

# Antidepressants for bipolar depression: Tips to stay out of trouble

## When it makes sense to use them and for how long

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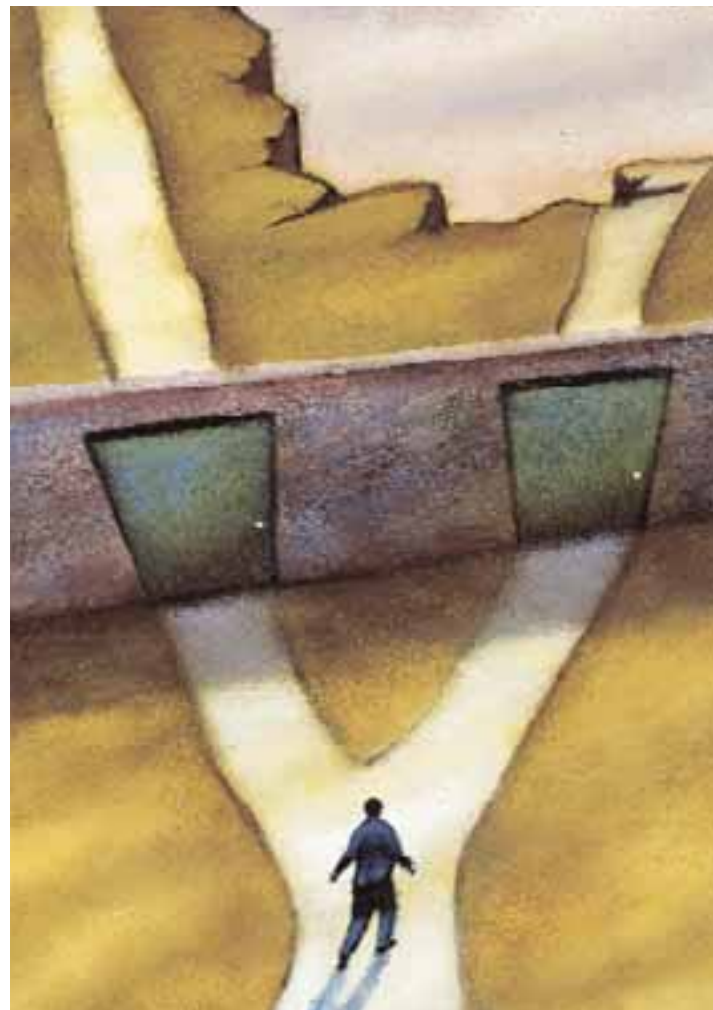
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**I**n clinical practice, 50% to 80% of bipolar patients receive long-term antidepressants,<sup>1</sup> although potential benefits probably outweigh risks in 20% to 40%. This gap suggests that psychiatrists could do more to stay out of trouble when prescribing antidepressants for patients with bipolar depression.

Antidepressants have not shown efficacy in long-term treatment, and evidence of their effectiveness in acute bipolar depression is limited. They appear to pose greater risk of switching and mood destabilization for some patients and certain types of bipolar illness, and some antidepressant classes are more worrisome than others.

Because carefully analyzing risks and benefits is essential when considering antidepressants for a patient with bipolar illness, this article clarifies that delicate balance and offers evidence-based recommendations for using antidepressants in bipolar depression.

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### ACUTE THERAPY

Clinical trials support antidepressants as the treatment of choice for unipolar depression, but less evidence supports efficacy and safety in acute bipolar depression. Depressive episodes predominate in bipolar disorder, with chronic subsyndromal symptoms being most characteristic.<sup>2,3</sup> Compared with mania or hypomania, depressive episodes:

- last longer and are more frequent
- contribute to greater morbidity and mortality
- pose a greater treatment challenge.

Antidepressants have shown benefit in multiple double-blind, bipolar depression trials and were as effective as mood stabilizers in one small study.<sup>4</sup> Even so, no trials have found them more effective than mood stabilizers in acute bipolar depression.

**Controlled trials.** Two randomized, double-blind, placebo-controlled trials have examined antidepressant use in bipolar depression.<sup>5,6</sup> The larger and better-designed—a prospective 10-week study by Nemeroff et al<sup>6</sup>—examined 117 outpatients with type I bipolar disorder.

Subjects who had been taking lithium (serum levels 0.5 to 1.2 mEq/L) for  $\geq 6$  weeks and were experiencing moderate breakthrough depression then received paroxetine (mean dosage 32.6 mg/d), imipramine (mean dosage 166.7 mg/d), or placebo. Therapeutic response was defined as  $\leq 7$  on the Hamilton Rating Scale for Depression (HRSD) or  $\leq 2$  on the Clinical Global Impression (CGI) scale—normally considered criteria for depressive remission.

The authors hoped to show a statistically significant medication-placebo difference, but the antidepressants' effects were similar to those of placebo. Thus, adding antidepressants to lithium conferred no added benefit, though the small sample size may have created a false negative.

Interestingly, a post-hoc analysis found differ-

ent treatment outcomes when patients were separated into two groups by lithium serum levels:

- low therapeutic ( $\leq 0.8$  mEq/L)
- high therapeutic ( $>0.8$  mEq/L).

Adding antidepressants significantly reduced HRSD scores compared with placebo in the low lithium group but not in the high lithium group. Thus, therapeutic lithium levels may have moderate antidepressant effects, and adding antidepressants may help patients who cannot tolerate therapeutic lithium levels.

Antidepressants may help bipolar patients who cannot tolerate therapeutic lithium levels

### MAINTENANCE THERAPY

Antidepressants may have modest efficacy in acute bipolar depression, but they have not shown benefit—with or without mood stabilizers—in 7 studies of bipolar depression maintenance therapy. Most were double-blind, long-term trials comparing tricyclic antidepressants (TCAs) with lithium or adding TCAs to lithium; 3 were placebo-controlled.<sup>7</sup> Antidepressants were not more effective than mood stabilizers such as lithium or lamotrigine in preventing bipolar depression.

**Type II patients.** For depression in type II bipolar disorder, the only data on using antidepressants as acute or maintenance therapy come from post-hoc analyses of unipolar depression trials and retrospective assessments of “manic switches.” No specific mania rating scales have been used.<sup>8,9</sup>

**Long-term antidepressants.** Two naturalistic studies by Altshuler et al<sup>10,11</sup> explored continuing antidepressants as bipolar depression maintenance treatment. The larger trial<sup>11</sup> included 84 patients (most with type I bipolar disorder) who experienced breakthrough depression while taking a mood stabilizer. This subset (15%) of the Stanley Foundation Bipolar Network had tolerated antidepressants at least 2 months without switching into hypomania/mania and remained in remission at least 6 weeks. None were rapid cyclers.

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With counseling from clinicians, patients chose to continue or discontinue taking antidepressants. Relapse rates after 1 year were 70% in patients who stopped antidepressants after <6 months, compared with 24% in those who continued taking them for 1 year. The authors concluded that bipolar patients may benefit from staying on antidepressants at least 6 months and perhaps 12 or more months after depressive remission.

Keep in mind, however, that these findings may not apply to all bipolar patients. This study pertains to a minority of robust responders—none of whom were rapid cyclers—who tolerated the medication well and were not randomly assigned to continue or discontinue antidepressants. Other evidence suggests that depressed bipolar patients are three times more likely than unipolar patients (54% vs 16%) to develop tolerance to antidepressants.<sup>12</sup>

### ANTIDEPRESSANT RISKS

Risks of using antidepressants in bipolar patients include acute switches into hypo/mania, usually within 8 weeks of starting an antidepressant, and new-onset mood destabilization—with cycle acceleration or rapid cycling—or worsening of pre-existing rapid cycling (*Table 1*).<sup>1</sup>

**Switching risk.** Some researchers have reported antidepressant-induced switches to be milder and more brief than spontaneous hypo/manias,<sup>13</sup> whereas others have observed more-severe mixed<sup>14</sup> and even psychotic episodes. Risk factors that may predispose patients to switching include:

- personal or family history of switches or mood destabilization
- family history of bipolar disorder
- exposure to multiple antidepressant trials
- history of substance abuse or dependence

Table 1

### Switches vs destabilization: Defining antidepressant risks

Risk	Definition
<b>Acute switches to hypomania/mania</b>	≤8 weeks by convention, unless dosage is increased
<b>Mood destabilization</b>	
Cycle acceleration	Increase of ≥2 mood episodes while taking antidepressants, compared with a similar exposure time before treatment
Rapid cycling	≥4 mood episodes in previous 12 months (new-onset or exacerbation of baseline pattern), according to DSM-IV-TR

Source: Reference 1

- early onset (age <25) and/or treatment of mood symptoms.<sup>15,16</sup>

True switch rates are difficult to estimate because clinical trials have used different switching definitions, durations, antidepressants (with or without mood stabilizers, and with different mood stabilizers), and cohorts (often excluding rapid cyclers). Except for the Nemeroff et al study,<sup>6</sup> no prospective, double-blind, placebo-controlled studies have examined switch rates, and even this study was not large enough to detect statistically significant differences.

Thus we must rely on naturalistic evidence that is less rigorous but more applicable to clinical practice. This literature reveals switch rates of:

- 30% to 60% with TCAs and monoamine oxidase inhibitors (MAOIs)
- 15% to 27% with selective serotonin reuptake inhibitors (SSRIs), bupropion, and venlafaxine.

Average switch rates are thought to be approximately 40% with TCAs/MAOIs and 20% with the newer antidepressants.<sup>1</sup> Preliminary data associate



Table 2

### Frequency of switching or mood destabilization with antidepressants

Bipolar risk	Causative agents	Frequency	Mood stabilizer effect
Acute switch	TCA, MAOIs	~ 40%	Variably protective; apparent partial risk reduction ~ 50%
	SSRIs, bupropion, venlafaxine	~ 20%	
Mood destabilization	TCA, SSRIs	~ 20%	Not as clearly protective against mood destabilization as against acute switching

TCA: tricyclic antidepressants; MAOIs: monoamine oxidase inhibitors; SSRIs: selective serotonin reuptake inhibitors  
Source: References 1, 15

venlafaxine with higher switch rates than SSRIs or bupropion, so perhaps antidepressants with some noradrenergic effects (including TCAs) facilitate the switching phenomenon.<sup>17</sup>

**Mood destabilization.** Three randomized, controlled trials suggest that antidepressants—especially TCAs—increase the risk of cycle acceleration or rapid cycling in bipolar patients. The best-designed study—sponsored by the National Institute of Mental Health—was a 10-year, prospective, double-blind trial of 51 rapid-cycling patients. The trial’s on-off-on design showed that 20% of these patients developed rapid cycling as a direct result of taking TCAs.<sup>18</sup>

Unfortunately, most randomized, controlled trials are not designed to show a relationship between antidepressants and mood destabilization. Observational literature is mixed but suggests that antidepressant use is associated with rapid cycling. Most evidence supports a relationship between antidepressants and long-term mood destabilization—especially cycle acceleration, which is believed to occur in approximately 20% of patients using TCAs or SSRIs.<sup>1</sup>

**Are mood stabilizers protective?** Some studies sug-

gest that mood stabilizers may help protect against switches. Most of the evidence—using lithium and TCAs—suggests a 50% drop in switch rates when patients receive mood stabilizers with antidepressants. In one study, lithium was more protective than anticonvulsants for SSRI-induced mania, but the difference was not statistically significant.<sup>19</sup>

Because study data variability, we don’t know if some mood stabilizers are more effective than others in preventing antidepressant-related switching. This variability is likely caused by:

- medication-specific factors (such as higher switch rates with TCAs and possibly dual-reuptake inhibitors than with SSRIs)
- illness-specific factors (such as rapid cycling and cycle pattern)
- patient-specific factors, already described.

Mood stabilizers appear to be more protective against switching than against mood destabilization, in which their effects are less clear (*Table 2*).<sup>15</sup>

### TREATMENT RECOMMENDATIONS

How does a clinician decide which bipolar depressed patients should receive antidepressants?

Combining mood stabilizers with antidepressants can reduce switch rates by half

The first step in treating bipolar depression (*Algorithm*) is to provide optimal dosages of the patient's mood stabilizers. Consensus guidelines<sup>20</sup> suggest lithium or lamotrigine as first-line treatments for bipolar depression. Evidence also shows efficacy for atypical antipsychotics, including the olanzapine/fluoxetine combination (OFC)—FDA-approved for acute bipolar depression<sup>21</sup>—and quetiapine monotherapy.<sup>22</sup> Dosages vary, but suggested ranges include:

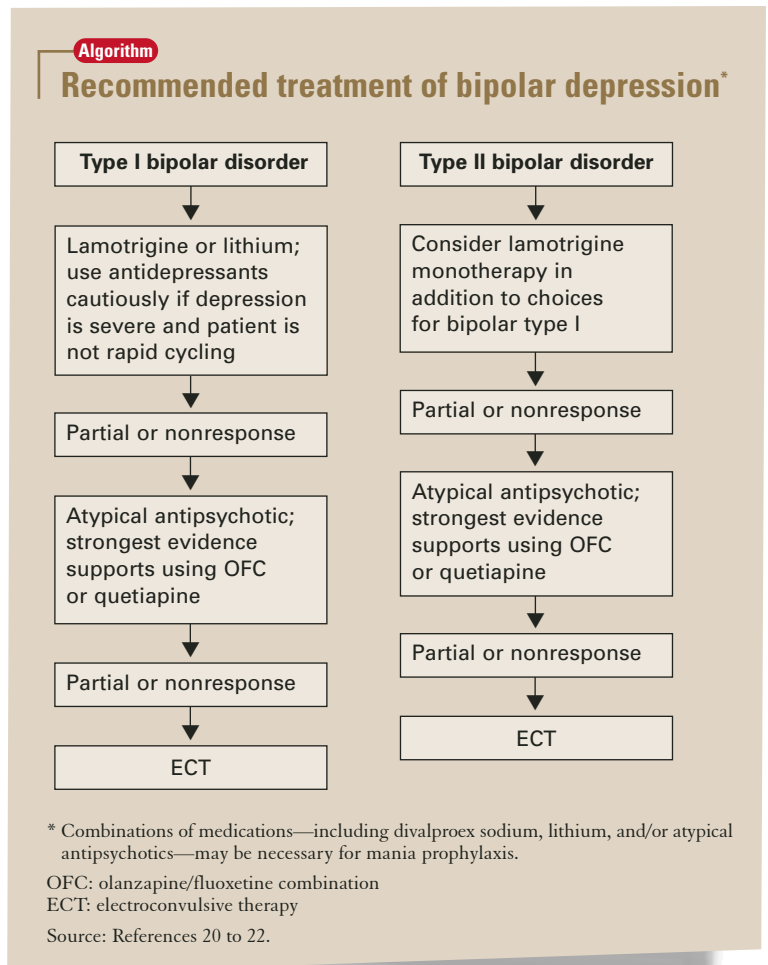
- lithium: 0.6 to 1.2 mEq/L; aim for approximately 0.8 mEq/L, but some data suggest 0.6 to 0.7 mEq/L may be sufficient
- lamotrigine: 50 to 250 mg/d (the higher dosage is based on maintenance studies)
- OFC: 6 to 12 mg olanzapine/ 25 to 50 mg fluoxetine
- quetiapine: 300 to 600 mg/d.

The next step is an antidepressant risk/benefit analysis, weighing the considerable risks of switching/mood destabilization with the patient's depressive illness severity, type of bipolar disorder (such as rapid cycling), and cycle pattern.

**Cycle patterns.** In a naturalistic study, Macqueen et al<sup>23</sup> used life chart data for 42 bipolar patients to assess how the mood state preceding a prospectively observed depressive episode affected treatment response:

- A euthymic mood state in the previous 2 months represented a uniphasic pattern and an isolated depressive episode.
- A preceding hypomanic/manic mood state indicated a biphasic pattern.

Approximately 60% of bipolar patients show a biphasic pattern, although the episode sequence is



usually depression-hypomania/mania rather than hypomania/mania-depression. These authors included patients whose breakthrough depressive episodes were treated with an antidepressant or a putative mood stabilizer but not an atypical antipsychotic.

In patients treated with an antidepressant, the response-to-switch ratio was 10:1 for those previously euthymic, compared with a less beneficial 0.75:1 in previously hypomanic/manic patients. This small study suggests that a patient's cycle pattern may help you decide whether to use an antidepressant for bipolar depression.

**How to use antidepressants.** As described, some



**Table 3**

**Antidepressants for bipolar depression?  
Consider 'ideal patient' traits**

Severe depression refractory to optimal doses of ≥1 mood stabilizers
Uniphasic cycle pattern
Not rapid cycling
No history of switching or mood destabilization
No comorbid substance abuse

depressed bipolar patients are better candidates for antidepressant therapy than others (Table 3).

Use antidepressants cautiously and conservatively in a minority of bipolar patients (approximately 20% to 40%) and usually for short periods (discussed below). SSRIs or bupropion are first-line agents because:

- they appear to be relatively less likely to cause switching than other antidepressant classes
- controlled trials have examined these antidepressants in bipolar depression.

Depressed patients with very mild, nonrapid-cycling, bipolar II disorder and no more than three previous hypomanic episodes might be candidates for antidepressant monotherapy. In other bipolar patients, always use at least one mood stabilizer if you decide to use an antidepressant.

**TREATMENT DURATION**

No randomized, controlled trial has examined what duration of antidepressant treatment may be optimum for bipolar depression, but consensus guidelines recommend:

- approximately 3 to 7 months, depending on depression severity

- approximately one-half that duration (2 to 4 months) for rapid-cycling bipolar disorder.<sup>20</sup>

Because of the switching risk, one could also argue for a shorter treatment duration in patients with a biphasic cycle pattern—especially with an episode sequence of depression to hypomania/mania to euthymia.

Ideally, patients would stay on antidepressants no longer than the natural course of their depression (usually 2 to 6 months in bipolar depression), although it could be shorter in rapid-

cyclers. Approximately 15% to 20% of patients may have a robust initial response to antidepressants and need to be maintained on these medications, especially after several tapers and relapses have failed.

Depression's severity and any rapid cycling dictate how long to try antidepressants

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### Related resources

- ▶ Bipolar Clinic and Research Program. Massachusetts General Hospital. Includes tools for clinicians and the clinical site for the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). [www.manicdepressive.org](http://www.manicdepressive.org).
- ▶ Goodwin FK, Jamison KR. *Manic-depressive illness*. New York: Oxford University Press, 1990.

#### DRUG BRAND NAMES

Bupropion • Wellbutrin  
Imipramine • Tofranil  
Lamotrigine • Lamictal  
Lithium • Lithobid, others

Olanzapine/fluoxetine • Symbyax  
Paroxetine • Paxil  
Quetiapine • Seroquel  
Venlafaxine • Effexor

#### DISCLOSURES

Dr. Altman is a speaker for Forest Pharmaceuticals, Janssen Pharmaceutica, AstraZeneca Pharmaceuticals, and Abbott Laboratories.

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Analyzing risks and benefits is essential when deciding whether to use antidepressants for bipolar depression. Evidence supports using antidepressants cautiously in approximately 20% to 40% of bipolar patients and usually for short periods. Mood stabilizers may protect against switching and destabilization.

**BottomLine**

## Have a case from which other psychiatrists can learn?



Check your patient files for a case that teaches valuable lessons on dealing with clinical challenges, including:

- sorting through differential diagnoses
- getting patients to communicate clinical needs
- catching often-missed diagnoses
- avoiding interactions with other treatments
- ensuring patient adherence
- collaborating with other clinicians.

Send a brief (limit 50 words) synopsis of your case to [pete.kelly@dowdenhealth.com](mailto:pete.kelly@dowdenhealth.com).

Our editorial board will respond promptly. If your synopsis is accepted, we'll ask you to write about the case for a future issue of CURRENT PSYCHIATRY.