16 Novel Anticonvulsants

Essential Concepts

- Novel anticonvulsants, as a class, have two main advantages over standard mood stabilizers: no weight gain and limited cognitive impairment (except topiramate).
- As a rule, they are not mood stabilizers, except lamotrigine, and thus should not be used by themselves in the treatment of bipolar disorder type I. They may provide some adjunctive mood benefits, however, and may be especially useful in bipolar disorder type II.
- Lamotrigine has controlled evidence of efficacy in the prevention of bipolar disorder, especially depressive episodes, but it has been proven ineffective in the treatment of acute major depression (bipolar or unipolar), acute mania, or mixed episodes and in the prevention of rapid cycling. It has a potentially serious and life-threatening rash risk (Stevens-Johnson syndrome) that should not be overlooked but which can be minimized by slow titration. Other drug allergies (such as to antibiotics) or autoimmune disorders are major risk factors for increased risk of rash with lamotrigine.
- Gabapentin is not effective in monotherapy in bipolar disorder type I. It may have utility as an adjunct for anxiety and insomnia symptoms or in patients with bipolar disorder type II.
- Topiramate is not effective as monotherapy for mania. It has a window of 100 to 200 mg per day in adjunctive use, where it leads to weight loss, and may have adjunctive benefits for mood, particularly in bipolar disorder type II if used with other mood stabilizers.

- Oxcarbazepine is similar to carbamazepine biochemically. Although it is safer and has no significant drug interactions or need for therapeutic blood tests, it is also likely less effective. It again may be most useful in bipolar disorder type II.

GENERAL CHARACTERISTICS

Novel anticonvulsants include lamotrigine, gabapentin, topiramate, oxcarbazepine, zonisamide, levetiracetam, and felbamate. General characteristics of this class that differentiate it from standard anticonvulsants and lithium are that they do not cause weight gain (some can cause weight loss), they mainly produce anticonvulsant effects by either inhibiting glutamate or enhancing GABAergic function (unlike standard anticonvulsants, which mainly block sodium channels), they generally do not cause cognitive side effects (except topiramate), and they do not require or have therapeutic blood levels. In general, these agents are better tolerated than standard mood stabilizers, but with the exception of lamotrigine, they are also less effective. Despite wishful thinking, they generally have been proven ineffective in acute mania and thus likely have no role in bipolar disorder type I as stand-alone mood stabilizers. This lack of efficacy in type I mania does not rule out benefit in bipolar disorder type II; time will tell on this topic. Further, these agents may have adjunctive benefits when used with proven mood stabilizers. In this chapter I focus on lamotrigine, gabapentin, topiramate, and oxcarbazepine (Table 16.1), with limited discussion of the others.

LAMOTRIGINE (LAMICTAL)

Lamotrigine, the most thoroughly studied of the novel anticonvulsant agents, is indicated by the Food and Drug Administration (FDA) to delay relapse into mood episodes in bipolar disorder type I. It is not indicated by the FDA for bipolar disorder type II (as many seem to believe). It has been proven ineffective for every other aspect of bipolar disorder (i.e., acute depression, acute mania/mixed episodes, rapid cycling).

TABLE 16.1. Novel Anticonvulsants with Probable Mood-Stabilizing Effects

Drug	*Effective Dose (mg/day)*	*Comments*
Lamotrigine (Lamictal)	50–200	Best established efficacy, but only for prophylaxis (not for acute mood episodes); 1 in 6,000 risk of Stevens-Johnson syndrome with slow titration (25 mg/week); avoid or use even slower titration if drug allergies present (especially antibiotics)
Gabapentin (Neurontin)	600–1,800	Well tolerated; no drug interactions; sedation occurs; not effective in monotherapy for bipolar disorder type I; effective for anxiety and pain
Topiramate (Topamax)	100–200	Causes weight loss and cognitive impairment; not effective in monotherapy for bipolar disorder type I
Oxcarbazepine (Trileptal)	900–1,200	Fewer side effects and probably less efficacy than carbamazepine; sedating; 2% hyponatremia risk

Pharmacologic Properties

Its biochemical effect involves inhibiting the presynaptic release of excitatory amino acid neurotransmitters such as glutamate and aspartate; this effect may or may not explain its psychotropic properties. Lamotrigine is metabolized by the liver and is moderately (over 50%) protein bound. Its half-life is 25 hours, which allows for simple once-daily dosing. Some patients find it to be slightly stimulating, so I generally recommend dosing it once daily. Divalproex competes with lamotrigine for hepatic glucuronidation, inhibiting lamotrigine's metabolism and increasing its half-life to 60 hours, whereas carbamazepine, phenytoin, and primidone enhance its metabolism, decreasing the half-life to 15 hours. When used with valproate, the dose of lamotrigine should be halved owing to the markedly longer half-life. Dosing for bipolar disorder is discussed in detail below, but efficacy has been shown in the 50 to 200 mg per day range, although the maximal dose can go up to 500 mg per day. It *never* should be dosed more quickly than 25 mg per day owing to serious rash risk (see below).

I do not dose lamotrigine above 200 mg per day mainly because there is no evidence of more benefit at higher doses (400 mg per day was similar to 200 mg per day in one study of prophylaxis). Further, the risk of rash is highest as long as one is increasing the dose, so the higher one goes, the longer is the period of risk. Lastly, I have noted cognitive side effects and induction of mania with lamotrigine in some cases, usually at high doses of around 400 mg per day.

Side Effects and Rash

Most side effects with lamotrigine are rare and mild. These include headache, tremor, somnolence, and dizziness; in clinical trials, only 2% of bipolar disorder patients discontinued lamotrigine owing to adverse events. However, about 10% to 20% of patients develop a common but nonserious rash. The FDA requires discontinuation of lamotrigine if rash occurs because of the risk of progression to the rare but potentially fatal Stevens-Johnson syndrome.

Stevens-Johnson syndrome is a serious rash in which patients can experience symptoms equivalent to a severe burn. A large proportion of patients die from bacterial superinfection; those who survive can be disfigured. While obviously severe, Stevens-Johnson syndrome is rare and seems mostly associated with the rapidity of titration of lamotrigine. In the early 1990s, when lamotrigine was first studied in large-scale clinical trials, Stevens-Johnson syndrome was observed in 1 in 1,000 adult patients and 4 in 1,000 children and adolescents. Consequently, lamotrigine is not allowed for use below age 15 for nonepileptic indications. The preceding rates were observed with relatively rapid titration of the medication.

KEY POINT

When titration was reduced to the current recommendation of 25 mg per week, the incidence of Stevens-Johnson syndrome fell to about 1 in 6,000 patients, which begins to approximate data reported in some research with other agents that also can cause this condition, such as carbamazepine.

Combined therapy with valproate and lamotrigine increases the nonserious rash rate and potentially the serious risk of rash.

My recommendation, and a common conservative practice, is to increase lamotrigine by 25 mg per week in the average patient and by 12.5 mg per week in any patient in whom other risk factors for rash are present. Thus, achieving a target dose of 100 to 200 mg per day may take up to 2 to 3 months. This slow titration is usually not much of a problem in the outpatient treatment of depression and prophylaxis of mood episodes.

The most important risk factor for rash, in my view, is other drug allergies, particularly allergy to antibiotics. Data on file with the manufacturer indicate that the risk of rash with lamotrigine increases four- to fivefold in persons who have antibiotic allergies. My forensic experience with cases of Stevens-Johnson syndrome with lamotrigine also has been that antibiotic allergies tend to be present in persons who develop Stevens-Johnson syndrome with lamotrigine. Other risk factors, suggesting immunologic reactivity, are asthma, autoimmune disorders, hayfever, allergic rhinitis, and food allergies. In such patients, I either avoid lamotrigine or automatically institute a 12.5 mg per week titration. This approach slows benefit even further, but I find that using this method, I can feel about as comfortable using lamotrigine as I do using carbamazepine. Clinicians who are afraid of using this agent owing to its potentially serious medical risks should feel much more comfortable using it with a conservative titration such as this one outlined here. Patients' fears also can be allayed by pointing out the marked lowering of the risk of serious rash with a slow titration. Also, the serious rash risk appears to be highest in the first months of treatment. Once patients are taking a stable dose of lamotrigine for long-term prophylaxis, they no longer appear to possess significant risk of serious rash.

KEY POINT

Always ask about other drug allergies, especially antibiotic allergies, which increase the risk of rash with lamotrigine many times. In such cases, either do not use lamotrigine, or move it down the list of treatment options, and if it is used, prescribe it at 12.5 mg per week increments. In persons with autoimmune disorders, my practice is to avoid lamotrigine altogether.

Since lamotrigine, like lithium, has a great deal of evidence supporting its efficacy, it is important that clinicians learn to manage its side effects and allay their patients' fears so that this effective medication can be used in patients who would benefit from it. I often summarize the situation to my patients in this manner: This is a very effective medication, with very few short- or long-term side effects, except for a potentially serious rash risk, which can be lessened by a slow titration. The nonserious rash variant occurs in 10% to 20% of patients. Otherwise, this medication is very tolerable.

However, clinicians should avoid simply prescribing lamotrigine without much thought given to the small but real risk of fatality. Patients also need to be cautioned explicitly and carefully to *never* increase lamotrigine dosing on their own. Sometimes patients are used to other drugs (such as amphetamines) that have immediate dose-related effects; they need to be educated about the fact that messing with lamotrigine dosing is literally a matter of life and death.

Efficacy

In the first edition of this book, I was rather effusive in my praise of emerging studies showing benefit with lamotrigine not only in prophylaxis of bipolar episodes but also in acute bipolar depression and rapid cycling. Recently, after some legal action against the pharmaceutical industry, it has become clear that negative studies on many medications are not published or are released slowly so as to create an overly positive image of a drug's efficacy. This appears, in my view, to have been the case with lamotrigine. To its credit, the manufacturer (unlike a number of other companies with bipolar drugs) has posted all these negative data on its website (www.gsk.com). Readers can find the following evidence:

1. Lamotrigine was effective in two of two studies in prevention of mood episodes in bipolar disorder.
2. It was ineffective in two of two studies of acute mania.
3. It was ineffective in three of three studies of acute unipolar major depression.
4. It was ineffective in five of five studies of acute bipolar depression.
5. It was ineffective in two of two studies of rapid cycling.

Almost all these studies were either not published or were published only in partial form as summary results combined with other studies. A few studies were published as positive, based on secondary analyses, despite negative primary outcomes. What this means is that the drug was the same as placebo in its main analysis, although sometimes later analyses suggested some benefits in a particular subgroup. The latter subgroup benefits were not replicated in follow-up studies, however (e.g., possible benefit in a type II rapid-cycling subgroup in one study was not found in another study).

Overall, although I think that lamotrigine is a useful drug and very helpful to many patients, I fear that the glossing over of negative data, combined with the effects of marketing its real positive benefits, has resulted in clinicians forming an overly favorable impression of the extent of efficacy of this drug.

Now, I am not saying that it does not work at all; I am convinced that it has preventive benefits. I am saying that I think that the data strongly indicate that it does not have acute mood benefits and that it does not improve rapid-cycling bipolar disorder (which is not surprising; nothing does, except antidepressant discontinuation). Some would argue otherwise, suggesting, for instance, that its acute mood benefits are hard to demonstrate in 2-month studies of acute depression owing to its slow titration; this may be the case, but it remains the case that it has not been proven effective for acute depression (or mania or rapid cycling). And in this setting, Holmes' rule applies that all drugs are guilty until proven innocent (see Chapter 5).

This is the bad news. Now let's examine the good news that this agent seems to have preventive benefits, more so for depression than for mania. While this is the case based on its two maintenance studies, there is often the misconception that those same studies prove that lamotrigine is more effective than lithium in prevention of depression (and vice versa—lithium better prevented mania than lamotrigine). This may or may not be the case. Keep in mind that those studies were "enriched": They only included patients who had responded initially to lamotrigine *before* they entered the randomized maintenance study. Thus it was not a fair comparison with lithium (to do so, half the enrolled patients would have needed to be chosen based on responding initially to lithium before the study). Thus one can say that in lamotrigine responders for acute mood symptoms, lamotrigine is more effective than lithium in the prevention of depression. However, one cannot say, *in general*, that lamotrigine is more effective than lithium in the prevention of depression. In contrast, the fact that lithium was more effective in mania prevention, despite the initial preselection of patients as lamotrigine responders, *does* demonstrate that lithium is clearly more effective in the prevention of mania.

Hence, although one might call lithium a mood stabilizer "from above" (more antimanic than antidepressant) and lamotrigine a mood stabilizer "from below" (more antidepressant than antimanic), it is not clear that lamotrigine is more effective than lithium in the prevention of depression.

KEY POINT

Numerous negative studies are now available that indicate that the spectrum of lamotrigine's efficacy is sometimes overstated. Besides its maintenance benefits, it is otherwise an ineffective agent for acute mood episodes (whether mania or depression) and rapid-cycling bipolar disorder.

In sum, lamotrigine is a useful drug, but as with most new drugs, the hype may have been larger than the reality. It should be used where it is effective, not where it is not.

Medicolegal Concerns

Legal claims regarding Stevens-Johnson syndrome with lamotrigine have begun to occur, leading me to offer some basic forensic advice to clinicians. The usual issues are inadequate warning regarding the risk of Stevens-Johnson syndrome, too rapid dosing, or inappropriate indication of lamotrigine. First, with any patient given lamotrigine, the clinician should document, "Warned regarding Stevens-Johnson syndrome." Further detail also can be provided, such as warning regarding the risk of disfigurement, not only death, and spelling out of the dosing titration. Second, patients clearly should be

warned to *never* increase the dose on their own, and clinicians should not dose the drug faster than 25 mg per week. I am aware that the *Physicians Desk Reference* (PDR) dosing instructions and the sample pack differ from my recommendation (they recommend 25 mg per day for 2 weeks, then 50 mg per day for 2 weeks, then 100 mg per day for 1 month, and then 200 mg per day). This dosing titration, developed for epilepsy, is unnecessarily fast for the long-term prevention of mood episodes in bipolar disorder. Jumping from 100 to 200 mg per day overnight seems much too rapid to me. One will never be faulted for dosing this drug too slowly because it has no acute efficacy. Third, this drug has only one proven indication: the prevention of mood episodes in bipolar disorder type I. It is not indicated or proven in bipolar disorder type II or acute major depression in that setting, for instance. Clinicians should not turn to lamotrigine as their first-line drug for bipolar depression type II because it has not been shown to be effective in that setting and because it has real medical risks. If Stevens-Johnson syndrome should occur, this kind of indication would increase a clinician's legal risk. If lamotrigine is used, discussion of other standard mood stabilizers should occur and be documented, and the rationale for use of lamotrigine should be given.

TIP

For medicolegal reasons, always write "Warned regarding Stevens-Johnson syndrome" when prescribing lamotrigine, and make sure that the need for slow dosing titration is clearly explained to the patient.

GABAPENTIN (NEURONTIN)

Clinicians appear to have themselves been manic-depressive with this drug. At the height of gabapentin euphoria, it was being used for anything and everything; Massachusetts Medicaid spending, for instance, was greater with this drug than with the much better proven anticonvulsant divalproex. Partly because of the high expense, along with an off-label marketing scandal, criticism of gabapentin began to mount. When five placebo-controlled studies for acute mania proved negative, suddenly the drug was dropped. It became the butt of jokes ("A drug that has everything you would ever want except efficacy"). Ironically, it also went generic, so just when it became affordable, clinicians stopped prescribing it.

The gabapentin story tells us more about our own foibles in the profession of psychiatry than about the relative efficacy of this drug. It needs to be reconsidered with more objectivity.

Gabapentin is a synthetic analog of γ-aminobutyric acid (GABA), but its mechanism of action in epilepsy is not thought necessarily to involve GABA receptors. This mechanism might produce beneficial mood and anxiety effects. Gabapentin is eliminated primarily by the kidneys; it does not induce hepatic enzyme metabolism, nor does it have any known drug-drug interactions. The most frequently reported adverse events related to this agent include somnolence, dizziness, and ataxia. Such side effects generally are moderate and transient.

This is its main benefit: It is a safe and generally tolerable drug. Like similarly benign agents such as buspirone, academic psychiatrists have talked about how these are benign drugs searching for indications.

It is now clear that this drug should not be used by itself for acute mania and that it should not be seen as a mood stabilizer by itself for bipolar disorder type I. What has neither been proven nor disproven, because it has not been studied carefully, is whether this drug is effective in bipolar disorder type II or as an adjunct to proven mood stabilizers for bipolar disorder type I.

In the absence of randomized data one way or the other, I think that we should pay some attention to the observational evidence that suggests some benefit in those settings. Thus, in patients with bipolar disorder type II who are unable or unwilling to take standard mood stabilizers (even at low doses), gabapentin may be a safer and equally proven (or unproven) alternative to the commonly used option of antidepressants. Also, in patients with bipolar disorder type I who have partial improvement on standard mood stabilizers and/or antipsychotics, adding gabapentin may provide some additional benefit both for mood and target insomnia and anxiety symptoms. There is also some evidence that it may help with cocaine and alcohol withdrawal, and thus it may have some utility in bipolar disorder with comorbid substance abuse. Its use in pain syndromes is well proven, and thus it may be especially helpful if there is comorbid chronic pain syndrome.

Most observational studies of gabapentin tend to demonstrate utility in the 600 to 1,800 mg per day dosage range. There is no evidence of increased efficacy at doses above this range

for mood disorders. Mean doses in studies of bipolar disorder tend to cluster around 900 to 1,200 mg per day. The half-life of gabapentin is 6 hours, requiring twice- or thrice-daily dosing. In my experience, sedation tends to be the most limiting factor in tolerance of gabapentin. Most patients tolerate it extremely well.

Its active metabolite, pregabalin (Lyrica), has been marketed for chronic pain and studied in anxiety disorders, where there is benefit; its use in mood disorders has been avoided assiduously by the manufacturer, but it likely has a similar profile to gabapentin.

KEY POINT

Gabapentin may be useful in bipolar disorder type II or as an adjunct to proven mood stabilizers in bipolar disorder type I, especially in the setting of anxiety or pain comorbidities.

TOPIRAMATE (TOPAMAX)

This drug also has been proven ineffective for acute mania in five placebo-controlled studies. This means that it is not a stand-alone mood stabilizer for bipolar disorder type I. However, as with gabapentin, its potential role in bipolar disorder type II or as an adjunct in bipolar disorder type I should not be overlooked.

Topiramate functions by increasing the inhibitory action of GABA in the brain and also by blocking the effect of glutamate. It also may inhibit carbonic anhydrase and block sodium channels. Only 13% to 17% is bound to human plasma proteins; 70% of a dose is excreted unmetabolized in the urine.

Topiramate dosing in bipolar disorder is not completely established. When used alone, higher doses appear tolerable. In a double-blind monotherapy study, about 500 mg per day was somewhat more effective than about 250 mg per day. Hence, in monotherapy, this agent probably should be dosed to about 200 mg per day or more. Usually, topiramate is used in polypharmacy with other psychotropic medications. In this setting, especially if some of the other agents independently can cause cognitive impairment (such as benzodiazepines, lithium, and valproate), naturalistic evidence indicates that topiramate appears to have an effective window of about 100 to 200 mg per day. Below 100 mg per day, it is generally ineffective; above 200 mg per day, it is frequently associated with excessive side effects, often cognitive.

There are no known drug-drug interactions with lithium, carbamazepine, or divalproex sodium, but use with other carbonic anhydrase–inhibiting agents may increase the risk for renal stone formation, a side effect that occurs in 1.5% of patients. Other side effects include somnolence, dizziness, and ataxia, but these side effects are usually mild and transient.

The most troublesome side effect of topiramate is cognitive impairment, which can occur in some persons, usually consisting of word-finding difficulty, difficulty with attention, or short-term memory impairment. In some cases these effects are mild; in other cases they are more severe. This effect is dose-related and, in my experience, seems to occur more at doses exceeding 200 mg per day in combination therapy of bipolar disorder.

The most beneficial side effect of topiramate is weight loss, which appears to average about 10 to 20 pounds in patients with bipolar disorder over 3 months. Weight loss occurs in about half of patients and is also dose related, with higher prevalence above 125 mg per day. Generally, weight loss is noted after 3 months of treatment and levels off 12 to 15 months later.

TIP

The weight benefits of topiramate are a major advantage, and it is probably most useful in patients who respond well to an agent such as valproate but want to discontinue the valproate owing to weight gain. In this setting, the addition of topiramate might augment the mood effects of valproate and lead to weight loss that allows compliance.

OXCARBAZEPINE (TRILEPTAL)

Too often I see clinicians or patients using oxcarbazepine as if it was carbamazepine. It is certainly a kinder, gentler version of the latter, but it is not the same thing, just as Diet Coke is not real Coke. The two drugs have not been compared head to head in bipolar disorder, but this simply means, using Holmes' rule (Chapter 5), that one cannot assume efficacy with this agent similar to carbamazepine: It needs to be proven. Unfortunately, the manufacturer of this drug has not sponsored much research along those lines partly because clinicians were already using oxcarbazepine as if it were a

mood stabilizer. Some small studies are mixed, mostly not finding it to be better than placebo for acute mania or for long-term treatment. My own clinical experience is that it has mild benefits, if any, that seem less than what is seen with carbamazepine.

Nonetheless, owing to its fewer side effects and drug interactions, it may be an alternative once the option of carbamazepine has either been tried or at least seriously considered.

Oxcarbazepine is a chemical analogue of carbamazepine with fewer side effects. It does not require blood levels because no therapeutic ranges for efficacy have been established. It also has much less risk of hepatic abnormalities or leukopenia than carbamazepine and no significant risk of agranulocytosis or Stevens-Johnson syndrome. Hence it does not require routine laboratory monitoring of hepatic or hematologic function, and it has no common serious medical risks. Its only risk is a 2.5% incidence of hyponatremia, which, if severe, can lead to seizures. This risk can be controlled easily by occasional monitoring of serum sodium levels. The most common side effect is sedation, which is usually mild but in some patients can limit adequate dosing. Oxcarbazepine also causes quite mild induction of hepatic cytochrome P450 enzymes, thereby not usually leading to clinically significant drug interactions.

Where effective, the usual dose range of oxcarbazepine appears to be about 600 to 1,500 mg per day, with about 900 to 1,200 mg per day being the most common effective dose. It is dosed twice daily owing to a half-life of about 8 hours.

Given its limited evidence of benefit in mania or bipolar disorder type I, I would again view this drug as an alternative primarily for bipolar disorder type II or only as an adjunct in bipolar disorder type I but not as a stand-alone mood stabilizer in bipolar disorder type I.

Its active metabolite, licarbazepine, is under current study.

In sum, oxcarbazepine is not carbamazepine, for better or for worse.

KEY POINT

Oxcarbazepine is not carbamazepine, either in side effects or in efficacy. It likely has fewer benefits than carbamazepine, but in some patients (especially bipolar disorder type II), those benefits still may be sufficient. It has fewer side effects.

OTHER POTENTIAL MOOD STABILIZERS: ZONISAMIDE, LEVETIRACETAM, TIAGABINE, FELBAMATE

Of these other anticonvulsants, a few reports on tiagabine have suggested that it is likely not notably effective in the treatment of bipolar disorder. Early reports with felbamate were very encouraging, with significant efficacy reported in some severely ill patients. Recognition of a serious risk of agranulocytosis led to an FDA-imposed restriction on use of felbamate in the United States only for patients diagnosed with epilepsy. In those cases where it might be available, however, felbamate indeed may have effective mood-stabilizing effects (see Table 16.2 for dosing guidelines).

Some clinical experience has suggested moderate adjunctive mood-stabilizing benefits with zonisamide and levetiracetam, but these results have not been robust, and no further randomized studies have been either conducted or at least publicly reported. Zonisamide has the advantage of causing weight loss but having fewer cognitive side effects than topiramate; it has a very long half-life and potential overlap of risk of rash in persons with sulfa allergies, however.

TABLE 16.2. Other Novel Anticonvulsants

Drug	*Epilepsy Dose (mg/day)*	*Comments*
Felbamate (Felbatol)	1,200 (tid)	Aplastic anemia risk; probably effective as mood stabilizer but FDA-restricted to epilepsy
Tiagabine (Gabitril)	32–56 (bid)	Not effective in early naturalistic bipolar studies; may be anxiolytic
Levetiracetam (Keppra)	1,000–2,000 (bid)	Appears well tolerated
Zonisamide (Zonegran)	200–600 (qhs)	Sedating; renal stones (2%–4%); contraindicated if sulfa allergic; 48- to 72-hour half-life
Pregabalin (Lyrica)	75–300 (bid)	Active metabolite of gabapentin

Levetiracetam has no drug interactions and a wide dosage range (like gabapentin) and some notable efficacy in epilepsy. However, in the absence of better efficacy data in bipolar disorder, it would seem wise to follow Holmes' rule of generally avoiding these agents until better proof of efficacy arrives.

Atypical Neuroleptic Agents

Essential Concepts

- Atypical neuroleptic agents are *not* mood stabilizers.
- All atypical neuroleptics are effective antimanic agents.
- Atypical neuroleptics may have adjunctive long-term preventive effects but little long-term efficacy in monotherapy for bipolar disorder (i.e., not mood stabilizers).
- Atypical neuroleptics (with the exception of ziprasidone and aripiprazole) possess more risk of weight gain than traditional neuroleptics.
- Differential side effects among these agents include seizures and agranulocytosis with clozapine, prolactin elevation with risperidone, elevated cholesterol and lipid and diabetes effects with clozapine and olanzapine, and some prolongation of the electrocardiogram (ECG) QT interval with ziprasidone.
- In mood disorders, atypical neuroleptics generally should be dosed at half the doses used in schizophrenia.

Since the first edition of this book, the National Institute of Mental Health (NIMH)–sponsored large Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study has been published. As with the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) and STEP-BD studies in unipolar and bipolar conditions, CATIE provides important data regarding the treatment of schizophrenia. For our purposes, its results regarding side effects will be relevant.