Nupura Krishnadev, MD, Beth L. Abramson, MD, FRCPC, Robert Chisholm, MD, FRCPC, Lawrence A. Leiter, MD, FRCPC, Sarah Hales, MD, Robert Schwartz, MD, Moumita Barua, MD, Susan Scarrow, MD, Ahmed Mansour, MD, Mark Pearce, MD, Laura R. Pacione, MSc, Lori Wasserman, MD, Tammy Shaw, MD, Adam Lenny, BSc, BA, Casimir Soare, BHSc, Shree Bhalerao, MD, FRCPC

Atypical antipsychotics, schizophrenia, and cardiovascular risk: What family physicians need to know

Patients using clozapine, olanzapine, or similar medications should be monitored for weight gain, blood glucose, and serum lipid levels.

ABSTRACT: Studies suggest that people with schizophrenia are two to three times more likely to die from cardiovascular disease than members of the general population. This increased risk results, in part, from adverse effects induced by atypical antipsychotics. To date, most of the research describing the effects of atypical antipsychotics on cardiovascular health has been published in psychiatric journals rather than in family practice journals. A comprehensive Medline search suggests that family physicians need to be aware of the cardiovascular risks associated with atypical antipsychotics when treating patients with comorbid psychiatric conditions. The literature consistently reports that the use of atypical antipsychotics, particularly clozapine and olanzapine, is associated with obesity, diabetes mellitus, and dyslipidemia. Ziprasidone, a newer atypical antipsychotic that may soon be licensed in Canada, has been associated with these atherogenic risk factors as well as prolongation of the corrected QT interval. The literature also suggests that clozapine may be associated with myocarditis and pericarditis. Balancing increased cardiovascular risk with psychiatric symptom control must be done on a patient-by-patient basis. To assist with this, further prospective studies are needed to quantify the atherogenic risks posed by different antipsychotic medications. Guidelines for monitoring cardiac risk factors are also needed to ensure that patients using atypical antipsychotics for schizophrenia and other psychiatric conditions receive the best care.

Cardiology is one of the specialties consulted most frequently by health professionals working on the psychiatric ward, where a significant number of inpatients suffer from schizophrenia.[1] This highlights the need for both consulting specialists and also the multidisciplinary health care team caring for patients with psychiatric conditions to be aware of the complex interplay between mental illness, unhealthy lifestyle choices, and atherogenic psychotropic medications. Atypical antipsychotics have been shown to be associated with weight gain, dyslipidemia, and type 2 diabetes. These adverse effects act synergistically in patients with schizophrenia, who have an elevated cardiovascular risk.

Dr Krishnadev is a dermatology resident at the University of Toronto in Ontario. Drs Abramson and Chisholm are staff cardiologists at St. Michael's Hospital in Toronto. Dr Leiter is a staff endocrinologist at St. Michael's Hospital. Dr Hales is a psychiatry fellow at the University of Toronto. Dr Schwartz is a general surgery resident at the University of Toronto. Dr Barua is an internal medicine resident at the University of Toronto. Drs Scarrow and Mansour are psychiatry residents at the University of Toronto. Dr Pearce is a staff psychiatrist at the Centre for Addictions and Mental Health in Toronto. Ms Pacione is a senior medical student at the University of Toronto. Dr Wasserman is a psychiatry resident at the University of Toronto. Dr Shaw is a family practice resident at St. Michael's Hospital. Mr Lenny and Mr Soare are senior medical students at the University of Toronto. Dr Bhalerao is a staff psychiatrist at St. Michael's Hospital.

Studies suggest that people with schizophrenia are two to three times more likely to die from cardiovascular disease than members of the general population.[2] Patients with schizophrenia are predisposed to obesity, type 2 diabetes, abnormal variations in cardiac rate, and sudden death, independent of medication use.[3-6] These risks are combined with high rates of smoking, unhealthy diets, and a sedentary lifestyle. In fact, a diagnosis of schizophrenia has been shown to reduce a patient's average life expectancy by 10 years.[7]

The advent of atypical antipsychotics in the 1990s transformed the treatment of schizophrenia and other psychotic disorders. Over the last 10 years, the beneficial effects of these medications on mood, cognition, and perceptual disturbances have led to their establishment as first-line therapy. While typical antipsychotics, such as haloperidol and chlorpromazine, act through nonspecific blockade of dopamine D_2 receptors, atypical antipsychotics have a higher affinity for serotonin $5HT_{2A}$ receptors. Serotonin modulates dopamine secretion; consequently, atypical antipsychotics have a selective effect on dopamine, enhancing its transmission in the basal ganglia and frontal cortex, while reducing it in the limbic system.[8] This results in effective treatment of both negative and positive symptoms of schizophrenia, while limiting the extrapyramidal side effects found with typical antipsychotic use. Reduced rates of tardive dyskinesia and other extrapyramidal symptoms have been observed with the use of atypical antipsychotics such as clozapine, olanzapine, risperidone, quetiapine, and ziprasidone.[9] In a double-blind trial comparing clozapine with haloperidol, the more tolerable side effect profile of the atypical antipsychotic was linked to greater compliance and reduced hospitalization.[10] One retrospective study also noted reduced hospitalization in patients with chronic schizophrenia treated with risperidone.[11]

However, the widespread use of atypical antipsychotics has raised another concern—the effect of these medications on cardiovascular health. The association of these medications with weight gain and undesirable blood glucose and serum lipid levels leads to an important question: Are atypical antipsychotics indeed safer and better tolerated than conventional neuroleptics, or do they merely differ in their side effect profiles?

An understanding of the roles played by both schizophrenia and its treatment is critical for the appropriate management of cardiovascular issues in patients who are taking atypical antipsychotics. Despite the need for all members of the health care team to be aware of the cardiovascular risks associated with the use of atypical antipsychotics, the vast majority of research describing these adverse effects has been published only in psychiatric journals.[12]

In order to explore the effects of atypical antipsychotic use on cardiovascular risk factors in schizophrenia, and assess their clinical relevance for family physicians and other professionals dealing with this population, we conducted a comprehensive Medline search using the words weight gain, diabetes mellitus, cholesterol, dyslipidemia, hyperglycemia, myocarditis, pericarditis, risperidone, clozapine, olanzapine, quetiapine, ziprasidone, predictors, and obesity. A review of the studies we identified indicates that atypical antipsychotics are associated with weight gain and obesity, hyperglycemia and diabetes mellitus, dyslipidemia, prolongation of the QT interval, and possibly myocarditis and pericarditis.

Adverse effects of atypical antipsychotics

Weight gain and obesity

Excessive weight is a major health concern in Canada, where studies have indicated that approximately 50% of Canadians are overweight, and 14.9% are considered obese.[13] Data suggest that obesity can be two to three times more prevalent in those with serious mental illness.[14] The comorbidities associated with obesity include hypertension, coronary artery disease, sleep apnea, stroke, osteoarthritis, respiratory problems, and certain cancers, such as those of the prostate, breast, and colon.[15-19] Weight gain also causes noncompliance,[20] leading patients to discontinue medications to prevent this unwanted effect.[21] Unlike many other medication side effects, weight gain persists beyond the duration of treatment, and is more problematic in patients with schizophrenia due to additional psychosocial factors.[22,23]

Even before the first release of atypical antipsychotics in the United States, the 1989 National Health Interview survey revealed that in women with schizophrenia, a greater proportion had body mass index (BMI) distributions in the overweight and obese range when compared with their counterparts in the general medical population.[24] A trend toward greater BMI was also found in male patients with schizophrenia.

Using data from the 1948 Framingham Heart Study's public use data set and the 1999 US age and sex distribution data, Fontaine and colleagues[25] estimated the impact of weight gain on selected mortality and incidence rates of diabetes and hypertension. While weight gain was more deleterious in those with a higher initial BMI, it increased the rate of diabetes and hypertension independent of baseline BMI. Interestingly, a

clozapine-induced weight gain of 10 kg over a 10-year period was found to correlate statistically with the prevention of 492 suicide deaths per 100 000 patients with schizophrenia, but was offset by 416 additional deaths due to antipsychotic-related weight gain. The similarity of these numbers suggests that the reduction in suicide rates from antipsychotic use may not, in fact, compensate for the negative impact of an associated weight gain.

While all atypical antipsychotics produce some degree of weight gain, individual differences exist between the various drugs. A comprehensive review and meta-analysis by Allison and colleagues[26] compared the change in body weight after 10 weeks of standardized treatment with several antipsychotics. The largest weight increase occurred with clozapine (4.0 kg) and olanzapine (3.5 kg), while ziprasidone produced the smallest weight increase (0.04 kg).

Similar results have been found in other studies.[22,27-33] In a prospective naturalistic study of 2967 patients with schizophrenia, weight gain was significantly more frequent in the olanzapine group than in the control group.[34] Other reports suggest that olanzapine treatment leads to approximately double the rate of clinically significant weight gain, as does risperidone treatment. In a randomized double-blind study of 377 patients with schizophrenia or schizoaffective disorder, 27% of olanzapine-treated patients experienced a weight gain of more than 7% body weight, compared with 12% of patients treated with risperidone.[35]

Ziprasidone, the newest atypical antipsychotic, has been marketed based on its propensity to cause minimal weight gain. A double-blind study of 599 patients with schizophrenia concluded that weight gain was less common in those treated with ziprasidone than in those treated with haloperidol.[36] Furthermore, switching patients from olanzapine to ziprasidone has been shown to improve weight and BMI.[37] However, ziprasidone has yet to be used extensively in clinical settings, and further studies are warranted.

Hyperglycemia and diabetes mellitus

In late 2003, concerns about the hyperglycemic effect of atypical antipsychotics led the US Food and Drug Administration (FDA) to recommend that all atypical antipsychotics be labeled with a warning regarding their association with diabetes.

It has been suggested that schizophrenia is an independent risk factor for diabetes.[23,38] Even before the advent of antipsychotics, patients with schizophrenia were shown to have insulin resistance and abnormal glucose homeostasis.[39] A 10% current prevalence rate and a 14.9% lifetime prevalence rate of type 2 diabetes in patients with schizophrenia was reported in the United States,[40] compared with a current prevalence of 1.2 and a lifetime prevalence of 6.3% in the general population.[41] Studies of drug-naive patients demonstrate higher rates of insulin resistance in those with schizophrenia.[38] Furthermore, an increased frequency of diabetes has been found in the relatives of people with schizophrenia, suggesting a genetic association between the two conditions.[42]

Several studies have examined the prevalence of diabetes mellitus in relation to various atypical antipsychotics. These studies found that antipsychotic-related hyperglycemia was not dose-related, that it resolved after discontinuation of the medication, and that it returned upon reintroduction of the antipsychotic.[43-48] While it appears that clozapine and olanzapine may be more strongly associated with glucose abnormalities than risperidone or quetiapine, this is confounded by the fact that the first two drugs have also been the most studied. In a retrospective review of 38 622 patients diagnosed with schizophrenia, Sernyak and colleagues[49] determined that patients who received atypical neuroleptics were 9% more likely to have diabetes than those who received typical neuroleptics, after controlling for age. Diabetes was significantly increased in patients who received clozapine, olanzapine, and quetiapine, but not risperidone. However, when patients younger than 40 years were isolated, all of the atypical neuroleptics were associated with a significantly increased prevalence of diabetes. In a 5-year naturalistic study of 82 patients treated with clozapine, 36.6% were diagnosed with diabetes, and of these, 72.0% required medication for blood sugar control. Weight gain was not a significant risk factor for developing diabetes.[50]

In patients with schizophrenia, diabetes-related complications rank as the third leading cause of death, after suicide and epilepsy.[23] A spectrum of antipsychotic-related diabetic abnormalities have been reported, including new onset type 2 diabetes, diabetic ketoacidosis, and worsening of pre-existing diabetes control. Hedenmalm and colleagues[51] used the World Health Organization database for adverse drug reactions to review reports of glucose intolerance associated with olanzapine, clozapine, and risperidone. Their results indicate that hyperglycemia and diabetes mellitus were the most common types of glucose abnormalities reported, with diabetic coma being the least frequent. Diabetic ketoacidotic coma has been most commonly reported with olanzapine and clozapine.[52]

Dyslipidemia

Reports of dyslipidemia associated with antipsychotic use continue to accumulate. While studies have shown elevated levels of multiple serum lipoproteins, hypertriglyceridemia is the lipid abnormality most consistently reported. In a 5-year study of 82 patients treated with clozapine for 1 year, triglycerides were significantly elevated at the 60-month mark, while the mild rise in serum cholesterol noted was not statistically significant.[50] Other studies have shown similar elevations in serum triglycerides with olanzapine use.[53,54]

Clozapine and olanzapine appear to be more strongly associated with lipid elevation than risperidone. In a 14-week randomized double-blind trial comparing atypical and typical antipsychotics, Lindenmayer and colleagues[55] found elevated cholesterol levels with clozapine and olanzapine when comparing these agents with haloperidol and risperidone. While the increases were statistically significant, actual levels remained within clinically normal ranges. In addition, normalization of triglyceride levels was noted when four clozapine-treated patients were switched to risperidone.[56]

In patients with schizophrenia, accurate assessment of serum lipid levels is hindered by their limited compliance with fasting protocols before laboratory testing. Thus, it may become difficult to ascertain whether an abnormal value is truly a fasting level. Measurement of apolipoprotein B, an alternative to non-HDL and LDL cholesterol, may pose a solution to the fasting problem while providing additional predictive power over the lipids.[57,58] In addition to elevated plasma triglyceride levels and lower high-density lipoprotein levels, higher apolipoprotein B levels in patients treated with olanzapine than those given risperidone were demonstrated by Almeras and colleagues.[59] They concluded that metabolic risk factor profiles were more impaired in patients using olanzapine.

QT prolongation

Prolongation of the QT interval is associated with a greater risk of arrhythmia and sudden cardiac death. Studies exploring the higher rates of sudden death in patients with schizophrenia suggest antipsychotic-associated QT prolongation and resulting torsade de pointes (TdP) as possible etiologies.[60] In an FDA-requested study of 164 patients, the manufacturers of ziprasidone compared the corrected QT (QTc) changes of patients on six different antipsychotics. Of the atypicals, ziprasidone had a mean change in QTc of 20.3 milliseconds, followed by quetiapine at 14.5 milliseconds, risperidone at 11.6 milliseconds, and olanzapine at 6.8 milliseconds. In such studies, elevation of the QTc by 10 or more milliseconds is considered clinically significant.[4] Other reports have also documented relatively greater QTc prolongation with ziprasidone than with other atypical antipsychotics, and there is preliminary evidence to suggest that ziprasidone antagonizes the delayed potassium rectifier channel in cardiac cells, resulting in delayed repolarization and QT lengthening[61-63] However, an increased risk for sudden death or TdP has yet to be demonstrated with ziprasidone use.[63]

Concerns about QT prolongation with atypical antipsychotic use indicate that careful patient selection and monitoring are necessary. In particular, multiple reports recommend that ziprasidone be used cautiously in psychiatric patients with cardiovascular risks, and that electrocardiograms be done periodically.[64,65] Furthermore, given the subtleties of ECG interpretation, a recent review suggests that these patients be referred to cardiologists for specialist ECG analysis.[63]

Myocarditis and pericarditis

In addition to the adverse effects previously discussed, clozapine may also be associated with myocarditis, pericarditis, cardiomyopathy, and electrocardiography changes.[66] From a Swedish database, Hagg and colleagues[67] identified eight cases of cardiac disease consistent with a diagnosis of myocarditis during treatment with clozapine out of an estimated 15 100 patients who started the medication during the study period. This corresponds to an absolute risk of approximately 1 in 2000 patients treated with the antipsychotic. In these patients, six developed myocarditis within 1 month of starting clozapine therapy (doses ranged from 50 to 600 mg/day) and three died. Of the deceased, autopsies confirmed signs of myocarditis and blood congestion in spleen. In three subjects, symptoms of myocarditis resolved within 2 weeks of ceasing to use clozapine, and in the remaining two subjects severe heart disease resolved within a few days of ceasing to use clozapine and beginning treatment with high-dose corticosteroids.

Limitations of the review

The studies described here all provide evidence in support of an association between atypical antipsychotic use and cardiovascular risk factors such as diabetes, hyperlipidemia, obesity, QT prolongation, myocarditis, and pericarditis. However, the published data come largely from prevalence studies, case reports, and cross-sectional studies. These non-prospective data sources make it difficult to prove a causal relationship.[68] Definitions of clinically significant risks vary between studies, and it becomes difficult to sort out the interrelated effects of

each cardiac risk factor. How does one clearly delineate between the inherent effects of schizophrenia, the influence of an unhealthy lifestyle in these patients, and the role of antipsychotic medications? There is a dearth of well-designed prospective studies that control for the many confounders possible. Such studies are needed to clearly determine the degree of atherogenic risks posed by different antipsychotics, to quantify this risk, and to compare antipsychotic-related risk with established risk factors such as age and family history.

Clinical implications

Atypical antipsychotics increase cardiovascular risk as a result of their propensity to cause weight gain and obesity, type 2 diabetes, dyslipidemia, prolongation of the corrected QT interval, and possibly myocarditis and pericarditis (**Table 1**). The application of this knowledge is certainly not limited to patients with schizophrenia, as antipsychotics are also used in the treatment of other psychiatric conditions, such as mood disorders. Family physicians should therefore be able to recognize and monitor cardiac risk factors when caring for a patient using an atypical antipsychotic. All patients being treated with these medications should undergo baseline screening and then regular monitoring of glucose, weight, lipids,[69] and cardiac troponin I[70,71] (**Table 2**).[72,73] Unfortunately, there are few guidelines outlining how patients using atypical antipsychotics should be monitored for cardiac risk factors. As the use of these medications continues to grow, the need for such guidance will become more urgent.

Balancing the cardiovascular risks of psychotropic medications with their psychiatric benefits must be done on a patient-by-patient basis. The decision to alter or discontinue antipsychotics based on detrimental metabolic changes is one that must be made using a collaborative approach; the health care team and the patient must examine the risk-benefit ratio in the context of that patient's particular cardiac risk profile.

Table 1. Cardiovascular risk factors associated with five atypical antipsychotics.

	Weight gain*	Type 2 diabetes†	Dyslipidemia	QT prolongation	Myocarditis, pericarditis
Clozapine	✓	✓	✓		✓
Olanzapine	✓	✓	✓		
Quetiapine	✓	✓		✓	
Risperidone	✓	✓		✓	
Ziprasidone				✓	

*Weight gain associated with clozapine and olanzapine is greater than weight gain associated with quetiapine and risperidone.
†More cases of type 2 diabetes are associated with clozapine and olanzapine than with quetiapine and risperidone.

Table 2. Screening and monitoring for cardiovascular risk factors in first 6 months of atypical antipsychotic use.[72,73]

Baseline screening					
History:	Cardiovascular and diabetes risk factors, family history, diet, exercise				
Physical exam:	BMI, waist circumference				
Investigations:	Fasting plasma glucose, fasting lipids, electrolytes (potassium, magnesium), ECG				
Monitoring*					
	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone
BMI at 1, 3, and 6 months	✓	✓	✓	✓	
Fasting plasma glucose at 1, 3, and 6 months	✓	✓	✓	✓	
Fasting lipids at 6 months	✓	✓			
Electrolytes monthly			✓	✓	✓
ECG monthly			✓	✓	✓
Cardiac troponin I†	✓				

*More rigorous monitoring is needed in cases involving higher dosage and polypharmacy.
†May be measured with other blood work at 1, 3, and 6 months OR if signs/symptoms suggest myocarditis or pericarditis.

Competing interests
None declared.

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