

Atypical Antipsychotics and the Burden of Disease

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Abstract

The atypical antipsychotics are defined by improved tolerability in comparison with conventional antipsychotics. Specifically, the atypicals are substantially less likely to cause troubling extrapyramidal symptoms and prolactin elevation. This reduction in adverse effects (AEs) is attributed to their short duration of occupancy at dopamine-2 receptors in the central nervous system and a high degree of activity at serotonin receptors of various subtypes. The main AEs associated with the atypicals are weight gain and metabolic effects, including disturbances in glucose metabolism and a risk of induced diabetes. However, the atypicals are not interchangeable: the risk of incurring these effects is high with clozapine and olanzapine, moderate with risperidone and quetiapine (but perhaps increasing at higher doses), and minimal with ziprasidone and aripiprazole. The atypicals have proved useful as monotherapy in treating schizophrenia and in combination with other psychoactive agents in treating bipolar disorder. Because of their improved tolerability, the atypicals offer the prospect of improved compliance and reduced risk of relapse, thus decreasing costs by the need for less hospitalization.

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In 1990, the US Food and Drug Administration (FDA) approved clozapine for treatment of schizophrenia, marking the advent of the second-generation or atypical antipsychotics. Several other atypicals were subsequently introduced and approved: risperidone (1993), olanzapine (1996), quetiapine (1997), ziprasidone (2001), and aripiprazole (2002). Other compounds classified as atypicals but not currently approved in the United States include sertindole, zotepine, and amisulpride.

Because clozapine has been associated with rare but potentially fatal cases of agranulocytosis, its use has become generally restricted to patients with treatment-resistant psychosis. The other atypicals are accepted as first-line oral therapy for schiz-

ophrenia. More recently, their utility in bipolar disorder has been recognized, and research into their use in other psychiatric disorders is under way.

The main advantage of the atypicals over the conventional (first-generation or typical) antipsychotics such as haloperidol is improved tolerability. Although the atypicals differ in terms of mechanism of action, their propensity to cause extrapyramidal symptoms (EPS, including parkinsonism, akathisia, and dyskinesias, as well as a long-term complication known as tardive dyskinesia) and elevations in prolactin is substantially lower than that of conventional agents. This clinical characteristic is the most widely accepted criterion for atypicality within the antipsychotic class of drugs.

All effective antipsychotics—conventional and atypical—modulate activity at the dopamine-2 receptors in the central nervous system. Except for aripiprazole, which is a partial D₂ agonist, all antipsychotics function as D₂-receptor blockers. However, whereas conventional agents are tightly bound and exert a prolonged duration of effect, atypical agents are more loosely bound, exerting a more transient effect. The atypicals also offer a variety of modulating effects at several serotonin receptor subtypes, whereas conventional agents have little or no serotonergic effects. The shorter duration of D₂ occupancy and their serotonergic effects are believed to account for the overall improved tolerability of the atypicals in comparison with conventional agents, and possibly also for their occasionally reported ability to improve cognitive function, their ability to reduce the negative symptoms of schizophrenia (ie, apathy, flat affect), as well as the more easily recognizable positive symptoms (ie, hallucinations, delusions, disordered speech).

Nevertheless, the atypical antipsychotics are not interchangeable. The specific recep-

tor-binding characteristics of each of the various atypicals are reflected in differences in their individual clinical profiles. For example, the risk of EPS has been reported to increase with dose with risperidone (and possibly with olanzapine and ziprasidone) but not with quetiapine.¹ In addition, the atypicals as well as the conventional agents vary in terms of their anticholinergic activity, which can cause familiar symptoms such as dry mouth as well as impaired cognition, a serious concern in older patients.

Prolongation of the QT_c interval on electrocardiography has been reported with ziprasidone and, less frequently, with other antipsychotics.

However, the main adverse effects (AEs) associated with the atypical antipsychotics are metabolic abnormalities, including weight gain, diabetes, and abnormal lipid profile. These risks are considered relatively high with clozapine and olanzapine, intermediate with risperidone and quetiapine, and low with ziprasidone and aripiprazole (Table).²⁻⁵ The burden of obesity is especially serious among patients with psychosis, many of whom are overweight even before antipsychotic pharmacotherapy is initiated because of poor diet and a sedentary lifestyle.⁶ Weight gain is the most frequent reason for noncompliance to antipsychotic therapy.⁷

There has also been concern about inducing or exacerbating insulin resistance, with consequent risks of hyperglycemia and diabetes, in patients who are started on atypicals, and these agents are now labeled with warnings about this risk. Antipsychotic-induced weight gain accounts for some but

not all of this risk; cases of new-onset diabetes have been reported without undue weight gain, and even untreated patients with schizophrenia may show an elevated prevalence of impaired glucose metabolism. The abnormalities associated with some atypical antipsychotics are increased cholesterol and triglyceride levels, which are independent risk factors for cardiovascular disease.^{3,5}

This article focuses on the use of atypical antipsychotics in schizophrenia, the archetypical psychotic disorder, and bipolar disorder, a more common condition associated with psychotic symptoms.

Schizophrenia

Epidemiology. Schizophrenia affects approximately 1% of the population, and this prevalence seems to be similar for men and women across different countries and cultures.⁸ Despite its relatively low prevalence, schizophrenia is a major contributor to long-term disability. The most frequent clinical manifestations are psychosis, apathy, withdrawal, and cognitive impairment. With onset typically in late adolescence or young adulthood (peak age range, 16-30), the condition is long term and is usually persistent throughout life. The cause is unknown, although genetic and early environmental influences have been suggested.

Disease Burden. Schizophrenia incurs a heavy burden on patients, in terms of medical and psychiatric comorbidity; social, educational, and occupational dysfunction; and overall quality of life (QOL). Potentially lethal medical conditions that are more prevalent in patients with schizophrenia than in normal populations include cardiovascular disease (related to cigarette smoking, obesity, diabetes, and hypertriglyceridemia), human immunodeficiency virus, and hepatitis (related to substance abuse and high-risk sexual activity).⁹ In addition, poor compliance with treatment and with preventive measures may contribute to the incidence and severity of these associated conditions.

Psychiatric conditions linked to schizophrenia include depression, attention deficit/hyperactivity disorder, behavioral disturbances, substance abuse, and neurocognitive deficits. Poor insight into the illness itself is very com-

Table. Atypical Antipsychotics and Metabolic Abnormalities

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

+ indicates effect; -, no effect; D, discrepant results.
 *Newer drugs with limited long-term data.
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mon and significantly correlated with general poor judgment, social withdrawal and poor rapport, preoccupation with their psychotic symptoms, and lower levels of education, reliability, work performance, and income.¹⁰

The burden of schizophrenia, which may be lifelong, is heavy not only for patients but also for their families. The burden can be physical (direct care), emotional (uncertainty about the course of the disease), social (embarrassment, stigmatization, lack of support), and financial (cost of treatment, support of the patient). Moreover, these stresses may eventually create a negative atmosphere characterized by tension between patients and their families, to the detriment of all.¹¹

Two rating instruments—the Quality of Life Index and the Burden Assessment Scale—were used in a comparison between the parents of outpatients with schizophrenia and a normal reference group. The parents of the patients, bearing the brunt of the responsibility for providing care, showed significantly lower scores on QOL, which were correlated with significantly higher ratings of perceived burden.¹² Indeed, the burden of schizophrenia is at least as great as the burden of physical illness. In a large-scale survey from Italy, families of patients with schizophrenia or brain diseases were found to face greater burdens with less social support and help than the families of patients with physical disorders. Commonly reported adverse consequences for family caregivers included constrained social activities and feelings of loss.¹³

Treatment. Despite the long-term and persistent nature of schizophrenia, treatment can significantly reduce the symptoms and burden of disease. Antipsychotic agents are used alone or in combination with antidepressants, anxiolytics, or other psychoactive medication. Cognitive behavioral therapy may be a useful adjunct to pharmacotherapy.

The overall strategy of treatment relies on careful individualized patient assessment to select the optimal regimen and monitoring to detect AEs of treatment (weight gain and disturbances in glucose and lipid metabolism). Even so, rehospitalization is very much the rule rather than the exception, and only about 1 in 3 patients will achieve an outcome good enough to permit a satisfactory degree of

social functionality.¹⁴ AEs of medication—especially EPS and hyperprolactinemia from conventional antipsychotics and weight gain from atypical agents—contribute substantially to noncompliance with treatment. In turn, noncompliance contributes substantially to the high rate of relapse requiring rehospitalization, which greatly increases the overall cost of treatment.

Atypical antipsychotics are now the mainstay of pharmacotherapy for schizophrenia. Initial decisions (choice of drug and dosage regimen) and subsequent adjustments in therapy are aimed mainly at minimizing the incidence and severity of AEs, while maintaining effective control of psychotic symptoms. Once antipsychotic medication has been initiated, monitoring for effectiveness and safety is essential. If the initial regimen is unsatisfactory (ineffective and/or intolerable), the options are dosage adjustment, add-on therapy, or switching therapy.

As stated, weight gain is the AE most likely to interfere with compliance with atypical antipsychotics, just as EPS is the AE most likely to interfere with compliance to conventional agents. Weight gain is substantial with clozapine. Among the first-line agents, risperidone is considered to incur a moderate risk of weight gain. The risk of EPS with risperidone is dose-related,¹⁵ but the risk of weight gain does not appear to be so.² Risperidone is also associated with a risk of prolactin elevation, which may cause such manifestations as galactorrhea and diminished libido.¹⁶ An injectable formulation designed for biweekly administration may permit improvements in symptom control and QOL.^{15,17}

Olanzapine, like clozapine, is associated with substantial weight gain, especially at higher dosages. A retrospective survey of 1191 patients treated with olanzapine for schizophrenia or schizoaffective disorder for up to 52 weeks revealed that rapid weight gain (increase of at least 7% over baseline weight within 6 weeks) occurred in approximately 200 patients.¹⁸ In another study conducted to assess the prevalence of weight gain with olanzapine, 27 patients with schizophrenic or schizoaffective disorder took olanzapine over a mean duration of 22 months. The results showed that the mean weight gain over the study period was 9.2 kg or 20.28 pounds.¹⁹

These findings illustrate the importance of close monitoring of weight, to identify those patients likely to gain the most weight, so that appropriate countermeasures (ie, dose adjustment as needed, dietary counseling, exercise program, switching medications) can be taken.^{3,20} A Cochrane Database Review comparing risperidone with olanzapine found scant differences in terms of antipsychotic efficacy; however, risperidone was associated with worse EPS, while olanzapine caused more weight gain.²¹

Quetiapine provides effective treatment of schizophrenia with minimal risk of EPS or prolactin elevation, and moderate weight gain.^{22,23} Among the atypicals, quetiapine appears to be associated with the shortest period of D₂ receptor occupancy and has relatively limited serotonin antagonism. It has also been found that because of quetiapine's H₁ receptor-binding profile, sleep induction and continuity can be improved.²⁴ These sleep-improving qualities of quetiapine may be important because results from studies have shown that patients with schizophrenia have different sleep patterns than the general population and due to that often have inadequate sleep. Lack of sleep can exacerbate their symptoms and increase stress, as well as significantly reduce the patients' QOL.^{25,26}

Ziprasidone was the first atypical antipsychotic that incurred little or no risk of weight gain.²⁷ In a double-blind clinical trial, 296 patients with acute schizophrenia or schizoaffective disorder were randomized to twice-daily treatment with either ziprasidone or risperidone for 8 weeks.²⁸ Both drugs were effective in reducing psychotic symptoms, but ziprasidone was associated with fewer problems related to weight gain, prolactin elevation, and EPS.²⁸ Similarly, in a study comparing ziprasidone with olanzapine, 269 patients were randomized to receive either ziprasidone or olanzapine for a 6-week period. After 6 weeks of treatment, both drugs shared comparable efficacy, but body weight, total cholesterol, triglycerides, low-density lipoprotein, and insulin levels significantly increased in the patients taking olanzapine.²⁹

These results were sustained during a 6-month continuation study. The efficacy between the 2 drugs continued to be comparable but there were significant tolerability dif-

ferences as well. Weight, glucose metabolism, and lipid levels increased in the patients in the olanzapine group while the patients in the ziprasidone group had nonsignificant metabolic changes and continued weight loss.³⁰

In another study, 565 patients were randomized (in a 3:1 ratio) to receive ziprasidone or haloperidol, with flexible dosing during acute management (up to 3 days of intramuscular treatments) and also during 6 week follow-up with the oral formulation of the same drug. Assessments by blinded observers showed significantly greater clinical improvement with ziprasidone IM as compared with haloperidol in the acute phase. Efficacy of oral treatments was equivalent through 6 weeks. Across formulations, ziprasidone had fewer problems with EPS among patients treated with ziprasidone, compared with those treated with haloperidol.³¹

The newest atypical to receive FDA approval is aripiprazole. Because of its partial agonist activity at D₂ receptors, aripiprazole is described as a dopamine modulator rather than a dopamine blocker. Like ziprasidone, weight gain and EPS appear to be minimal with this agent, and it is considered to be as effective as other agents of its class.³² In a double-blind study of aripiprazole or risperidone versus placebo in 404 patients with schizophrenia, both drugs reduced positive symptoms, aripiprazole reduced negative symptoms, neither drug caused EPS or substantial weight gain, but risperidone caused substantial elevations in prolactin.³³ In a placebo-controlled trial as maintenance in patients with chronic stable schizophrenia, aripiprazole produced a significant delay in the mean time to relapse.³⁴

Bipolar Disorder

Bipolar disorder refers to a group of affective disorders in which episodes of depression alternate with nondepressed or elevated moods. The major types are bipolar I disorder, in which patients experience episodes of mania and, in some cases, psychotic symptoms; and bipolar II disorder, in which there may be hypomanic episodes (elevated or irritated mood not fulfilling the clinical criteria for mania) as well as depressive episodes, but no manic episodes and no psychotic symptoms. Atypical antipsychotics have been studied mainly in the treatment of manic

episodes in patients with bipolar I disorder. All atypical agents are approved for bipolar mania, olanzapine and aripiprazole are approved for bipolar maintenance,³⁵ and olanzapine/fluoxetine combination is approved for bipolar depression.³⁶

Epidemiology. The prevalence of bipolar disorder has been estimated variably at anywhere from 1.3%³⁷ to 3%-5%,³⁸ with the diagnosis usually made before age 30.³⁷ Bipolar II is more common than bipolar I, affecting up to 5% of the population.³⁹ Both sexes are affected equally across age groups.³⁷ The cause of bipolar disorder is unknown, but familial patterns suggest a genetic component.

Disease Burden. Bipolar disorder carries a substantial risk of death, as approximately 1 in 4 patients attempt suicide at some point, and up to 15% of patients die by suicide.^{38,40} Comorbid conditions are common, and may easily complicate the diagnosis and compromise the therapeutic outcome.

The most frequent form of psychiatric comorbidity is alcohol abuse; other substance abuse disorders, anxiety disorders (such as panic disorder and obsessive-compulsive disorder), and impulse control or conduct disorders are also frequently encountered. Common forms of medical comorbidity include migraine, thyroid disorders, metabolic disorders, and cardiovascular disorders.⁴¹

Bipolar disorder is a chronic condition characterized by a high rate of relapse and often suboptimal responses to conventional pharmacotherapy. The social and economic impact of bipolar disorder is heavy. Patients experience functional impairment and occupational disability or dysfunction, and utilize a disproportionate share of health services. As with schizophrenia, the emotional burden on the family of the patient with bipolar disorder can also be heavy, especially in the case of pediatric patients.

Treatment. The proper diagnosis is exceedingly important, because reliance on antidepressants alone, to treat depressive episodes, may actually induce more severe rapid cycling in patients with bipolar disorder.⁴² Acute manic episodes in patients with bipolar

I disorder have been treated with such diverse agents as lithium, antiepileptic drugs such as carbamazepine and valproate, and conventional antipsychotics; however, clinical outcome is often poor, in large part because of noncompliance related to the AEs of these agents.⁴³

The advent of the atypical antipsychotics offered a new, better tolerated approach to pharmacotherapy in bipolar disorder.⁴⁴ In some patients, these agents are used in combination with antidepressants or other psychoactive agents. Atypical antipsychotics are recommended as first-line treatment for bipolar disorder, as demonstrated by 2 important recently published guidelines.

The Texas Implementation of Medication Algorithms (TIMA) expert consensus panel advise physicians to use atypical antipsychotics, lithium, or valproate as first-line therapy. Evidence from clinical trials demonstrated that the atypical antipsychotics share a common antimanic "class effect." Therefore, physicians choosing one of these therapies should base their decision on the patient's history, potential AEs, and the patient's response to the individual drugs.⁴⁵

The American Psychiatric Association's guidelines concur with TIMA's guidelines although they suggest lithium in combination with an antipsychotic, or valproate in combination with an antipsychotic for those patients who are severely ill. For less ill patients, monotherapy with an antipsychotic, lithium, or valproate is considered sufficient. The APA prefers atypical antipsychotics over the typical antipsychotics due to their more favorable AE profile.⁴⁶

Role of the Atypical Antipsychotics

Before the era of atypical antipsychotics, the treatment of schizophrenia and bipolar disorder were distinct from each other. Conventional antipsychotics were the mainstay of treatment of schizophrenia, and mood stabilizers were used in bipolar disorder. The proved effectiveness of the atypical antipsychotics in treating both conditions has led to a growing "convergence" in pharmacotherapy.⁴⁷ In patients with bipolar I disorder, atypicals are used mainly in the acute manic phase, and comprehensive therapy often requires combination with conven-

tional mood stabilizers and antidepressants; in patients with schizophrenia, monotherapy is more common. Until more precise diagnostic and therapeutic modalities are established, the atypicals have assumed a key role in the treatment of both conditions.

Notwithstanding their improved tolerability in comparison with conventional antipsychotics, the atypicals are certainly not free of AEs. Weight gain and metabolic disturbances can be serious impediments to treatment. However, these effects are especially uncommon with the newer agents of this class, ziprasidone and aripiprazole, and the fact that the atypicals are not interchangeably alike offers clinicians many options for optimizing therapy in each patient.

For example, 270 patients with persistent symptoms or intolerable AEs during treatment with conventional antipsychotics, olanzapine, or risperidone were switched to ziprasidone in a 6-week, open-label study, which showed that the change resulted in reduced symptoms and was well tolerated.⁴⁸

Patients who successfully completed that trial were then followed up for 1 year while continuing to take ziprasidone. The weight loss in patients switched from olanzapine or risperidone to ziprasidone continued to drop over the year. For patients switched from olanzapine to ziprasidone, additional weight loss was 22 lb. For those switched from risperidone to ziprasidone, the additional weight loss was 15 lb. The patients' cholesterol and triglyceride levels also decreased. Cholesterol levels in patients switched from olanzapine to ziprasidone decreased 18 mg/dL and their triglyceride levels decreased 55 mg/dL, while patients switched from risperidone to ziprasidone experienced a 13 mg/dL decrease in cholesterol levels and a 37 mg/dL drop in their triglyceride levels.⁴⁹

Overall, the atypical antipsychotics have resulted in improved QOL for patients.⁵⁰ They have also proved cost effective, as their improved tolerability in comparison with conventional agents is reflected in improved compliance, which in turn reduces the risk of relapse, and the need for costly hospitalization. For example, in schizophrenia, an analysis of outcomes after switching from conventional to atypical antipsychotics decreased symptom days by 33%, reduced

EPS days by up to 50%, and decreased total medical costs by 19% over a 3-year period.⁵¹ Again, the differences between atypicals must be recognized. Recent research showed that rates of rehospitalization and emergency department visits were significantly lower after initiation of quetiapine than after initiation of olanzapine or risperidone.⁵² However, as with most claims of superiority of one agent over another, these studies need to be replicated.

The early atypical antipsychotics represented a substantial advance over the conventional agents in terms of tolerability, yet poor compliance remains a problem. The newest atypicals may likewise prove to be a substantial advance over the first agents introduced in this class, offering effective control of psychotic symptoms with minimal AEs, which may be reflected in better compliance and fewer relapses.

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