Antipsychotic Medications: Metabolic and Cardiovascular Risk

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Individuals with serious mental illness experience excess morbidity and mortality, including an increased prevalence of diabetes mellitus and cardiovascular disease. Cardiovascular disease is the leading cause of death in persons with serious mental illness, and the elevated prevalence of obesity in this population is of particular concern. Obesity is an independent cardiometabolic risk factor that impacts morbidity and mortality and contributes to the development of other cardiometabolic risk factors, such as dyslipidemia and hypertension. In addition, obesity is a major risk factor for type 2 diabetes, with the relative risk of diabetes increasing with body mass index. Increased abdominal fat is strongly associated with insulin resistance, which can lead to impaired glucose regulation. Abdominal obesity, hyperglycemia, hypertension, and dyslipidemia are key components of the metabolic syndrome, a constellation of cardiometabolic risk factors linked by their common association with insulin resistance. Evidence from large clinical samples indicates a high prevalence of metabolic syndrome and all of its components in persons with serious mental illness, particularly in patients with schizophrenia. In addition, psychotropic agents, including some antipsychotic medications, are associated with substantial weight gain, as well as with adiposity-dependent and possibly adiposity-independent changes in insulin sensitivity and lipid metabolism, which increase the risk of diabetes and cardiovascular disease. Among the second-generation antipsychotics, clozapine and olanzapine are associated with the highest risk of substantial weight gain, similar to the weight gain potential associated with low-potency first-generation antipsychotics such as thioridazine or chlorpromazine, as well as with an increased risk of diabetes and dyslipidemia. Various strategies for monitoring cardiometabolic risk factors in patients with mental illness are discussed in this review.

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Compared to persons without psychiatric disorders, individuals with serious mental illness experience increased morbidity and mortality, especially due to cardiovascular illness.[1–3] In a meta-analysis[1] of 152 mortality studies, patients with schizophrenia (N = 35,815) demonstrated a 2-fold greater risk of premature death from medical causes compared to the general population. Recent U.S. public sector data confirm that cardiovascular disease is the leading cause of death in persons with major mental illness.[4] Further, a 2000 study[2] from Sweden that assessed mortality after a first hospitalization for schizophrenia indicated that death from cardiovascular causes increased dramatically during the period from 1976 to 1995. This increase was greatest from 1991 to 1995, with male and female patients having an 8.3-fold and 5-fold increase in cardiovascular mortality, respectively. Among those with serious mental illness, however, increased mortality is not limited to patients with schizophrenia. In a study[3] of 15,386 individuals with bipolar disorder, the standardized mortality ratio (observed deaths in study population/

expected deaths in general population) for all deaths from medical causes was increased by a factor of 1.9 among men and 2.1 among women.

Recognition of the increased cardiometabolic risk associated with serious mental illness has prompted interest in the factors that contribute to this problem. Key risk factors for cardiovascular disease that have been established by large-scale population-based studies[5] include obesity, dyslipidemia, hypertension, smoking, and hyperglycemia. Table 1 lists the prevalence of these key modifiable risk factors in patients with schizophrenia and bipolar disorder.[6–14] While poverty, urbanization, and reduced access to medical care continue to be concerns for persons with serious mental illness, there is growing interest in the contribution of psychotropic treatment to the prevalence of such risk factors as obesity, hyperglycemia, and dyslipidemia.[15] The purpose of this review is to evaluate the clinical importance of cardiometabolic risk factors among persons with mental disorders, address the contribution of antipsychotic medications to increased cardiometabolic risk, and suggest monitoring strategies for modifiable risk factors relevant to the treatment of serious mental illness.

THE PROBLEM OF OBESITY

As defined by World Health Organization criteria,[16] a body mass index (BMI) between 18.5 and 25 kg/m^2 is considered "normal," while a BMI from 25 to 30 kg/m^2 is "overweight" and a BMI ≥ 30 kg/m^2 is "obese," although thresholds can vary with ethnicity (e.g., Asians). Obesity has become a major clinical focus, based on the association of overweight and obesity with other cardiovascular risk factors[17,18] and because it is an independent risk factor for both morbidity and mortality. The U.S. Department of Health and Human Services[19] recently reported that following tobacco use, obesity is the second leading cause of preventable death in the United States. Even in patients who are not obese, increasing adiposity is associated with an increasing risk of significant medical morbidity, producing significant risk beginning in the range of moderate-to-severe overweight related to the

Table 1. Cardiometabolic Disease Risk Factors in Schizophrenia and Bipolar Disease[a]

| Modifiable Risk Factor | Schizophrenia | | Bipolar Disease, Estimated Prevalence of Risk Factor (%) |
	Estimated Prevalence of Risk Factor (%)	Relative Risk[b]	
Obesity	45–55	1.5–2 ×	26
Smoking	50–80	2–3 ×	55
Diabetes	10–14	2 ×	10
Hypertension	≥ 18		15
Dyslipidemia		Up to 5 ×	

[a]Data from references 6–14.
[b]Compared with the general population.

increased risk of diabetes mellitus, coronary heart disease (CHD), and other conditions.[17]

In addition to the association between obesity and overall morbidity and mortality, there is a strong relationship between obesity and the risk of type 2 diabetes, with the relative risk of diabetes increasing sharply with increasing BMI in comparison to the adiposity-related increase in risk associated with other common conditions (e.g., hypertension, CHD, and cholelithiasis).[5] For instance, in women, a dramatic rise in the relative risk of diabetes occurs as BMI increases from the "overweight" (25 to 30 kg/m²) to the "obese" range (≥ 30 kg/m²).[18] The prevalence of both obesity and diabetes has been rising dramatically in the United States, increasing among U.S. adults by 74% and 61%, respectively, from 1991 to 2001.[20]

DIABETES, INSULIN RESISTANCE, AND OBESITY

In patients at risk for type 2 diabetes, increased insulin resistance and inefficient glucose utilization work together to exhaust β-cell insulin reserves, resulting in the hyperglycemia of diabetes.[21] In patients with type 2 diabetes, the risk of a cardiovascular event is equivalent to that in individuals with established CHD.[22] This risk equivalence impacts the need for monitoring and treatment, with the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP] III) guidelines[23] indicating that in persons with diabetes, risk factors such as blood pressure and plasma lipids should be addressed as aggressively as they are in persons who have already suffered a prior myocardial infarction.

Underlying the association between obesity and diabetes described earlier is substantial evidence that increased abdominal fat, in particular, visceral adipose tissue volume, is related strongly to reductions in insulin sensitivity (i.e., insulin resistance). Insulin sensitivity has been shown to decrease as the amount of visceral adipose tissue increases.[24] In addition, the relationship of visceral adiposity to diabetes risk extends to the elderly.[25] In a study[25] of 2964 elderly subjects (mean age: 73.6 years), intermuscular fat and visceral abdominal fat were significantly greater in subjects with type 2 diabetes and impaired glucose tolerance as compared to fat measurements in those with normal glucose tolerance. The importance of adiposity was underscored by the finding that greater intermuscular fat and visceral abdominal fat were associated with higher fasting insulin levels (indicating insulin resistance) in both subjects with a normal BMI (between 18.5 and 25 kg/m²) and obese subjects, suggesting that regional adipose tissue distribution is a key determinant of insulin resistance and altered glucose homeostasis. Therefore, even elderly people with

a "normal" BMI may be at cardiometabolic risk if they have increased visceral abdominal and/or intramuscular fat.

With respect to recommended clinical assessments, the ATP III criteria define abdominal obesity as a waist circumference > 102 cm (> 40.2 in) in men and > 88 cm (> 34.6 in) in women.[26] However, either an increased waist circumference or an elevated BMI can serve as a predictor of insulin resistance.[27]

THE METABOLIC SYNDROME

Abdominal obesity and increased fasting plasma glucose levels constitute 2 components of the metabolic syndrome, a constellation of cardiovascular risk factors that includes metabolic abnormalities associated with insulin resistance and/or compensatory hyperinsulinemia.[28] Among patients with metabolic syndrome, the relative risk for diabetes and CHD ranges from 1.5 to 5 times that of the general population.[29] In particular, patients' CHD risk increases with the number of metabolic syndrome risk factors present.[30,31]

Metabolic syndrome is diagnosed when ≥ 3 of the following abnormalities are present: (1) increased waist circumference (> 40 in for men and > 35 in for women), (2) elevated triglyceride levels (≥ 150 mg/dL), (3) low high-density lipoprotein cholesterol (< 40 mg/dL in men and < 50 mg/dL in women), (4) blood pressure ≥ 130/85 mm Hg, and (5) fasting glucose ≥ 110 mg/dL,[32] with recent modification of the fasting glucose criteria to ≥ 100 mg/dL.[33] Increases in adiposity,[34,35] reductions in fitness,[36] and genetic factors[37–42] may all contribute to insulin resistance and hyperinsulinemia. Hyperinsulinemia, in turn, has been implicated in the development of all of the following: abnormal glucose and uric acid metabolism; hemodynamic abnormalities, such as hypertension, increased sympathetic nervous system activity, and sodium retention; atherogenic dyslipidemia; and prothrombic and proinflammatory states.[43]

Metabolic syndrome and its components are prevalent among persons with mental illness. Analyzing data from the National Health and Nutrition Examination Survey (NHANES) III (N = 17,689), Allison and colleagues[44] reported that patients with schizophrenia, especially women, had a significantly higher BMI than did women without schizophrenia (BMI: 27.36 vs. 24.50 kg/m², p < .001). Highlighting the increase in risk of metabolic syndrome associated with increases in BMI, Park and colleagues[45] observed that among men who participated in NHANES III, metabolic syndrome was present in 4.6%, 22.4%, and 59.6% of normal weight, overweight, and obese individuals, respectively, with a similar distribution in women. Compared to age-matched individuals in the general population, a significantly higher prevalence of metabolic syndrome was observed in persons with schizophrenia in the National Institute of Mental Health–sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial,[46] in which metabolic syndrome was estimated to be present in 51.6% of women and 36.0% of men.

In general, individuals are more likely to develop metabolic syndrome if they have the following risk factors: older age (≥ 65 years), postmenopausal status, Mexican-American ethnicity, higher BMI, current smoking, low household income, high carbohydrate intake, no alcohol consumption, and physical inactivity.[45] Mental illness is associated with an increased prevalence of smoking, reduced income, and overweight and obesity, as well as medication effects that include sedation and weight gain.

ANTIPSYCHOTICS AND OBESITY

In the long term, weight gain is a potential problem for many patients receiving antipsychotic therapy. "Clinically significant" weight gain is commonly defined as a ≥ 7% increase in body weight from baseline. Using this definition, the pooled incidence of clinically significant weight gain reported in the U.S. product labels for second-generation antipsychotics (SGAs) is as follows: olanzapine 29%,[47] quetiapine 23%,[48] risperidone 18%,[49] ziprasidone 10%,[50] and aripiprazole 8%.[51]

Consistent with the manufacturers' percentages reported above, long-term data (up to 52 weeks) from several clinical trials[52–54] have suggested that olanzapine has the highest propensity to produce weight gain among the SGAs. This effect may be somewhat dose-related if one includes very low doses outside the antipsychotic dose range, with 1-year mean weight increases of approximately 6 kg for pooled doses of olanzapine from 2.5 to 17.5 mg/day[53] compared to a 1-year mean of 12 kg for commonly used antipsychotic doses (12.5 to 17.5 mg/day).[54] With olanzapine treatment, as with other agents, higher levels of weight gain are associated with lower starting weights at treatment initiation.

Pooled weight gains associated with the other SGAs over 52 weeks in other clinical trials conducted during their developmental phase have also been documented. Quetiapine has been reported[55] to cause a mean weight increase of approximately 3.6 kg at 52 weeks; however, it should be noted that this result was documented from an "observed case" analysis in contrast to "last observation carried forward" analyses used for the other medications discussed. Risperidone treatment has been associated with a mean weight increase of 2.2 kg at 52 weeks, whereas aripiprazole and ziprasidone treatment each were associated with a mean weight increase of approximately 1 kg over 52 weeks.[56] In a randomized double-blind trial[57] comparing aripiprazole and olanzapine over 52 weeks, the effect of aripiprazole on weight gain was significantly less than for olanzapine at all time points (p < .001). In an effort to rank SGAs according to their relative propensity to cause weight gain, Tandon and Halbreich[58] tentatively expressed the order as follows: clozapine > olanzapine > risperidone = quetiapine > ziprasidone = aripiprazole. Weight gain is not only a problem associated with second-generation antipsychotic medicines. Increased risk of weight gain has long been associated with treatment using low-potency first-generation antipsychotic medications like chlorpromazine, thioridazine, and mesoridazine.[44] High-potency first-generation medications like haloperidol and fluphenazine are associated with minimal mean increases in weight during treatment.[44]

Evidence regarding the mechanism(s) underlying antipsychotic-induced weight gain includes studies[59] of the relationship between weight gain and drug interactions with various neurotransmitter receptors. The level of H_1 antagonism associated with different antipsychotic medications is hypothesized to modulate feeding behavior (increased appetite and decreased sensation of satiety), based on the significant association of weight gain and the binding affinity for this receptor. Antipsychotics with minimal affinity for H_1 receptors, such as aripiprazole, ziprasidone, and haloperidol, are associated with limited weight gain, while antipsychotics with a high affinity for H_1 receptors, such as clozapine, olanzapine, thioridazine, and chlorpromazine, are associated with clinically significant increases in weight. Based on the differential association of various medications with mechanisms that

support weight gain, it can be hypothesized that a switch from a weight gain–inducing antipsychotic (such as olanzapine) to an antipsychotic with a limited risk for weight gain (such as aripiprazole and ziprasidone) would result in reductions in mean weight.[60,61] This effect has been observed in several studies, including a 2003 report[62] in which a switch to aripiprazole from certain SGAs produced a mean weight loss of 1.3 kg to 1.7 kg over a period of 8 weeks. An extended discussion of the effect of antipsychotic "switching" on weight and plasma lipids is presented by Weiden[63] elsewhere in this supplement.

ANTIPSYCHOTIC EFFECT ON DIABETES RISK

An increased prevalence of impaired glucose tolerance and diabetes mellitus has been observed in persons with schizophrenia. Type 2 diabetes has been reported[9] to affect 10% to 14% of this patient population. In addition, impaired glucose tolerance has been documented[64] in 15% of a small sample of drug-naive, first-episode patients as compared to 0% in matched control subjects, although cohort-specific effects and hospitalization- and acute illness–related increases in plasma cortisol may have contributed to this finding. Dixon and colleagues[9] examined Medicare and Medicaid data from the pre-SGA era and reported elevated prevalence rates of diabetes, ranging from 5.1% to 14.9% in patients with schizophrenia compared to nonschizophrenia patients.

Overall, published findings from case reports, chart reviews, database analyses, and clinical trials demonstrate differing metabolic effects with the various first-generation antipsychotic (FGA) and SGA medications.[56] Evidence is strongest for clozapine and olanzapine, with findings from published reports, including controlled experimental studies and randomized clinical trials, indicating that olanzapine and clozapine are associated with an increased risk of diabetes. Weight gain is a drug-induced adverse event that occurs to a differing degree among SGAs, with clozapine and olanzapine commonly associated with clinically significant weight gain. There is a reasonable hypothesis that much of the effect on glucose regulation observed with the different SGAs can be explained as a function of their effect on weight and adiposity,[65] although drug effects independent of adiposity have been reported and may add to the effects of adiposity.[66] Evidence of the effects of risperidone treatment on the risk of diabetes is less extensive than for clozapine and olanzapine, with similar numbers of database analyses, but fewer chart reviews and observational reports and fewer controlled studies. The published data do not support the suggestion that risperidone treatment is associated with a reliable increase in diabetes risk.[56] Even fewer data are available concerning the relationship between quetiapine treatment and diabetes risk.[56] Studies with ziprasidone and aripiprazole do not support the hypothesis that these agents adversely affect blood glucose regulation in treated patients.[56]

To test the hypothesis that some antipsychotic medications may have adiposity-independent effects on glucose metabolism, Newcomer and colleagues[66] used modified oral glucose tolerance tests in groups of antipsychotic-treated but adiposity-matched patients with schizophrenia. These investigators[66] demonstrated that patients treated with clozapine or olanzapine had significant glucose elevations at all time points compared with patients receiving FGAs and untreated healthy control subjects (p < .05). Similarly, Henderson's group[67] used a frequently sampled

intravenous glucose tolerance test to analyze the effects of SGAs on glucose metabolism in patients with schizophrenia, again matching treated patient groups for adiposity. They reported[67] significant reductions in insulin sensitivity in patients treated with clozapine (p < .001) and olanzapine (p = .001) compared to those treated with risperidone.

ANTIPSYCHOTIC EFFECT ON DYSLIPIDEMIA

Dyslipidemia, another modifiable cardiovascular risk factor, also may be affected by antipsychotic therapy.[68] Koro and colleagues[14] reported the results from a large population-based study that found that olanzapine, but not risperidone, was associated with a nearly 5-fold increase in the risk of developing hyperlipidemia compared with no antipsychotic exposure and a more than 3-fold increase compared with FGA treatment. More recently, results from the randomized CATIE schizophrenia trial[69] and Stroup et al.[70] demonstrated that the greatest risk for dyslipidemia was associated with olanzapine therapy. A 52-week open-label trial[71] comparing the effects of aripiprazole (not included in CATIE) and olanzapine on mean changes in serum triglycerides found that while baseline values were similar for both aripiprazole and olanzapine treatment groups (137 and 128 mg/dL, respectively), patients treated with olanzapine had higher mean changes in fasting triglycerides compared with those treated with aripiprazole at week 52 (29.87 vs. 0.6 mg/dL) and at endpoint (24.78 vs. 4.91 mg/dL). These reports are representative of the available literature[56] and consistent with conclusions from the 2004 joint American Diabetes Association/American Psychiatric Association Consensus Development Statement,[15] which found olanzapine and clozapine to be associated with the greatest risk of causing dyslipidemia among the SGAs, whereas aripiprazole and ziprasidone were noted to show no evidence of an effect on serum lipid levels.

MONITORING CARDIOMETABOLIC RISK

Several consensus panels have recommended approaches for monitoring cardiometabolic risk factors in patients receiving antipsychotics. For example, the Expert Consensus Guideline for the Treatment of Schizophrenia[72] indicates concern regarding the issue of SGA-related weight gain and the risk of type 2 diabetes and cardiovascular disease in patients with mental illness. The Expert Consensus Guideline[72] concluded that it is important to monitor for all treatment-related complications in patients taking SGAs, with 60% and 56% of the experts in this group stating that obesity and diabetes, respectively, were the most important complications that should be monitored.

Similarly, 4 professional organizations—the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity—cosponsored a Joint Consensus Statement[15] based on an examination of the relationship between SGAs and weight gain, dyslipidemia, and the risk of diabetes (Table 2). The Consensus Statement[15] issued a monitoring schedule for the assessment of cardiometabolic risk in patients receiving SGAs, regardless of the patients' initial level of perceived risk (see Sernyak's[73] article elsewhere in this supplement). This schedule includes a review of family history and measurement of weight, BMI, waist circumference, blood pressure, fasting plasma glucose level, and fasting lipid profile at or near baseline during initiation of antipsychotic treatment. Once

Table 2. Metabolic Disturbances Associated With Antipsychotic Agents[a]

Drug	Weight Gain	Diabetes Risk	Dyslipidemia
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole	+/–	–	–
Ziprasidone	+/–	–	–

[a]Adapted with permission from the American Diabetes Association.[15]
Abbreviation: D = discrepant results.
Symbols: + = increased effect, – = no effect.

the patient has begun SGA treatment, the monitoring schedule calls for a reassessment of weight at 4, 8, and 12 weeks, and quarterly thereafter. Blood pressure, fasting plasma glucose level, and fasting lipid profile measurements should be repeated at least 12 weeks after SGA initiation. In the absence of abnormalities, blood pressure, plasma glucose, and plasma lipids should be monitored annually, although more frequent monitoring is suggested for patients with a higher baseline cardiometabolic risk and those with rising values during treatment or in whom interventions are being made. The presence of symptoms such as polyuria or polydipsia, indicators of hyperglycemia, or additional symptoms of diabetic ketoacidosis, such as nausea, vomiting, or altered levels of consciousness, require immediate evaluation and treatment. Weight gain ≥ 5% of baseline body weight or the emergence of dyslipidemia or hyperglycemia should prompt intervention, including consideration of a switch to a medication with lower weight gain liability and lower metabolic risk.

A similar monitoring schedule was proposed by the Mount Sinai Conference.[74] According to this expert group,[74] all patients receiving an SGA should have BMI and weight assessments at every visit for the first 6 months after starting a new medication. A gain of 1 BMI unit should prompt consideration of a switch to an agent with a lower weight gain liability. Similarly, a baseline glucose level measurement should be collected from all patients before initiating antipsychotic therapy. Subsequently, patients with significant risk factors for diabetes should have fasting glucose or HbA$_{1c}$ levels assessed at 4 months postinitiation and yearly thereafter. In addition, psychiatrists should ensure that lipids are monitored and any abnormalities are treated appropriately.

CONCLUSION

Individuals with schizophrenia have an increased risk for obesity, type 2 diabetes, and other cardiometabolic risk factors. In particular, obesity can have a important negative impact on patients' overall health in relation to changes in insulin sensitivity and the associated risk of hypertension, hyperglycemia, and hyperlipidemia—all additional cardiometabolic risk factors. Based on substantial evidence that some treatments can increase adiposity, alter plasma lipids, and increase the risk of hyperglycemia, clinicians must be alert for potential negative effects on cardiometabolic risk. Clinicians should monitor and appropriately treat cardiometabolic risk in patients with schizophrenia.

Drug names: aripiprazole (Abilify), chlorpromazine (Thorazine and others), clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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