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.

MECHANISMS OF ACTION

Unlike traditional neuroleptics, which required over 90% D_2 blockade to produce antipsychotic effect, the atypical neuroleptics produce antipsychotic effects with less than 80% D_2 blockade (often in the 40% to 60% range). Further, all atypical neuroleptics tend to block almost all (>90%) serotonin-2 (5HT-2) receptors. Third, atypical neuroleptics appear to possess greater selectivity for dopamine receptor blockade in the limbic regions of the brain (that subserve mood and thought) rather than the nigrostriatal areas (that produce extrapyramidal side effects).

A GENERAL CLASSIFICATION OF TRADITIONAL AND ATYPICAL NEUROLEPTIC AGENTS

A common way of classifying traditional neuroleptic agents has been to divide them into high-, middle-, and low-potency classes based on D_2 blockade (Table 17.1). I find it helpful to analogously categorize atypical neuroleptic agents based on D_2 and 5HT-2 blockade. I list clozapine and quetiapine as low-potency atypical neuroleptic agents because they do not block over 90% of 5HT-2 receptors (more in the 40% to 80% range), and they do not block D_2 dopamine receptors at higher than 60% levels, even at higher doses. Further, like their traditional neuroleptic counterparts, these atypical agents block multiple other receptor systems, with anticholinergic, antihistaminic, and antiadrenergic effects. I list olanzapine as a middle-potency agent because it blocks over 90% of 5HT-2 receptors at all doses, it produces dose-related increased D_2 blockade reaching over 80% at 20 mg per day, and it has anticholinergic, antihistaminic, and antiadrenergic effects. I list risperidone ziprasidone and aripiprazole as high-potency agents because they block over 90% of serotonin receptors, they produce dose-related D_2 blockade that exceeds 80% to 90% at high doses, and they have few other receptor effects. As with traditional neuroleptics, potency differences among atypical neuroleptics influence side effects. Lower-potency atypical agents have fewer parkinsonian extrapyramidal symptoms (EPSs), more anticholinergic effects, and more weight gain; higher potency atypical agents possess more parkinsonian side effects and less weight gain; and middle-potency agents are midway on all accounts. However, with atypical neuroleptics, some other differences apply owing to

TABLE 17.1. Classification of Traditional and Atypical Neuroleptics Based on Potency

	Low Potency	*Middle Potency*	*High Potency*
Traditional neuroleptics	Chlorpromazine (Thorazine) Thioridazine (Mellaril) Less D_2 potency Fewer parkinsonian EPSs Multiple receptor blockade effects	Perphenazine (Trilafon) Trifluoperazine (Stelazine) Intermediate on all counts	Haloperidol (Haldol) Fluphenazine (Prolixin) More D_2 potency More parkinsonian EPSs Few other receptor blockade effects
Atypical neuroleptics	Clozapine (Clozaril) Quetiapine (Seroquel) Less D_2 potency Less 5HT-2 potency Fewer parkinsonian EPSs Multiple receptor blockade effects More weight gain*	Olanzapine (Zyprexa) Intermediate, with exception of weight gain*	Risperidone (Risperdal) Ziprasidone (Geodon) Aripiprazole (Abilify) More dose-related D_2 potency More parkinsonian EPSs Few other receptor blockade effects Less weight gain

Note: Akathisia and TD do not differ in general between potency groups for either traditional or atypical neuroleptic classes.

*Olanzapine produces more weight gain than quetiapine, which may have to do with the greater serotonin blockade of olanzapine and the potential contribution of such blockade with weight gain (in addition to histamine blockade, which occurs with both agents).

the added effect of serotonin blockade, which may predispose to weight gain. Owing to the complex influences of serotonin and histamine blockade on weight gain, olanzapine causes more weight gain than quetiapine. As with traditional neuroleptics, risk of tardive dyskinesia (TD) and akathisia does not seem to differ significantly between potency groups.

USE OF TRADITIONAL NEUROLEPTICS IN MOOD DISORDERS

Traditional neuroleptics have been and are still used widely in the treatment of mood disorders, mainly bipolar disorder. However, two double-blind studies have demonstrated that traditional neuroleptics added to lithium are ineffective in the prevention of mania in bipolar disorder compared with lithium alone. In fact, the use of neuroleptics simply tended to worsen long-term depression. Thus, outside of treating acute mania, these agents are simply not proven effective in the long-term prevention of mania and actually may cause or worsen depressive symptoms in patients with mood disorders. In addition to limited evidence regarding efficacy in bipolar disorder, the safety of traditional neuroleptic use remains controversial. Numerous studies have suggested that patients with bipolar disorder may be at increased risk for the development of EPSs and TD compared with patients with schizophrenia when treated with traditional neuroleptic agents. It is generally agreed that traditional neuroleptics should be avoided or used only temporarily in patients with bipolar disorder. However, until recently, manic inpatients treated with traditional neuroleptics ostensibly for acute mania generally were not tapered off their traditional neuroleptics after the acute manic episode resolved.

EFFICACY OF ATYPICAL NEUROLEPTICS IN BIPOLAR DISORDER

Given the disadvantages of traditional neuroleptics, atypical neuroleptics have emerged as a much preferable alternative in mood disorders. There is a biochemical rationale why this may be the case. Mechanistically, dopamine blockade likely

confers an antimanic effect. Since traditional neuroleptics only possess dopamine blockade effects, they tend to bring mood down from mania, but they continue to exert a downward effect on mood, leading to depression in many persons. Serotonin-2 receptor blockade may produce some antidepressant effects by means of increasing neurotransmission along 5HT-1 receptors, which is the serotonin receptor system thought to mediate antidepressant effects. Yet 5HT-2 blockade by itself is likely weak in its antidepressant effects; standard antidepressants that share this mechanism also have other effects (such as serotonin reuptake blockade for nefazodone or alpha-2 adrenergic blockade for mirtazapine).

Atypical neuroleptics differ in their other effects, which may be relevant to antidepressant properties. In addition to 5HT-2 blockade, risperidone is a strong alpha-2 blocker (which blocks a negative-feedback loop, resulting in increased serotonergic and noradrenergic transmitter availability). Olanzapine increases frontal lobe serotonin neurotransmission preferentially, which may assist with antidepressant efficacy. Ziprasidone is a rather potent blocker of serotonin reuptake at a level in vitro similar to that of tertiary tricyclic antidepressants (TCAs). Some combination of these kinds of effects with antidopamine effect may allow atypical neuroleptics to exert antimanic effects without leading to depression (which is the most clear clinical effect observed in bipolar disorder). Further, this biochemical profile could explain mood-stabilizing properties with this class.

ACUTE MANIA

Consequently, numerous double-blind studies have been conducted with olanzapine and risperidone in acute mania, and one double-blind study has been conducted with clozapine, quetiapine, and ziprasidone each. All these studies have found these agents to be effective in treating acute mania. The entire class clearly seems effective as antimanic agents.

Initial randomized clinical trials found that risperidone and olanzapine produced fewer EPSs in acute mania than haloperidol. This finding was not surprising, but it was important because all previous comparisons had occurred in schizophrenia, and we know that patients with bipolar disorder are likely more sensitive to EPSs.

However, in the CATIE study, there were hardly any differences in EPSs between atypical neuroleptics and perphenazine

(Trilafon). Yet low doses of perphenazine were used, and somewhat lower akathisia rates were seen with quetiapine than with perphenazine.

KEY POINT

One of the key findings with most of these studies is that atypical neuroleptics treat acute mania without any worsening of depression. In other words, resolution of acute mania is not followed frequently by a switch into acute depression. This finding differs from the research with traditional neuroleptics in bipolar disorder, many of which were associated with a depressogenic effect.

PROPHYLAXIS OF BIPOLAR DISORDER

As discussed in Chapter 7, I do not see atypical neuroleptics as mood stabilizers. This is so because I do not believe that their maintenance studies demonstrate efficacy in the prophylactic phase of treatment. I reviewed my rationale on this topic in Chapter 7, and I am aware that my interpretation of trials contrasts with current Food and Drug Administration (FDA) indications for maintenance treatment in bipolar disorder for olanzapine and aripiprazole.

KEY POINT

Neuroleptics, including olanzapine and aripiprazole, are not mood stabilizers and should not be used by themselves for long-term treatment of bipolar disorder in place of proven mood stabilizers such as lithium.

My view is that these agents should not be used in monotherapy for long-term treatment of bipolar disorder as if they were mood stabilizers in place of proven mood stabilizers such as lithium. However, they may have some utility as adjunctive mood-stabilizing medications combined with proven mood stabilizers. Since the randomized evidence for their long-term benefit is not very strong, adjunctive neuroleptic medication should be continued long term only if patients do not remain stable on mood stabilizers alone.

ACUTE BIPOLAR DEPRESSION

In Chapter 12 I discussed the use of atypical neuroleptics for treatment-refractory unipolar depressive symptoms. In acute bipolar depression, olanzapine alone has been shown to be minimally different from placebo. However, the combination of olanzapine and fluoxetine has received an FDA indication for acute bipolar depression. Also, two large studies with quetiapine alone now indicate that it is much better than placebo for acute bipolar depression, also leading to an FDA indication. It is important to keep in mind that these indications are only for *short-term* treatment, meaning 8 weeks of efficacy. These medications should not be continued automatically for long-term treatment of bipolar disorder; either they have not been studied for prophylactic efficacy, or they have not been shown to have prophylactic efficacy. Many clinicians mistake acute depression efficacy for long-term benefits, and it is very important to make this distinction.

KEY POINT

The benefit of quetiapine in acute bipolar depression may be due mainly to a depressive mixed state as opposed to a true antidepressant effect.

It is my impression that this efficacy with quetiapine may be due to the depressive mixed state, as discussed in Chapter 4. As noted there, since the current definition of a mixed state in DSM-IV is quite strict, one can have a major depressive episode with up to three manic symptoms and still be included in bipolar depression clinical trials. Probably about one-half of patients with bipolar disorder who experience a major depressive episode have at least one or two or more manic symptoms, thus meeting the criteria for the depressive mixed state. It is my impression that antipsychotics such as quetiapine may be especially effective in the depressive mixed state as opposed to pure major depression. However, these studies have not yet been analyzed to clarify this question.

Biochemically, the atypical neuroleptics that might have the most antidepressant effects are ziprasidone, which possesses significant serotonin reuptake blockade, and aripiprazole, which is a direct 5HT-1A agonist. Early clinical trials with aripiprazole in acute bipolar depression have been negative, and randomized data with ziprasidone will be forthcoming.

Some research design matters may explain the early negative data with aripiprazole; it is my clinical experience that it seems to help some patients with acute bipolar depression.

SIDE EFFECTS OF ATYPICAL NEUROLEPTICS

Tardive Dyskinesia (TD)

There is a myth that the risk of TD worsens with time, that TD is irreversible, that acute EPSs predict an increased risk for later TD, and that all neuroleptics have been shown to cause TD. However, schizophrenia is associated with a spontaneous TD rate in healthy young adults of about 0.5% per year. This contrasts with the normal population and patients with affective disorders, who do not have any notable incidence of spontaneous TD below age 60 years. After age 60, however, in the nonpsychiatrically ill general population, there is a spontaneous incidence of TD that approximates about 0.5% per year. These spontaneous rates probably reflect abnormalities in the extrapyramidal neuronal tracts of the brain. Hence there is a TD risk throughout life in schizophrenia possibly owing to abnormal brain structures in that condition in those areas, and there is a TD risk occurring in late life in the general population presumably owing to gradual degeneration of brain function in susceptible persons in those areas. Consequently, TD occurs unrelated to neuroleptic medications. We are interested in the risks related to those medications, and thus we must be careful not to attribute spontaneous TD to neuroleptics.

Probably the most carefully conducted long-term study of TD with traditional neuroleptics was conducted at Yale University. In that study, 398 patients with psychotic disorders (mostly schizophrenia) were followed prospectively with TD rating scales every 3 months for 8 years (1985–1993). An average TD incidence of about 5% per year was noted, but the important finding, which conflicts with accepted opinion, was that almost 20% of patients developed TD in the first 3 years of treatment. After the first 3 years, the TD rate seemed to plateau at about 1% per year. It is important to remember that the spontaneous TD rate in schizophrenia is about 0.5% per year. Thus the added risk owing to neuroleptics is about 0.5% per year after the first 3 years of treatment. The earlier TD literature seems to suggest overall TD rates of about 40% to 50% after about 20 years of neuroleptic

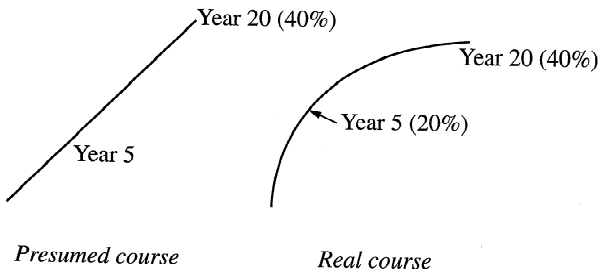

FIG. 17.1. Real versus presumed courses of TD.

treatment. The myth is that this risk is linear (Fig 17.1); the Yale study shows that the risk is asymptotic, with half the TD occurring in the first few years of treatment and the other half occurring very gradually over the following two decades. In other words, as the Yale study investigators note, in contrast to accepted wisdom, TD risk is highest early in treatment, in the first few years of new treatment with neuroleptics in a person never previously treated with those agents. If a person has taken a neuroleptic for 19 years, he or she is not very likely to develop TD in year 20. After the first few years of treatment, those who have not developed TD represent a relatively TD-resistant cohort of patients. Such patients are much less at risk for TD than someone who has never taken neuroleptics before and is newly being prescribed them.

TIP

There is no indication to stop a neuroleptic owing to fear of future TD in someone who has taken it for longer than 5 to 10 years without developing TD.

It is also important to bear in mind, in relation to the preceding figures, that not all these cases represent irreversible TD. TD is often temporary, resolving after a time. Thus patients observed to develop TD in the preceding reports may not have continued to manifest symptoms years later.

The findings of the Yale study generally have been confirmed by a number of other prospective studies of TD, with

the added proviso that the risk of TD in the elderly (above age 60 years for the purposes of research) patient with schizophrenia is even higher. In the first year of treatment with a traditional neuroleptic, the risk of TD has been shown to be 25% to 38%, and after only 2 years, about 34% to 66% in various studies. Hence the elderly patient has about as much TD risk in 1 year as occurs in 5 years in a young adult.

I emphasize these points because they bear directly on our ability to know whether atypical neuroleptics possess much risk of TD. I frequently hear from clinicians that we do not have enough experience with atypical neuroleptics to understand their TD risk. These clinicians assume that we need 10 to 20 years of follow-up to be able to make such assessments. However, based on the data provided earlier with traditional neuroleptics, 3 to 5 years of data should provide evidence on the highest risk period, and we do have such data with most atypical neuroleptics. For risperidone, double-blind, controlled data on its use in the first year of treatment in clinical trial conditions (n = 3,298) indicate a TD incidence of 0.6% versus 2.7% with haloperidol. With olanzapine, in clinical trials of 1,714 patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder treated for up to 2.6 years with either olanzapine or haloperidol in a double-blind fashion, the 1-year risk of TD was 0.52% with olanzapine versus 7.45% with haloperidol (p = 0.002). The risk ratio was 11.86 [95% confidence interval (CI) = 2.30, 61.14]; thus the risk of TD is almost 12 times higher with haloperidol than with olanzapine. The rates with risperidone and olanzapine were equal to the spontaneous rate in schizophrenia. We would expect rates in the 5% to 10% range, as seen with the haloperidol control, if atypical neuroleptics were as risky as traditional agents in the first year of treatment. The first year of treatment is the highest risk period for TD. Risk of TD with risperidone also has been studied in the high-risk elderly population with schizophrenia, with a TD rate of about 5% for risperidone at 9 months of treatment versus about 30% for haloperidol (total n = 122).

I am not asserting that TD never occurs with atypical neuroleptics or that it never should be attributed to atypical neuroleptics. However, such TD is extremely rare, and there is enough evidence to feel relatively certain that when it occurs, it is mild.

It should be noted that in the CATIE study, patients who had pre-existing TD were excluded from assignment to treatment with perphenazine, and thus TD risk comparisons could not be made between atypical and typical neuroleptics in that study.

Extrapyramidal Symptoms (EPSs)

Most clinicians appear to identify EPSs with parkinsonian tremor and rigidity, and they often will include TD as part of EPS. This definition omits akathisia, which I believe is the most important type of EPS because it is associated with suicidality, is easily confused with other conditions, and is most highly associated with noncompliance.

A common idea is that there is a relation between acute EPSs and future risk of TD, which has not been shown to be the case. High-potency typical neuroleptics do not appear to be more likely to cause TD than low-potency agents. Further, since clinicians tend to mean acute side effects in reference to EPSs (i.e., occurring in the first weeks to months of treatment), I will exclude TD from the definition of EPSs I will use here. EPSs consist, therefore, of acute parkinsonian tremor or rigidity, acute dystonia, acute dyskinesias (usually reversible and not progressive to TD), and akathisia (Table 17.2).

Of these, parkinsonian tremor and rigidity often elicit the most clinical attention because they are objective and relatively easily observable. Such parkinsonian side effects are responsive to anticholinergic effects. Hence low-potency traditional neuroleptics demonstrate a lower amount of parkinsonian symptoms than high-potency agents. Alternatively, anticholinergic drugs, such as benztropine (Cogentin), can reduce these parkinsonian effects. On the other hand, those anticholinergic effects cause their own side effects (including dry mouth, constipation, and cognitive impairment).

In contrast to parkinsonian side effects, akathisia is more difficult to detect and treat.

Akathisia: The Most Important EPS

About half of EPSs represent akathisia. If akathisia is missed, half the cases of EPSs will be misinterpreted as other conditions. Conservative estimates indicate that about 25% of

TABLE 17.2. Extrapyramidal Symptoms (EPSs)

1. Parkinsonian tremor 2. Rigidity 3. Acute dystonia 4. Acute dyskinesia	50% of cases
5. Akathisia	50% of cases

patients treated with traditional neuroleptics develop akathisia. About half the cases of akathisia are delayed, not occurring until after the first month of treatment, but most cases occur within 3 months. (There are rare cases of extremely delayed and chronic, or "tardive," akathsia.)

Akathisia has subjective and objective components. Subjectively, it consists of an intense feeling of dysphoria and extreme anxiety, such as occurs with panic attacks. Objectively, it is associated with observed physical restlessness and an inability to sit still. This restlessness is not necessarily consistent, but it can be intermittent, occurring for a few hours in a day or less. Hence akathisia cannot be ruled out based on lack of observed physical restlessness during an office visit. Clinicians often ask patients whether they feel like they need to "jump out of their skin." In my experience, if positive, this symptom is almost pathognomonic of akathisia, but its absence does not rule out akathisia.

Based on these characteristics, akathisia frequently is confused with other conditions (Table 17.3). In my experience, the most common misdiagnosis is vaguely observed *agitation*. Frequently, such agitation is simply ascribed to the offending medication, but this vague description gives no guidance to a clinician about how to manage it. The same issue holds for the more vague term *activation*, which I often hear in relation to atypical neuroleptics, as well as serotonin reuptake inhibitors (SRIs) such as fluoxetine. Especially with SRIs, many of these cases of "activation" or "agitation" are cases of akathisia. Another common misdiagnosis is mania; this mistake is linked to the agitation problem. Sometimes clinicians will observe agitation in a patient with bipolar disorder and conclude that it represents mania (rather than systematically assessing mania criteria). It is my hunch that many purported cases of "mania" related to atypical neuroleptic use really represent undiagnosed akathisia. Lastly, such agitation can be misinterpreted as worsening psychosis in patients with schizophrenia.

TABLE 17.3. Potential Misdiagnoses of Akathisia

Mania
Agitation
Psychosis
Activation
Panic attack

KEY POINT

One of the leaders in research on akathisia in the 1970s and 1980s, Theodore Van Putten, conducted a number of studies that indicated that up to 10% of patients with schizophrenia experienced worsening psychosis driven by akathisia. In those patients, the distinction from psychosis unrelated to akathisia was crucial because in the case of akathisia-related apparent psychosis, the symptoms improved with lowered antipsychotic dosing, whereas in other cases of psychosis, the appropriate treatment would have been to increase the antipsychotic dose.

Besides the fact that akathisia represents half of the cases of EPSs, it is important to diagnose this side effect because it is associated with noncompliance and suicidality. My experience agrees with much of the literature on the issue of noncompliance. I find that many patients can tolerate a mild degree of parkinsonian tremor or rigidity, but even mild akathisia is highly disagreeable, and patients need immediate relief. This usually requires reduction in dosing of the neuroleptic or, where reduced dosing leads to less efficacy, the addition of a beta blocker such as propanolol. I usually dose propanolol at 10 mg bid, gradually increasing if needed to effect, with a maximum dose of 40 mg bid. It is important to check a baseline pulse and to follow the pulse as one increases the dose, not increasing the dose beyond a minimal pulse of 50 beats per minute.

There are no clearly informative studies comparing different kinds of beta blockers in the treatment of akathisia. Cardioselective agents, such as atenolol, are helpful at times and have the advantage of not crossing the blood-brain barrier, unlike propanolol. Sometimes clinicians will avoid propanolol because of the reported risks of depression or sedation related to its central nervous system (CNS) activity. Meta-analyses indicate that the relative risk of depression with propanolol is quite low, and in my experience, patients with bipolar disorder rarely appear to develop depressive symptoms in relation to propanolol. Propanolol also has the advantage of providing some direct CNS anxiolytic relief for the subjective experience of akathisia. I therefore tend to begin with propanolol and move to cardioselective agents only if intolerance to propanolol occurs. Other general risks with beta blockers

sometimes can limit their use, such as the risk of elevation of cholesterol in long-term use, sexual dysfunction (impotence) in men, and a relative contraindication in patients with severe diabetes or asthma.

Consequently, akathisia sometimes can be sufficient reason to change the neuroleptic medication, when lowered dosing or the addition of beta blockers is either ineffective or not indicated. In any case, akathisia never should be allowed to fester; this side effect calls for immediate and quick relief.

When missed or ignored, akathisia can lead to suicidality. This process sometimes involves a lack of recognition on the part of patients that their intense dysphoria, anxiety, and restlessness may be a side effect; these symptoms are attributed more frequently to their depressive or manic syndromes, leading to demoralization, and sometimes suicide is seen as the only viable form of relief. This process may have been related to a number of the cases of fluoxetine-related suicide that have been published. Again, clinicians need to educate their patients about the nature of akathisia, and when it is suspected, all efforts should be made to resolve akathisia as soon as possible so as to reduce the suicide risk.

Differential Risks of Atypical Neuroleptics for EPSs

It is important to emphasize that all atypical neuroleptic agents cause EPSs. The difference with traditional neuroleptics is that atypical neuroleptics cause fewer EPSs, not that the atypical agents do not cause any EPSs. Clinicians often see reports of clinical trials where EPS rates with atypical neuroleptics are described as equal to those of traditional neuroleptics; this does not mean that there are no EPSs with those agents. Clinical trial patients are "clean," lacking medical and other psychiatric comorbidities that may increase EPS rates and leading to lowered rates in their cases. Such side effects often are obtained more accurately in the "uncontrolled" environment of real-world clinical experience ("naturalistic" studies). A good example of this is the case of sexual dysfunction with SRIs, which initially was denied in clinical trials but became obviously common in clinical practice.

Consequently, to summarize the relation of atypical neuroleptics to EPSs, parkinsonian side effects may be lower with the less potent atypical neuroleptics (Table 17.4), but akathisia rates differ less in the different potency classes.

TABLE 17.4. Dosing of Atypical Neuroleptics in Bipolar Disorder and Recommended Laboratory Tests

	Typical Dose in Mood Disorders (mg/day)	*Dose Schedule*
Clozapine	200–600	qhs
Risperidone	2–6	qhs
Olanzapine	5–20	qhs
Quetiapine	300–600	bid
Ziprasidone	80–160	bid
Paliperidone	3–12	qhs

Recent community-based studies on risperidone similarly report more EPSs than previously expected. In one study, EPS prevalence with risperidone (49%) was similar to that with haloperidol (48%). In another, 50% of elderly patients with dementia demonstrated moderate parkinsonism with risperidone. Two other reports on small samples, one in schizophrenia and another in bipolar disorder, found an akathisia prevalence of 14%.

One study that compared EPSs in patients treated with clozapine (n = 19), risperidone (n = 9), and typical neuroleptics (n = 22) found the prevalence of akathisia to be 10.5% with clozapine, 11.1% with risperidone, and 22.7% with typical neuroleptic agents. Parkinsonian symptoms were reported to be 0% with clozapine, 11.1% with risperidone, and 31.8% with typical neuroleptics.

With olanzapine, double-blind clinical trials report akathisia rates of about 7% to 14% compared with 21% to 33% with haloperidol.

In summary, akathisia rates tend to run in the 10% to 20% range with atypical neuroleptic agents, and while they appear lower than traditional neuroleptic comparators, they are not insignificant.

Atypical Neuroleptic–Induced Mania

Much controversy existed in the past about whether atypical neuroleptics could cause mania. Most of this speculation has been put to rest with the clear efficacy of these agents in treating mania. However, current clinical experience suggests that perhaps some of the newer agents, such as ziprasidone and

aripiprazole, in fact may cause mania in some cases. These agents have antidepressant-like biochemical mechanisms that may put them at higher risk of such effects. More studies are needed to determine whether this possibility in fact reflects a drug effect as opposed to natural history.

OTHER RELEVANT PHARMACOLOGY: DOSING AND LABORATORY TESTS

My experience, supported by a number of studies, is that atypical neuroleptics need to be dosed in bipolar disorder at about half the dose used in schizophrenia. This lower dose may reflect increased side effects in bipolar disorder (particularly EPSs) and/or increased efficacy at lower dose (where the atypical profile of maximal serotonin blockade and moderate antidopamine effect is most evident). Hence, with risperidone, 2 to 4 mg per day is usually sufficient; with olanzapine, 5 to 15 mg per day; with quetiapine and clozapine, 100 to 200 mg per day; and with ziprasidone, 20 to 80 mg per day. In my experience, it is rare to need higher doses in bipolar disorder. With the exception of ziprasidone, all these agents (including risperidone) can be dosed once daily.

Clearly, there are two major side-effect problems with atypical neuroleptics: metabolic syndrome and EPSs. I discussed EPSs earlier. Turning to metabolic syndrome, the agents most associated with this outcome are clozapine and olanzapine, although there also may be some risk with quetiapine and risperidone. The newest agents, ziprasidone and aripiprazole, do not appear to have this risk. Nonetheless, the FDA has put a black box warning on all drugs in this class for potential risk of diabetes and lipid abnormalities. In Tables 17.5, the current guidelines of the American Diabetes Association are provided for testing to assess, prevent, and manage metabolic risks with atypical neuroleptics. It is important to note that the risk of metabolic syndrome is independent of weight gain, although, obviously, if there is weight gain, there also will be an even higher risk of metabolic syndrome.

As summarized in Table 17.6, atypical neuroleptics differ in other side effects besides EPSs and weight gain and metabolic syndrome. Clozapine has a serious risk of seizures and agranulocytosis, requiring weekly or biweekly blood monitoring. Risperidone is associated with prolactin elevation; whereas this effect is common at the laboratory level, clinically associated side effects are infrequent (5% to 10% of patients, mainly

ADA/APA CONSENSUS STATEMENT

The Prevalence of Obesity, Diabetes, and Dyslipidemia Differ among the Second-Generation Antipsychotics

Ziprasidone and aripiprazole are associated with little or no significant weight gain, diabetes, or dyslipidemia. Clozapine and olanzapine are associated with the greatest weight gain, as well as dyslipidemia and diabetes. Risperidone and quetiapine appear to have discrepant effects.

The American Diabetes Association (ADA) and the American Phychiatric Association (APA) examined the relative risk of second-generation antipsychotics in treating psychiatric disorders.

ADA/APA Consensus Guidelines

Recommend that physicians consider the metabolic side effects associated with each antipsychotic agent before choosing a therapy.

Doctors should consider switching the atypical agent in patients who gain more than 5% of initial body weight or who develop worsening glycemia or dyslipidemia.

Source: American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity, Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care.* 2004; 27:596–601.

TABLE 17.5. American Diabetes Association Monitoring Guidelines for Risk of Metabolic Syndrome with Atypical Neuroleptics

Drug	*Weight Gain*	*Risk for Diabetes*	*Worsening Lipid Profile*
Olanzapine	+++	+	+
Clozapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/−	−	−
Ziprasidone*	+/−	−	−

Note: +, increase effect; −, no effect; D, discrepant results.
*Newer drugs with limited long-term data.

Sources: Adapted from *Diabetes Care.* 2004; 27:596–601; and *J Clin Psychiatry.* 2004; 65:267–272.

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