants in suitable patients.** For patients with no risk factors for mood destabilization from antidepressants (Table 3), these drugs may be worth incorporating, keeping in mind the following guiding principles:

- In patients with bipolar I depression, it is preferable to add an antidepressant to an antimanic mood stabilizer (ie, lithium, divalproex, carbamazepine, or an antipsychotic) rather than prescribing antidepressant monotherapy. There is greater diversity of opinion about the safety of antidepressant monotherapy for bipolar II depression.

- Consider using antidepressants that have at least 1 positive randomized controlled trial in bipolar disorder and low risk for mood destabilization (bupropion,[12,14] sertraline,[14] fluoxetine,[4,5] tranylcypromine,[3,28] or venlafaxine in bipolar II depression[20]) before using those with reported increased risk for inducing mania or hypomania (TCAs[1,2] or venlafaxine in bipolar I depression[19]), multiple negative controlled trials (paroxetine,[12,13]), or no controlled data in bipolar depression (citalopram, escitalopram, fluvoxamine, mirtazapine, duloxetine, desvenlafaxine, nefazodone, and selegiline transdermal). Combinations of antidepressants have not been adequately studied in bipolar depression.

- The optimal duration of antidepressant therapy is unknown. However, longer-term treatment may be worthwhile in patients who show robust acute antidepressant response and experience infrequent mania or
In the mania signs emerge new hypomania or antidepressant until to continue an antidepressant indefinitely until the absence of rapid cycling, manic/hypomanic features, or worsening suicidal features, and in the presence of an unequivocal acute response and a greater predisposition to depression than mania, it is reasonable to continue an antidepressant indefinitely until new signs of mania or hypomania emerge.

- Emerging signs of mania or hypomania should signal the need to discontinue the antidepressant. Dosage reductions alone may not diminish emerging manic or hypomanic symptoms, and “counterbalancing” maneuvers (ie, adding antimanic agents while continuing an antidepressant) may not effectively stabilize mood.

**Step 4: Consider novel strategies.** In the absence of a response to the strategy outlined above—particularly among poor candidates for continued antidepressant therapy—other novel strategies have support from at least 1 randomized controlled trial, including pramipexole,32,33 modafinil,34 riluzole,35 and n-acetyl cysteine.36 Other interventions worth considering include:

- adjuctive thyroid hormone
- cognitive therapy
- light therapy (if a seasonal component is evident)
- electroconvulsive therapy.

**References**


**Disclosure**

Dr. Goldberg is a consultant to Eli Lilly and Company and a speaker for AstraZeneca, Eli Lilly and Company, GlaxoSmithKline, Merck, and Pfizer Inc, and has received speaking honoraria from Janssen-Cilag.


References


Table 1
References


Table 2
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Table 3
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Table 4

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