Overview of Safety and Tolerability of Atypical Antipsychotics Used in Primary Care

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Data on the safety and tolerability of atypical antipsychotics such as clozapine, risperidone, olanzapine, quetiapine, and ziprasidone are still accumulating because these agents are relatively new compared with conventional antipsychotics. Current research and clinical practice indicate that atypical antipsychotics are generally safer and better tolerated than and as effective as conventional antipsychotics. The incidence of motor side effects such as extrapyramidal symptoms and tardive dyskinesia, anticholinergic side effects, prolactin elevation, and QTc prolongation appears to be low with most atypical antipsychotics. Clozapine and olanzapine are associated with more anticholinergic side effects than are other atypical antipsychotics; risperidone, with more prolactin elevation; and ziprasidone, with greater QTc prolongation. Weight gain is a problematic side effect of antipsychotic treatment, especially with olanzapine and clozapine. Most side effects of antipsychotics are dose related, and physicians should, therefore, use the lowest efficacious dose for the individual patient. In evaluating the risk/benefit profile of an atypical antipsychotic, physicians should determine the likelihood of occurrence of its common side effects and the degree of impairment or discomfort associated with these side effects. During the course of treatment, patients should be monitored regularly for the emergence of side effects, especially those that have the potential to negatively impact the physical well-being of the patient. *(Primary Care Companion J Clin Psychiatry 2003;5[suppl 3]:14–21)*

Clozapine was introduced in 1989, risperidone in 1994, olanzapine in 1996, quetiapine in 1997, and ziprasidone in 2001. Data on the safety and tolerability of these drugs are still accumulating because these agents are relatively new compared with conventional antipsychotics, which were introduced in the 1950s. However, existing controlled trials and experience from clinical practice may help physicians to assess a patient's risk of developing side effects with specific medications.

Because clozapine is associated with a high risk of agranulocytosis, seizure, and orthostatic hypotension, this drug is reserved for patients with schizophrenia that has not responded to trials with at least 2 other antipsychotics[1] and is generally not prescribed by primary care physicians. Therefore, clozapine will be less extensively covered in this article than risperidone, olanzapine, quetiapine, and ziprasidone.

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EVALUATING THE RISK-BENEFIT PROFILE OF AN ANTIPSYCHOTIC

Before prescribing an antipsychotic, the potential side effects should be weighed against the likely reduction in target symptoms. When evaluating the risk-benefit profile of an antipsychotic, physicians should ask several questions. First, what are the most impairing or intolerable side effects the medication might cause? Second, what is the likelihood that each of these side effects will occur? Third, how successfully can these side effects be managed by available interventions? Fourth, are the side effects a tolerability issue (e.g., sedation) or a safety issue (e.g., diabetes)? Last, is the side effect reversible, or will it continue even after the drug therapy has been stopped? Following this framework will help the physician determine the cost to the patient in terms of side effects, as the physician tries to achieve optimum antipsychotic efficacy.

SIDE EFFECTS

Several side effects that may occur with atypical antipsychotics will be reviewed: drug-induced movement disorders such as extrapyramidal symptoms (EPS) and tardive dyskinesia, anticholinergic side effects, weight gain, diabetes mellitus, prolactin elevation, QTc prolongation, and sedation. Most of the research on side effects of atypical antipsychotics has been conducted in young to middle-aged

adults and may not reflect the incidence and severity of these side effects in children and adolescents or in geriatric populations.

Reversible Drug-Induced Movement Disorders

Reversible motor side effects (such as EPS) include parkinsonian symptoms, acute dystonic reactions, and akathisia. Akathisia, which patients might find to be the most distressing of these side effects, is a sense of restlessness and the need to move about; parkinsonian symptoms include tremor, rigidity, and bradykinesia; and an acute dystonic reaction is a sustained involuntary painful contraction of muscles. These side effects generally occur soon after antipsychotic treatment is begun rather than appearing later in treatment. As a class, atypical antipsychotics are much less likely to cause acute motor side effects than are conventional antipsychotics. However, some atypical antipsychotics are associated with higher rates of these movement disorders than are others. Research has found a dose-related risk of EPS in short-term trials with risperidone,[2] olanzapine,[3] and ziprasidone,[4] but quetiapine[5] and clozapine[6] are associated with little risk of acute EPS even at high doses. Therefore, prescribing risperidone, olanzapine, and ziprasidone at the lowest therapeutic dose is key to avoiding these side effects.

Positron emission tomography scans in patients taking atypical antipsychotics have shown that acute motor side effects generally occur when an atypical antipsychotic dose results in dopamine-2 (D_2) receptor occupancy of about 80% or higher.[7] However, antipsychotic efficacy can be achieved with D_2 receptor occupancy in the 60% to 80% range.[7] Kapur et al.[8] found that doses associated with 60% to 80% D_2 receptor occupancy were 10 to 20 mg/day for olanzapine and 2 to 6 mg/day for risperidone, which fall within the dose ranges shown to be efficacious in patients with schizophrenia.[2,3] Therefore, if a patient taking an atypical antipsychotic develops acute motor side effects, his or her dose should be lowered because it is probably higher than the therapeutic dose required for that patient.

Among the 3 atypical antipsychotics with dose-related risk of acute motor side effects, only risperidone and olanzapine have been compared in double-blind trials.[9,10] The results of the first double-blind trial,[9] which were published in 1997, may not be predictive of these movement disorders in current clinical practice because the mean modal dose of risperidone used in the study, 7.2 mg/day, was higher than doses currently used in clinical practice.[11,12] In this study, a significantly ($p < .05$) smaller percentage of the olanzapine-treated patients than the risperidone-treated patients experienced pseudoparkinsonism (12.5% vs. 22.3%), akathisia (15.9% vs. 27.3%), and dyskinetic symptoms (4.6% vs. 10.7%).

In another double-blind trial in 376 patients with schizophrenia or schizoaffective disorder, Conley and Mahmoud[10] used mean doses that are more commonly recommended today: about 12.4 mg/day of olanzapine and 4.8 mg/day of risperidone. Three different measures found that the incidence of EPS was similar in both treatment groups. Similar numbers of patients in each group reported that they experienced EPS: 38 of the olanzapine-treated patients (20.1%) and 45 of the risperidone-treated patients (23.9%). Also, the change from baseline to endpoint in Extrapyramidal Rating Scale scores in the 2 groups was not significantly different: the least squares mean ± SE was –1.2 ± 0.3 for the olanzapine group and –0.9 ± 0.3 for the risperidone group. The use of antiparkinsonian medications, which reflects the presence of EPS, was also not significantly different between the olanzapine (N = 53, 28.0%) and the risperidone (N = 61, 32.4%) groups. The results of this study show that when prescribed at the correct dose, atypical antipsychotics associated with dose-related risk of EPS result in comparable amounts of EPS.

Table 1. Incidence of Tardive Dyskinesia in Patients Taking Conventional Antipsychotics

Study	N	Mean Age (y)	Patients With Tardive Dyskinesia (%) According to Length of Cumulative Exposure		
			1 y	2 y	3 y
Kane et al, 1988[13]	> 850	28	5	10	15
Woerner et al, 1998[15]	261	77	25	34	53
Jeste et al, 1999[16]	439	65	29	50	63

Persistent Drug-Induced Movement Disorders

An important limitation of the conventional antipsychotics is their association with a high incidence of persistent motor side effects such as tardive dyskinesia, which is involuntary movement of generally the mouth, lips, tongue, and limbs. In severe cases, tardive dyskinesia can also involve the truncal musculature and the diaphragm, which may interfere with speech and respiration when affected by tardive dyskinesia. Unlike acute motor side effects like EPS, tardive dyskinesia appears after long-term treatment, i.e., at least 3 to 6 months of exposure to antipsychotics, and may be irreversible. Possible risk factors for developing persistent motor side effects include older age, duration of exposure to antipsychotic treatment, total dose administered over time, female gender (which might not pose as high a risk as previously believed), and diabetes mellitus.[13,14]

Advancing age is the most important risk factor for developing persistent drug-induced movement disorders such as tardive dyskinesia (Table 1). After 3 years of cumulative exposure to a conventional antipsychotic, 15% of younger patients and 53% to 63% of older patients had developed tardive dyskinesia.[13,15,16] Even after only 1 year of cumulative exposure to a conventional antipsychotic, patients approximately 65 to 75 years of age may be 5 to 6

Table 2. Incidence of Tardive Dyskinesia With an Atypical Antipsychotic or Haloperidol

Study	Total N	Age, Mean ± SD (y)	Mean Dose (mg/d)	Median Length of Treatment (d)	Patients With Tardive Dyskinesia	
					N	%
Csernansky et al, 2002[17a]						
Risperidone	177	40.3 ± 10.6	4.9	364	1	0.6
Haloperidol	188	40.1 ± 10.4	11.7	288	5	2.7
Tollefson et al, 1997[18b]						
Olanzapine	707	37.1 ± 11.0	14.41	237	7	1.0
Haloperidol	197	36.4 ± 10.3	14.67	203	9	4.6

[a]All patients were considered stable before entering the study. The mean of the modal daily dose is reported.
[b]Patients with a prior diagnosis of dyskinesia or tardive dyskinesia were excluded. The mean dose at endpoint is reported.

times more likely to develop tardive dyskinesia than are patients approximately 30 years of age. Therefore, physicians should diligently monitor geriatric patients taking antipsychotics for signs of tardive dyskinesia.

Data are emerging that show the risk of developing tardive dyskinesia with atypical antipsychotics may be substantially lower than with the conventional antipsychotic haloperidol (Table 2). The incidence of treatment-emergent tardive dyskinesia was a secondary outcome in the study conducted by Csernansky et al.,[17] a multicenter, double-blind, randomized trial designed to assess the prevention of relapse in 365 patients who had received at least 1 year of risperidone or haloperidol treatment. The investigators reported the incidence of tardive dyskinesia was 0.6% among patients taking risperidone but 2.7% among patients taking haloperidol. Tollefson et al.[18] collected data on treatment-emergent tardive dyskinesia from 3 long-term, double-blind, randomized, haloperidol-controlled studies[19–21] of olanzapine. The study population included 904 patients with schizophrenia or schizoaffective disorder who had no prior diagnosis of dyskinesia or tardive dyskinesia and were exposed to olanzapine for a mean of 237 days or haloperidol for a mean of 203 days. According to patients' last 2 assessments with the Abnormal Involuntary Movement Scale before their participation in the trial ended, the incidence of tardive dyskinesia was 1.0% with olanzapine versus 4.6% with haloperidol.

The Csernansky et al.[17] and Tollefson et al.[18] trials were conducted in a younger patient population and did not explore the incidence of tardive dyskinesia in the group at greatest risk, older patients. Jeste et al.[22] conducted a single-blind comparison of 122 patients with a mean age of 66 years who received 9 months of treatment with 1 mg/day of risperidone or 1 mg/day of haloperidol for psychotic symptoms or severe behavioral disturbances associated with a mental condition such as schizophrenia, dementia, or a mood disorder. Although exact percentages were not given, the published results of the study showed that significantly ($p = .045$) more of the 61 patients who had taken haloperidol (about 30%) than the 61 patients who had taken risperidone (about 5%) developed tardive dyskinesia by the 9th month of treatment. In another long-term study of risperidone treatment, Jeste et al.[23] found that the 1-year cumulative incidence of treatment-emergent tardive dyskinesia was 2.6% in 255 elderly patients who continued open-label treatment with 0.5 to 2 mg/day of risperidone after participating in a 12-week, randomized, double-blind, placebo-controlled trial.[24] Jeste and colleagues[25] also recently presented data on the risk of developing tardive dyskinesia during long-term, i.e., 52 weeks, open-label treatment with quetiapine in 184 elderly patients (mean age = 76 years) with psychotic disorders. Kaplan-Meier estimation revealed the cumulative incidence of tardive dyskinesia in quetiapine-treated patients was only 2.7%, which is nearly identical to the rate reported for risperidone by Jeste et al.[23]

In addition to being associated with a lower incidence of treatment-emergent persistent motor side effects such as tardive dyskinesia than are conventional antipsychotics, atypical antipsychotics might reduce existing symptoms of these movement disorders in some patients. Case reports[26] suggest that when patients who have experienced tardive dyskinesia during conventional or atypical antipsychotic treatment are switched to a different atypical agent, the symptoms of tardive dyskinesia lessen or disappear.[27–32]

Anticholinergic Side Effects

Antipsychotics can cause a host of anticholinergic side effects. Mild central anticholinergic activity results in cognitive impairment, including reduced memory capacity. As the anticholinergic activity level increases, confusion and finally delirium may develop. Peripheral side effects include dry mouth; blurred vision; worsening of glaucoma; constipation, possibly leading to fecal impaction; urinary hesitancy or retention; and tachycardia (Table 3). All of these adverse events may occur in younger patients, but elderly patients are at greatest risk.

Among the atypical antipsychotics, clozapine is associated with the greatest incidence of anticholinergic side effects.[33] The extent of anticholinergic side effects with olanzapine is debated because the degree of anticholinergic activity reported in the in vitro literature does not correspond with the occurrence of anticholinergic side effects in clinical practice. Quetiapine, risperidone, and ziprasidone are generally associated with fewer anticholinergic side effects than conventional and other atypical antipsychotics.

Table 3. Occurrence of Peripheral Anticholinergic Side Effects During Antipsychotic Treatment

				Anticholinergic Side Effect			
Source	Antipsychotic	N	Length of Treatment (wk)	Abnormal Vision (%)	Constipation or Dysuria (%)	Dry Mouth (%)	Rapid/Irregular Heartbeat (%)
Clozaril PDR entry[1]	Clozapine	842	NR	5	14	6	25[a]
Conley and Mahmoud[10]	Olanzapine	189	8	10.1	NR[b]	22.2	NR[b]
	Risperidone	188	8	6.4	NR[b]	11.2	NR[b]
Geodon package insert[4]	Ziprasidone	702	≤ 6	3	9	4	2
Risperdal package insert[2]	Risperidone	324[c]	6–8	1	7	≥ 1[d]	3
Seroquel package insert[5]	Quetiapine	510	3–6	0.01–1[e]	9	7	7
Tollefson et al[18]	Olanzapine	1306	6	10.6	3.6	22.2	6.6
	Haloperidol	636	6	15.1	6.1	16.2	9.9
Zyprexa package insert[3]	Olanzapine	532	4–6	3	9	9	3

[a]Based on around 1700 patients included in the premarketing database.
[b]Symptoms experienced by less than 10% of both groups were not reported.
[c]Only patients taking ≥ 10 mg/day of risperidone are included because doses above this range are generally not recommended.
[d]Based on 2607 patients included in the premarketing database.
[e]Based on around 2200 patients included in the premarketing database.
Abbreviations: NR = not reported, PDR = Physicians' Desk Reference.

Table 4. Long-Term Weight Gain in Patients Treated With Atypical Antipsychotics

Drug	Design	N	Length of Treatment	Dose (mg/d)	Mean Change in Weight (lb)
Clozapine[35]	Naturalistic, clinical outpatient	82	1 y	NR[a]	+13.9
Olanzapine[36]	Meta-analysis	47	1 y	2.5–7.5	+15.0[b]
				12.5–17.5	+26.0[b]
Quetiapine[37]	Meta-analysis	360	9–12 mo	NR	+6.1
Risperidone[17]	Randomized, double-blind	177	1 y	4–8	+5.0
Ziprasidone[38]	Randomized, double-blind, placebo-controlled	67[c]	1 y	160	–6.4

[a]Although doses were not given, Henderson et al.[35] reported that dose was not correlated with increase in weight.
[b]Mean change in weight is estimated because the precise mean change was not given.
[c]Only 37 patients completed 1 year of treatment; however, the mean change in weight for all patients is reported.
Abbreviation: NR = not reported.

All atypical antipsychotics include the precaution that they may impair cognition.[1–5] Delirium may occur in some patients, especially elderly patients with high serum anticholinergic activity. In a study of 67 patients aged 75 years or older who were hospitalized for an acute medical illness, Flacker et al.[34] found that 20 patients (29.9%) experienced delirium. Compared with the patients who did not experience delirium, significantly ($p = .03$) more of the patients who experienced delirium were taking antipsychotics (0% vs. 10.0%). Flacker et al. also found that patients with the highest serum anticholinergic activity levels were most likely to have delirium. The incidence of delirium was about 60% in the patients with serum anticholinergic activity levels of 1.47 to 5.07 but only 35% in patients with levels of 0.89 to 1.46, 20% to 25% in those with levels of 0.24 to 0.42, and 8% in those with levels of 0 to 0.23. Therefore, atypical antipsychotics associated with high anticholinergic activity may not be appropriate for elderly patients or others at increased risk for delirium. If delirium does arise, the patient's dose might need to be lowered or the medication switched to one with a lower anticholinergic potential.

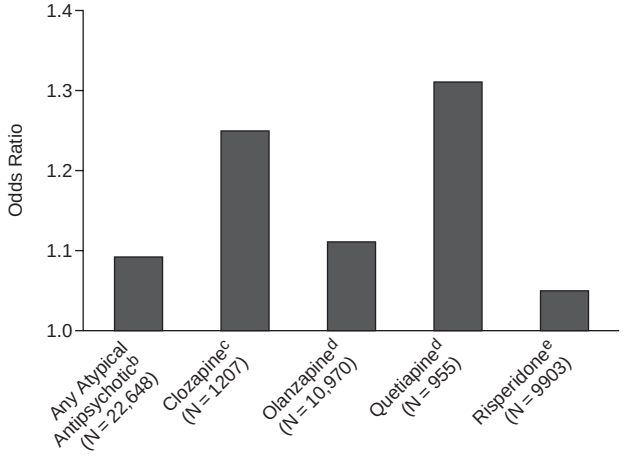
Weight Gain

Weight gain is a common side effect of most atypical antipsychotics. Much of the data on weight gain associated with antipsychotic treatment are from short-term trials. However, most of these drugs are used for several months or years, and, therefore, long-term weight gain data, i.e., after at least 1 year of atypical antipsychotic treatment, are more clinically relevant. Data from available longer-term studies show that the mean long-term weight gain is highest with clozapine and olanzapine (Table 4). Mean long-term weight gain with 12.5 to 17.5 mg/day of olanzapine is estimated to be approximately 26 lb.[36] Not all patients taking an atypical antipsychotic gain weight, and an individual patient may gain more or less than the average. With olanzapine, substantial weight gain, i.e., > 7% of one's body weight, occurs in more than 50% of patients.[39] Ziprasidone is generally not associated with long-term weight gain. Age under 60 years and concurrent use of lithium or valproate may increase the weight gain 2-fold to 3-fold in patients taking antipsychotics.[40]

Diabetes Mellitus

A predictable consequence of the weight gain associated with atypical antipsychotics is the development or exacerbation of diabetes mellitus. By reviewing the case report literature available on MEDLINE, one can see that all atypical antipsychotics are associated with cases of new-onset diabetes and diabetic ketoacidosis. Case reports in-

Figure 1. Odds Ratio for Diagnosis of Comorbid Diabetes Mellitus During Atypical Antipsychotic Compared With Conventional Treatment[a]



[a]Data from Sernyak et al.[43] An odds ratio of 1 indicates no difference in the risks of having the disorder for patients taking an atypical antipsychotic or a conventional antipsychotic, and a ratio of 2 indicates a 100% greater risk for patients taking an atypical antipsychotic.
[b]$p = .002$.
[c]$p < .005$.
[d]$p < .002$.
[e]$p = .15$, nonsignificant.

dicate only the need for further research. Because case reports are individual incidents in patients with distinct circumstances, they cannot be accurately compared to determine the exact risk of developing diabetes while taking a certain drug. However, the case report literature does suggest a greater risk of new-onset type 2 diabetes mellitus with clozapine and olanzapine relative to other atypical antipsychotics, and a substantial number of the patients in case reviews have had no apparent weight gain at the time they developed diabetes mellitus.[41]

Studies with larger and more homogeneous cohorts may present a more accurate assessment of the risk than case studies do. Gianfrancesco et al.[42] identified more than 7000 patients with a psychotic disorder from the databases of 2 health plans in the northeastern and southeastern United States. For patients without a diagnosis of type 2 diabetes mellitus 8 months before their index psychotic episode, Gianfrancesco et al. compared the risks of being diagnosed with this type of diabetes among individuals taking an antipsychotic for at least 60 days and those who received no antipsychotic treatment. After 1 month, patients taking a high-potency conventional antipsychotic were 6.5% more likely than patients who had received no antipsychotic treatment to have type 2 diabetes mellitus, and increased risks were also seen with olanzapine (9.9%), low-potency conventional antipsychotics (10.9%), and clozapine (18.2%). After 12 months, the increased risk for treatment with 1 of the above antipsychotics versus no antipsychotics ranged from 113% to 644%. Only patients who took risperidone did not demonstrate an increased risk of having type 2 diabetes mellitus compared with patients who did not receive antipsychotic treatment. Only olanzapine was associated with a significant ($p < .01$) dose-related risk (odds ratio = 1.161) for type 2 diabetes mellitus.

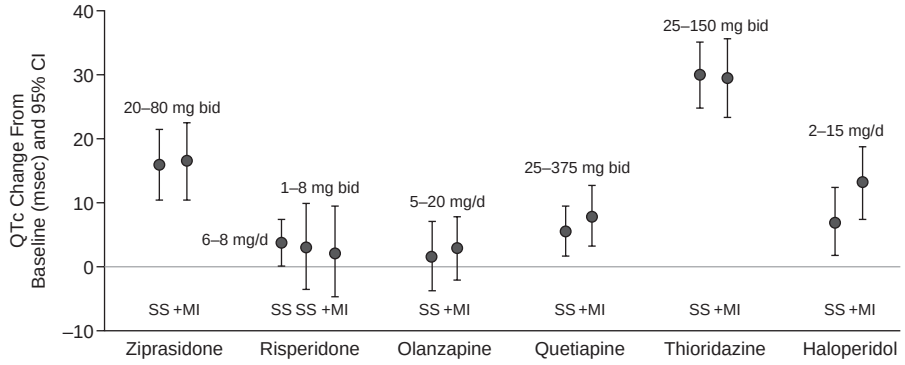
The risks of having type 2 diabetes mellitus with atypical antipsychotic treatment and conventional antipsychotic treatment were recently compared by Sernyak et al.[43] This study was conducted in 38,632 patients who were taking antipsychotic medication for schizophrenia between October 1998 and September 1999 from databases of the U.S. Veterans Health Administration of the Department of Veterans Affairs. Compared with patients taking a conventional antipsychotic, those taking an atypical antipsychotic were 5% to 31% more likely to have type 2 diabetes mellitus (Figure 1). The difference in the prevalence of diabetes for an atypical antipsychotic versus a conventional antipsychotic was significant for all atypical antipsychotics except risperidone, highest in patients under 40 years of age, and lowest in patients 60 years of age or older.

In a controlled trial of 48 patients with schizophrenia who were taking an antipsychotic and 31 healthy controls, Newcomer et al.[44] examined plasma glucose and insulin levels to determine the risk of developing diabetes mellitus associated with specific antipsychotics. Subjects were categorized into 5 groups: control (N = 31), conventional antipsychotic (N = 17), risperidone (N = 10), clozapine (N = 9), and olanzapine (N = 12). Mean plasma glucose levels were significantly ($p < .001$) different among the groups at baseline and 15, 45, and 75 minutes after subjects consumed 50 g of anhydrous dextrose. Mean plasma glucose levels in the control and conventional antipsychotic groups were around 75 to 78 mg/dL at baseline and 105 to 116 mg/dL 75 minutes postingestion. Levels in the risperidone group were significantly ($p < .005$) higher (87 mg/dL at baseline and 147 mg/dL at 75 minutes postingestion) than those in the control group but not those in the conventional antipsychotic–treated group. Levels in the clozapine and olanzapine groups (90–95 mg/dL at baseline and 156–163 mg/dL at 75 minutes postingestion) were significantly ($p < .005$) greater than those of both the control and conventional antipsychotic groups. Compared with insulin resistance in the conventional antipsychotic group, resistance was significantly ($p < .05$) higher in only the olanzapine and clozapine groups. All disturbances of glucose regulation associated with clozapine and olanzapine were independent of subjects' adiposity, and this finding suggests that the effect of these drugs on glucose metabolism was at least partially independent of their propensity to cause weight gain.

Prolactin Elevation

Conventional antipsychotics sometimes cause side effects related to the elevation of prolactin levels, such as

Figure 2. Effect of Antipsychotics on Mean QTc With and Without a Metabolic Inhibitor Measured by a Baseline Correction[a]



[a]From Pfizer Inc.[50]
Abbreviations: CI = confidence interval, +MI = with a metabolic inhibitor, QTc = correction of the QT interval for heart rate, SS = at steady state.

gynecomastia, galactorrhea, and amenorrhea.[45] In some patients, sexual dysfunction may also be related to an increase in prolactin level. Overall, atypical antipsychotics other than risperidone have only small, transient effects on prolactin levels and result in few of the related side effects.[19,45–48] Kleinberg et al.[48] found that prolactin levels in patients taking 4 to 6 mg/day or more of risperidone were significantly ($p \leq .01$) higher than those in patients taking 10 mg/day of haloperidol. The occurrence of side effects possibly related to prolactin elevation including amenorrhea, galactorrhea, ejaculatory dysfunction, erectile dysfunction, and gynecomastia was 8% to 19% in the 1483 risperidone-treated patients and 0% to 14% in the 313 haloperidol-treated patients.

The elevation of prolactin levels may be dose related, but the occurrence of these side effects generally is not related to dose or prolactin levels. Although the magnitude of prolactin elevation varies among individuals, those whose prolactin level is higher than 30 mg/L may be more likely to develop side effects.[49] Physicians should ask all patients taking antipsychotics whether they are experiencing prolactin-related side effects.

When patients taking an atypical antipsychotic experience side effects possibly related to elevated prolactin levels, physicians must examine the risks and benefits of altering treatment. If a patient has substantially improved while taking the drug and has few other complications, a dopamine agonist such as bromocriptine may be added or the dose of the antipsychotic may be lowered. An alternative for side effects that cannot be otherwise managed is to switch to another atypical antipsychotic.

QTc Prolongation

Prolongation of the QT interval occurs more frequently with certain antipsychotics than others. A comparison[50] of antipsychotics and changes in QTc (correction of the QT interval for heart rate) showed small increases, approximately 5 to 10 msec, with steady state levels of olanzapine, risperidone, quetiapine, and haloperidol (Figure 2). Ziprasidone prolonged QTc by about 15 msec and should, therefore, not be prescribed for patients who have a history of cardiovascular dysfunction including QTc prolongation or are taking a medication that prolongs the QT interval. However, ziprasidone was not associated with an increased risk of cardiac arrhythmia or sudden death. This study also revealed that thioridazine may prolong QTc by about 30 msec or twice as much as ziprasidone. Thioridazine now has a black box warning that states that the drug should be used in only patients who have failed trials of at least 2 other antipsychotics and should never be prescribed for patients with cardiovascular illness or who are taking drugs that may prolong the QT interval.[51]

Somnolence

All antipsychotics cause somnolence, a dose-related phenomenon, and many patients may experience only mild, transient somnolence during the beginning of treatment. However, the incidence of this side effect is higher with some atypical antipsychotics than others. The incidence of somnolence may be 30% with 10 mg/day of olanzapine,[3] 20% with 450 mg/day of quetiapine,[52] 14% with 5 mg/day of risperidone,[17] and 14% with 80 to 120 mg/day of ziprasidone.[53]

Somnolence is associated with fewer benefits than liabilities. In acute inpatient settings, somnolence associated with antipsychotic treatment may help regulate the sleep cycle and calm patients. However, in the long term, somnolence associated with antipsychotic treatment is a liability especially in elderly patients because it might lead to an increased risk of falls, negatively impact functioning, and reduce mental acuity. Patients generally dislike sedation, which can also lead to low physical activity and exacerbate the weight gain caused by some antipsychotics.

MONITORING RECOMMENDATIONS

All atypical antipsychotics have side effects, but many of them can be managed if detected and treated in a timely manner. Determining whether side effects are a result of the patient's current drug therapy, lingering or discontinuation effects of a previous drug, or symptoms of a disorder may be difficult. Physicians should routinely ask patients if they have experienced any adverse events and should encourage patients to report any side effects during office visits or, if necessary, over the phone. Also, physicians should perform tests to detect side effects that are considered safety issues such as weight gain, diabetes, and QTc prolongation.

Because weight gain can occur in patients taking any antipsychotic, all patients on antipsychotic treatment should be monitored for weight gain, although patients taking clozapine and olanzapine are at highest risk. Many primary care physicians already monitor patients' weight, in addition to their height, pulse, and blood pressure, as part of routine testing during office visits. Patients can also be asked to monitor their weight once a week at home and report gains, especially of 5 lb or more in the first month of treatment, to their physicians. For a patient who has gained a substantial amount of weight, switching to another antipsychotic should be considered.

The incidence of diabetes with atypical antipsychotics is uncertain, so all patients taking these medications should be monitored at baseline and once per year for diabetes. Patients on olanzapine or clozapine as well as individuals who have risk factors for diabetes such as having a family history of diabetes, being overweight, and being of African, Hispanic, or Asian descent should be monitored for new-onset diabetes more often, possibly every month for the first 3 months of treatment and every 3 months thereafter. The optimal test for diabetes is a fasting blood glucose level, but if that test cannot be performed, a random blood glucose level would be useful. A test of hemoglobin A1C level is probably the least sensitive because it is a longer term measure of empiric glucose metabolism.

Another concern in patients with schizophrenia is cardiovascular disease, which is often associated with poor diet, weight gain, and diabetes. Therefore, patients taking antipsychotics, especially those who gain weight, are overweight, or have diabetes, diabetes risk factors, or a family history of cardiovascular disease, should be monitored for lipid levels and receive an electrocardiogram yearly. A baseline electrocardiogram should also be performed to determine if a patient has a congenital QTc prolongation (QTc interval > 500 msec) and should, therefore, not receive treatment with an antipsychotic known to substantially prolong the QT interval.

The most important monitoring recommendation is to regularly evaluate patients for the side effects for which they *personally* are at greatest risk, whether because of the drug they are taking, their dietary or exercise habits, or their medical history.

CONCLUSION

Overall, atypical antipsychotics have more favorable side effect profiles than do conventional antipsychotics. Exactly defining the relative side effect profiles of atypical antipsychotic treatment is an evolutionary process that takes time. The registration trials provide only a preliminary window, but clinical experience over several years in the real world helps us to develop a more comprehensive picture of the side effect profiles of each drug. More research and reports on the use of atypical antipsychotics in clinical practice will better inform physicians about the likelihood of specific side effects developing with the use of these medications, especially in geriatric and pediatric populations.

Current research has indicated that the incidence of drug-induced movement disorders such as EPS and tardive dyskinesia, anticholinergic side effects, prolactin elevation, and QTc prolongation appears to be low with most atypical antipsychotics. Clozapine and olanzapine are associated with more anticholinergic side effects than are other atypical antipsychotics; risperidone, with more prolactin-related side effects; and ziprasidone, with greater QTc prolongation. Both short-term and long-term weight gain can be problematic with any atypical antipsychotic but especially with olanzapine and clozapine. Also, studies have shown that many side effects of antipsychotics may be dose related. Therefore, physicians should determine which side effects are likely to occur with an atypical antipsychotic, evaluate how susceptible the specific patient may be to the medication's side effects, prescribe the lowest efficacious dose for that individual, and regularly monitor the patient for side effects.

Drug names: bromocriptine (Parlodel and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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