TABLE 17.6. Differential Side Effects with Atypical Neuroleptics

Clozapine: Seizures and agranulocytosis
Clozapine and olanzapine (possibly, to a lesser extent, risperidone and quetiapine): Metabolic syndrome, hyperlipidemia, diabetes, and diabetic ketoacidosis
Risperidone: Prolactin elevation
Ziprasidone and paliperidone: QT-interval prolongation
Quetiapine: Possible cataract risk

galactorrhea, amenorrhea, and sexual dysfunction). This effect is most relevant to postmenopausal or dysmenorrheic women, in whom prolactin elevation is associated with an increased risk of osteoporosis. Ziprasidone is associated with prolongation of the QT interval on the ECG to a greater extent than other atypical neuroleptics, although less so than some traditional neuroleptics. The newest atypical neuroleptic, paliperidone, which is an active metabolite of risperidone, also appears to have some risk of QT-interval prolongation. In cases where cardiac history is present, baseline ECGs may be prudent.

18 Standard Antidepressants

Essential Concepts

- Overuse of antidepressants is the single most common mistake in the treatment of bipolar disorder.
- Generally, caution is advisable in using antidepressants in bipolar disorder.
- Antidepressants have been shown to be ineffective when compared with mood stabilizers in the treatment of acute bipolar depression (although they are better perhaps than no treatment i.e. placebo alone).
- Standard antidepressants can cause acute mania, new or worsened rapid cycling, or act as *mood destabilizers*, counteracting the benefits of mood stabilizers.
- Since antidepressants are mood destabilizers, all mood stabilizers that were ineffective in the presence of antidepressants (in refractory bipolar disorder) should be retried in the *absence* of antidepressants.
- The most advisable role for antidepressant use in bipolar disorder is for severe, suicidal, acute bipolar depression.
- Antidepressants probably are most risky in rapid-cycling bipolar disorder type I and least risky in non-rapid-cycling bipolar disorder type II.
- Since mania induction is probably dose-related, antidepressants should be dosed in bipolar depression lower and slower than in unipolar depression.

There are four main questions to address regarding the use of antidepressants in bipolar disorder: (1) Are they effective in treating acute bipolar depression? (2) Are they effective in preventing depressive episodes in the long-term treatment of

bipolar disorder? (3) Are they likely to cause acute mania? and (4) Are they likely to cause rapid cycling and more mood episodes over time?

EFFICACY AND SAFETY FOR ACUTE BIPOLAR DEPRESSION

Acute bipolar depression is defined as current depressive mood episode symptoms that last 2 weeks or longer. Treatment trials usually last 8 weeks. In this setting, a meta-analysis demonstrated that four studies comparing antidepressants with placebo (or in one study with olanzapine) found moderate benefit with the antidepressants (i.e., selegiline and fluoxetine). However, the two largest studies of acute antidepressant efficacy involved lithium or other standard mood stabilizers (i.e., valproate or carbamazepine) as baseline treatments. In these studies (including the largest one derived from the STEP-BD study), antidepressants added to proven mood stabilizers were not more effective than mood stabilizers alone (with placebo); the antidepressants studied were paroxetine, imipramine, and bupropion (see Table 18.1 for a summary of findings from acute studies of antidepressants in bipolar depression).

Thus the data are now more clear than previously believed. In replicated studies, antidepressants are better than nothing (no treatment) for acute bipolar depression, but they are not better than proven mood stabilizers (especially lithium). Since we generally use mood stabilizers in bipolar disorder, these data would indicate that antidepressants appear to be ineffective for acute major depressive episodes in bipolar disorder. Now, most clinicians will protest that they have experience to the contrary. Either their experience is wrong, or antidepressants sometimes may give benefit when added to mood stabilizers, but usually, the randomized studies show, they do not.

KEY POINT

Antidepressants are better than nothing but not better than mood stabilizers, such as lithium, in the treatment of acute bipolar depression.

TABLE 18.1. Summary of Findings from Acute Studies of Antidepressants in Bipolar Depression

TCAs:	High mania switch rate; no evidence of efficacy greater than lithium.
MAOIs:	Better efficacy than TCAs but high mania switch rate; moclobemide has a lower mania switch rate than TCAs in bipolar II depression; selegiline patch may be a safe alternative, although likely less effective.
SRIs:	As a class, low mania switch rate in bipolar depression type II but may differ in bipolar depression type I.
Fluoxetine:	Nondefinitive study failed to establish efficacy or safety benefits in bipolar depression type I compared with TCAs or lithium; may be safer in bipolar depression type II, although still more risky than in unipolar depression.
Paroxetine:	Highest amount of supportive data; lower mania switch rate than TCAs; efficacy same as placebo when added to mood stabilizers.
Sertraline:	Lower switch rate than venlafaxine and similar efficacy; similar switch rate to bupropion.
Citalopram:	Open, uncontrolled data find a low mania switch rate (6%).
Fluvoxamine:	No data.
Bupropion:	Lower mania switch rate than TCAs or venlafaxine, likely dose-related; efficacy same as placebo when added to mood stabilizers.
Trazodone:	No studies; avoid for insomnia in bipolar disorder.
Venlafaxine:	2.5 times more manic switch than bupropion or sertraline.
Mirtazapine:	No studies.
Selegiline:	May be less likely to cause mania.
Pramipexole:	Proven effective in bipolar depression with low risk of mania.

Given the very limited evidence of efficacy, any evidence of risk would be of concern. Of course, the main issue is the question of acute antidepressant-induced mania. The same meta-analysis mentioned previously found no evidence of antidepressant-induced mania. As with all meta-analyses, though, faulty results can happen if apples are compared with oranges, that is, if incompatible studies are

mixed. In fact, numerous studies have found evidence of mania with tricyclic antidepressants (TCAs), as did the studies in that meta-analysis; however, the STEP-BD & Stanley Foundation recant randomized studies of paroxetine, bupropion, and sertraline found no elevated risk beyond placebo.

These newer studies, which found that acute mania is not seen more with new antidepressants versus placebo in the setting of standard mood stabilizer treatment, lead to the conclusion that mood stabilizers may reduce that risk. Numerous other studies have suggested the same. On the other hand, randomized studies may not be the best setting to address this question; side effects often are best assessed in real-world nonrandomized populations [e.g., sexual dysfunction with serotonin reuptake inhibitor (SRI) antidepressants was understated in early randomized studies but robust in real-world populations].

My summary of this research is as follows: TCAs are the riskiest class of antidepressant in terms of acute mania, with irreversible monoamine oxidase inhibitors (MAOIs) having a similar risk. Among SRIs, fluoxetine likely has a similar risk than TCAs of causing acute mania in bipolar disorder type I, whereas paroxetine has been shown to have a lower risk. Bupropion and sertraline also have a lower risk of acute mania than TCAs. Venlafaxine has a 2.5-fold higher risk of causing acute mania than bupropion or sertraline. Other agents have not been studied rigorously in bipolar disorder type I, although there are some data with citalopram suggesting a relatively low mania switch rate. Switch rates are lower in bipolar disorder type II than in type I but higher than in unipolar depression. The general switch rates, in my reading of this literature, are about 50% with TCAs, about 20% with SRIs or other new antidepressants in bipolar disorder type I, and about 5% to 10% with SRIs or other new antidepressants in bipolar disorder type II. In unipolar depression, the switch rates for new-generation antidepressants are less than 1% based on many large randomized Food and Drug Administration (FDA) registration clinical trials.

Also, there may be a dose-risk relationship; at higher doses, these agents are quite liable to cause mania frequently. In my experience, I use half the dose of antidepressants for bipolar as opposed to unipolar depression.

TIP

In bipolar depression, it can be acceptable to use about half the dose of antidepressants that are recommended for unipolar depression. This approach lowers the risk of acute mania.

Such dosing is sufficient for efficacy and leads to much less acute mania. For instance, it is acceptable and in fact preferable to use bupropion at "low" doses in bipolar depression for quite a while before raising the dose; many patients respond to 100 to 200 mg per day, and I rarely go above 300 mg per day in dosing. Similarly, with paroxetine and citalopram, I rarely find a need to go above 30 mg per day, and when I do, I realize that I am increasing the mania switch risk.

EFFICACY FOR PROPHYLAXIS OF DEPRESSION IN BIPOLAR DISORDER

In the first edition of this book, I cited the TCA literature, which repeatedly demonstrated no benefit with TCAs compared with lithium in the long-term prevention of depressive episodes in bipolar disorder. Yet clinicians and patients seemed to wish strongly that matters would be different for SRIs and other new antidepressants. Many cite observational data from the Stanley Foundation Bipolar Network (SFBN), which found that patients who responded to and remained on new antidepressants had fewer relapses at 1 year than those who came off antidepressants after recovery from the initial acute major depressive episode. It was often underemphasized that these results applied only to 15% of patients in the SFBN sample. In other words, only 15% of patients given antidepressants responded acutely for a bipolar depressive episode and then remained stable for 1 year. The other factor was that the study was not randomized, and thus one could not establish causality. One could not know whether patients got better because they stayed on antidepressants or whether they stayed on antidepressants because they got better.

Thankfully, in this edition, I can discuss two new randomized studies of new antidepressants in long-term prevention

of depressive episodes in bipolar disorder. In the first, the Stanley Network found that bupropion, sertaline, and venlafaxine (added to standard mood stabilizers) were similarly effective for depression prevention (although venlafaxine caused more mania) but only in about 25% of patients at 1 year. There was no placebo group, so one cannot know whether this low 1-year remission rate is better than with no antidepressant treatment (mood stabilizers alone). We still await the first placebo-controlled maintenance study of a new antidepressant in bipolar disorder.

In the second study, by our group as part of the STEP-BD program, the Stanley Network observational study was repeated, except this time with randomization: After patients initially got better for an acute bipolar depressive episode with a mood stabilizer plus a new antidepressant (mostly SRIs), the antidepressants were randomly continued or stopped. We found no added benefit to continuing antidepressants for depressive symptoms.

Thus, just as with *acute* bipolar depression, the evidence now is more clear that antidepressants are not effective *ling-term* compared with mood stabilizers. I can now repeat, and expand the assertion to include SRIs and new antidepressants, that for prevention of future depression, antidepressants are not as effective as mood stabilizers. A subgroup of perhaps 15% to 25% of patients may get some long-term benefit from antidepressants, however (which may or may not be a placebo effect). Hence I am not saying that no patient should be treated with antidepressants. I am saying that the lion's share of patients—80% or so—have no long-term benefit with antidepressants in bipolar disorder and thus should not be treated with them.

LIABILITY TO CAUSING RAPID-CYCLING AND A LONG-TERM MOOD-DESTABILIZING EFFECT

There is also some evidence that standard antidepressants actually can worsen the long-term course of bipolar disorder. This evidence falls into two related categories: induction of rapid cycling and promotion of treatment resistance.

Induction of rapid cycling is equivalent to saying that patients experience more and more mood episodes over time. Once these episodes occur four times yearly, the definition of rapid cycling is met. A number of naturalistic studies have made this observation, with figures on new or worsening rapid cycling in the 25% range. This means that about

one-quarter of persons treated with antidepressants long term will have more and more mood episodes over time such that they become diagnosable with rapid cycling or such that their rapid-cycling bipolar illness becomes even more rapid.

It is worth emphasizing the two kinds of outcomes. In some patients, antidepressants appear to reduce the severity of depressive symptoms, frequently alleviating suicidality, yet while less severely depressed, the patient experiences many more cycles of mania and depression. This type of outcome is, in my experience, the best typical outcome with chronic antidepressant use in bipolar disorder type I: The patient oscillates around euthymia, never completely well yet still better off than the more severe mood episodes that occur without antidepressants. In the second group of patients, antidepressants lead to more frequent and *more severe* mood episodes, and stopping antidepressants leads to significant relief and sometimes complete remission of symptoms. This second group of patients is the group that I see most frequently in my clinical and especially my consultative practice.

The second large class of antidepressant effects in bipolar disorder is the promotion of treatment resistance. This effect is similar to what I just described at the end of the last paragraph. Usually associated with severe antidepressant-related rapid cycling, patients are also treatment-refractory. They do not respond to standard mood stabilizers such as lithium or even those anticonvulsants with reportedly more benefit in rapid-cycling illness. Combinations of mood stabilizers are ineffective. In these patients, the antidepressant frequently appears to be acting as a mood destabilizer, counteracting the benefits of the *mood stabilizers*. The term *mood destabilizer* highlights the essentially antitherapeutic effects of antidepressants in these patients.

Discontinuation of the antidepressant is preliminary to any appropriate assessment of mood stabilizer benefits. As noted earlier, up to 40% of patients can obtain remission by stopping antidepressants. The single most effective intervention that I make in patients with refractory bipolar disorder that leads to the most improvement is not the addition of an agent but rather the discontinuation of antidepressants. I often observe a history of aggressive antidepressant use and minimal mood stabilizer use, and yet the patient is judged to be treatment-refractory to mood stabilizers.

For example, a person might have received one antidepressant or another without any break off antidepressants for a decade, and during that time, the patient may have had

trials (usually brief, months) with lithium, valproate, and carbamazepine. The patient did not respond and is judged to be nonresponsive to those mood stabilizers. I would conclude that the patient never received a therapeutic trial of a single mood stabilizer because the concomitant antidepressant use throughout that period may have interfered with mood stabilizer benefits. One option would be to stop the patient's antidepressants and repeat trials of mood stabilizers in the absence of antidepressant agents.[1]

HOW DO YOU CONVINCE PEOPLE TO STOP TAKING (OR PRESCRIBING) ANTIDEPRESSANTS?

Patients love antidepressants; to some extent, they are fooled by the word, which seems to imply that if they are depressed, these are the medications they should take. In my experience, a great deal of education needs to go on to convince patients to stop taking antidepressants. Sometimes the education goes the other way: Patients need to convince doctors to stop prescribing antidepressants. What we doctors call *noncompliance* is often the patient's intelligent response to realizing that these medications do not work for them. This section is my attempt to convince clinicians to limit the use of antidepressants in bipolar disorder; assuming that readers are convinced, Table 18.2 will help clinicians or family members who need to try to convince reluctant patients to try to engage in treatment without antidepressants. The basic message is to teach patients that the drugs have been proven ineffective and that they have notable risks of making the illness worse. If this description coincides with the patient's clinical history, then a new, fresh approach can be taken of using mood stabilizers without antidepressants. This is often a slow process, but for many people, it is the only road to recovery.

[1]I want to acknowledge that there are many researchers and clinicians who would object to my advocacy of the cautious use of antidepressants in bipolar disorder. This setting is not the place to detail my views, which I have published in the Annotated Reading List at the end of this book. But I do want readers to know that there are those with other views. I want to emphasize here only that I am not suggesting that major depression be undertreated or ignored or that suicidality not be taken into account. I am not arguing that we should *never* use antidepressants in bipolar disorder, only that we should not use them *routinely*. I uphold using antidepressants in a minority of patients with bipolar disorder, not the majority, but this is not the same as not using them at all.

TABLE 18.2. Tips for Educating Patients about Mood Stabilizers

1. Be comfortable with the evidence of relative benefit with mood stabilizers in bipolar depression and serious risks with antidepressants. If the patient senses your lack of certainty, he or she likely will avoid mood stabilizers owing to fears about them.
2. Focus on efficacy. Explain that mood stabilizers work for the acute depressive symptoms as well as to prevent future symptoms, whereas antidepressants may work only acutely. Antidepressants may be little more than a Band-Aid, whereas mood stabilizers are necessary in the long run.
3. Explain that no antidepressants (with the exception of MAOIs) have been proven more effective than lithium in the treatment of bipolar depression.
4. Focus on long-term risks with antidepressants. Explain that antidepressants are not proven to prevent bipolar depression, unlike mood stabilizers such as lithium and lamotrigine, and that at least one-quarter of patients who take antidepressants long term worsen over time.
5. Explain that antidepressants have not been shown to reduce suicide risk or long-term mortality, whereas lithium has been shown to do so.
6. Turn to side effects. Explain that some mood stabilizers have as few or fewer side effects as standard antidepressants (e.g., gabapentin, topiramate, and oxcarbazepine). Depending on the severity of the patient's bipolar disorder, those agents might be considered. Other, more clearly proven effective mood stabilizers have some risks, but those risks can be monitored or lessened in various ways (e.g., lamotrigine, lithium, and valproate).
7. Ask the patient what he or she thinks a mood stabilizer does, and follow that with your definition. Mood stabilizers can be viewed as "antidepressants plus" because they have antidepressant and antimanic effects, stabilizing mood in the middle, whereas antidepressants are "only" antidepressants, thus leading to serious risk of mania or rapid cycling.
8. If a patient is recalcitrant or seems focused on obtaining a specific antidepressant (a common scenario), remind him or her that ongoing treatment implies a treatment plan in which the patient and the clinician agree on a course of therapy. The patient does not have to accept the clinician's recommendation, nor must the clinician follow the patient's wishes. For instance, if a patient with bipolar disorder type I insists on antidepressant monotherapy and refuses mood-stabilizing treatment, the clinician need not, and perhaps should not, treat the patient (at least pharmacologically). In my experience, this circumstance is rare. Most patients will compromise at some level, and clinicians also must compromise in certain aspects.

WHAT IS THE APPROPRIATE ROLE FOR ANTIDEPRESSANTS IN BIPOLAR DISORDER?

There is no simple answer and no consensus on this topic, but I summarize my personal viewpoint in Table 18.3. In many cases of acute bipolar depression, antidepressants are unnecessary. Certainly in patients not currently taking a mood stabilizer, they should take one. A mood stabilizer is needed for long-term treatment and also could be sufficient for acute antidepressant effect. If a patient is currently taking a mood stabilizer and has relapsed into a depression, adding another mood stabilizer makes sense because that patient needs more prophylactic mood-stabilizing effect. The second mood stabilizer also may provide enough acute antidepressant effect. However, patients may have too many side effects from multiple mood stabilizers. In such a case, one of them might be tried at a lower dose, or perhaps an antidepressant might be added. There is also the case of someone with very severe depression with serious suicidal thoughts; in this case, as rapid antidepressant treatment as possible is the first imperative, and thus use of an antidepressant along with a mood stabilizer from the start is likely warranted.

In patients who respond to antidepressants, an attempt at tapering off the antidepressant should be made. If depressive relapse occurs, another mood-stabilizing agent should be added while the antidepressant is tapered off. If antidepressant discontinuation is clearly unsuccessful owing to depressive relapse, then such patients may need long-term antidepressant treatment. These patients represent at most 20% of cases, in my experience. In the other 80%, bipolar disorder, including depressive symptoms, can be treated with minimal to no antidepressant use.

TABLE 18.3. Appropriate Roles of Antidepressants in Bipolar Disorder

1. Severe bipolar depression
2. Serious suicidality associated with pure bipolar depression
3. Acute bipolar depressive relapse despite adequate mood stabilizer use
4. Intolerability of multiple mood stabilizers for acute bipolar depression

TABLE 18.4. Diagnostic and Course Criteria for Antidepressant Use

	Type I	*Type II*
Rapid cycling	Avoid*	Cautious use
Non–rapid-cycling	Cautious use	Use*

*These are suggested rules of thumb that are not absolute. One would use antidepressants in occasional bipolar disorder type I rapid-cycling patients, and one would avoid them in some bipolar disorder type II non-rapid-cycling patients.

Source: This chart is based on a personal communication from Terrence Ketter, M.D.

Another way of thinking about who should receive antidepressants has been suggested by Terrence Ketter, and this approach involves making assessments regarding diagnostic subtype and rapid cycling (Table 18.4). These rules of thumb rely on the evidence, limited but suggestive, that antidepressants may be less risky in bipolar disorder type II than in bipolar disorder type I and that they may be more risky in rapid-cycling than in non-rapid-cycling bipolar disorder. If the patient has bipolar disorder type I and is rapid cycling, antidepressants generally should be avoided. If the patient has bipolar disorder type I and is not rapid cycling or has bipolar disorder type II but is rapid cycling, antidepressants can be used in appropriate circumstances such as those described earlier. If the patient has non-rapid-cycling bipolar disorder type II, antidepressant use may be less risky. None of these rules of thumb are absolute, of course, with the occasional bipolar disorder type I rapid-cycling patient requiring antidepressants long term, as well as poor outcome with antidepressants in some patients with non-rapid-cycling bipolar disorder type II.

ANTIDEPRESSANT-LIKE AGENTS

Given the risks of standard antidepressants, I find it clinically useful to think about other psychotropic medications that might have antidepressant effects, but mildly so, and therefore might be less likely to cause mania or long-term mood destabilization. Again, my experience is that raising the mood from acute depression is not so difficult in bipolar depression (with some exceptions); the difficulty lies in raising the mood without taking it too high into mania or rapid cycling. Hence "antidepressant-like" agents may be more useful in some

ways than full-blown standard antidepressants. What do I mean by *antidepressant-like*? I mean agents that raise mood gently and mildly, thereby producing less manic switch. In my experience, and based on naturalistic uncontrolled studies, the most useful agents of this ilk are mildly dopaminergic agents, with some evidence of benefit with selegiline and pramipexole and possible roles for other agents (such as ropinirole).

Selegiline (Deprenyl) is a selective MAOI that mainly inhibits MAO-B at low doses (mainly involved in dopamine catabolism) rather than MAO-A (mainly involved in serotonin and norepinephrine catabolism). Since MAO-A effects produce most of the serious risks associated with MAOIs (particularly tyramine-associated hypertensive crisis), use of selegiline at low doses (5 to 10 mg per day) does not require dietary restriction and poses little risk of serious drug interactions. Selegiline at these doses is indicated by the FDA for the treatment of Parkinson disease as an adjunct to levodopa. Yet selegiline at these same doses can have a mild to moderate antidepressant effect in some persons; in my experience, this effect can be quite beneficial in bipolar disorder. At higher doses (20 to 30 mg per day), selegiline also blocks MAO-A, and then it acts as another MAOI, with a need for dietary restriction and a risk of serious drug interactions (although still with perhaps somewhat lower risks for both issues than with other MAOIs). It is now available as a skin patch, which bypasses the gastrointestinal tract and thus minimizes the risk of a hypertensive reaction.

Pramipexole (Mirapex) is a selective D_3 dopamine receptor agonist, also indicated by the FDA for the treatment of Parkinson disease as an adjunct to levodopa. D_3 receptors tend to be localized to the limbic regions of the brain and appear to exert mood effects. In one double-blind study, pramipexole was more effective than placebo and equally effective as fluoxetine for acute unipolar depression. In two small double-blind studies, pramipexole was more effective than placebo in treating acute bipolar depression when added to standard mood stabilizers without induction of acute mania. (This is more evidence of efficacy in bipolar depression than we have with standard antidepressants or lamotrigine!) Naturalistic data indicate that as with all antidepressants, pramipexole can induce mania, but again, this risk appears to be dose related and generally low. Typical dosing for depression is 0.5 to 2.0 mg per day bid, which is a great deal less than the FDA-indicated doses for Parkinson disease (which are frequently double these doses or more). At high doses, there have been some cases of sleep attacks. Otherwise, it is safe and well tolerated. Occasionally, patients might feel somewhat anxious or overstimulated on it, as one might expect from its dopaminergic mechanism. Ropinorole (Requip) is in the same class and may have similar efficacy, but it has not been studied as rigorously in bipolar depression.