

Schizophrenia and Comorbid Metabolic Disorders

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Comorbid metabolic disorders in patients with schizophrenia are underrecognized by many health care professionals and patients. That lack of awareness can contribute to serious morbidity and mortality in patients with schizophrenia. Patients with schizophrenia may be at greater risk for metabolic disorders such as insulin resistance, lipid abnormalities, and weight gain. In addition, although the use of atypical antipsychotics in the treatment of schizophrenia offers many positive benefits and may reduce some of the factors related to the morbidity and mortality of the disorder, these drugs appear to be associated with varying degrees of comorbid metabolic disorders, such as metabolic syndrome, and more serious consequences, such as cardiovascular disease. Recent consensus guidelines recommend that metabolic risks be considered when initiating therapy with atypical antipsychotics. Thus, baseline screening and routine monitoring of patient weight, fasting lipid profile, and fasting plasma glucose are essential. In addition, optimal treatment for patients with schizophrenia and comorbid metabolic disorders is best achieved when all parties involved with patient care (mental health and medical community, caregiver/family, and patient) communicate and work together. With proper awareness and cooperation on the part of the medical community, caregivers, and patients, the detrimental consequences that may result from the metabolic disorders addressed in this article can be at least partially offset.

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Metabolic disorders, such as obesity and diabetes, are significant health care concerns. Globally, an estimated 300 million adults are considered obese.¹ Diabetes is a worldwide epidemic, expected to affect more than 366 million adults by 2030.² Epidemiologic data suggest that patients with mental illness are at greater risk of developing metabolic disorders, with diabetes and obesity estimated to be 1.5 to 2 times more common in patients with schizophrenia than the general population.³ A lack of awareness regarding this problem can contribute to serious morbidity and mortality among patients with schizophrenia, especially in the form of increased cardiovascular disease risk. In recent years, treatment with atypical antipsychotics has come under scrutiny for potential adverse metabolic effects. However, through increased awareness, early interventions, and cooperation among the medical community, caregivers, and patients with schizophrenia, the deleterious effects of comorbid metabolic disorders

may be offset and the positive profile of atypical antipsychotics can be maintained.

The purpose of this article is to discuss various metabolic disorders that can occur concurrently with schizophrenia. It will describe the effects that the disease and antipsychotic treatment can have on these disorders and focus on 4 metabolic disorders that are common in patients with schizophrenia: hyperprolactinemia, obesity, lipid abnormalities, and impaired glucose metabolism. Monitoring recommendations and treatment challenges in patients with schizophrenia and comorbid metabolic disorders also will be discussed.

HYPERPROLACTINEMIA

Hyperprolactinemia is a common adverse event caused by conventional antipsychotics. Data from imaging studies evaluating haloperidol indicate that dopamine-2 (D₂) receptor blockade of approximately 72% or more is associated with elevated prolactin levels.⁴ Although blockade of dopamine, specifically in the tuberoinfundibular system, is a likely explanation for antipsychotic-induced hyperprolactinemia, the influence of schizophrenia is unclear.⁵ In contrast to conventional antipsychotics, most atypical antipsychotics are less likely to cause sustained elevations in serum prolactin levels. A review of the literature suggests that risperidone, however, induces hyperprolactinemia to a degree similar to that of conventional antipsychotics.^{5,6} The risk of transient elevations in prolactin levels increases with olanzapine at dosages above 20 mg/day.⁷ The increased risk of hyperprolactinemia with

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risperidone and olanzapine may be related to the fact that, at recommended doses, both agents have the same level of D_2 occupancy as low-dose conventional antipsychotics.⁸ In contrast, clozapine has been shown to have a lower D_2 occupancy than risperidone, olanzapine, or the conventional antipsychotics, which may explain the low risk of developing hyperprolactinemia with this agent, even at high doses.^{8,9} Quetiapine is similar to clozapine in that it does not achieve the level of D_2 occupancy required for the development of sustained elevation in prolactin levels.¹⁰ In a fixed-dose study, there were no significant changes compared with placebo in prolactin concentrations in patients treated with quetiapine across the therapeutic dose range.¹¹ Data describing the effects of ziprasidone on prolactin concentration are limited; however, a review suggests that the effect is minimal compared with conventional antipsychotics and risperidone.⁶ The risk of hyperprolactinemia also appears to be minimal with aripiprazole.³

Clinical manifestations of elevated prolactin levels include sexual dysfunction, menstrual irregularities, impaired fertility, gynecomastia, galactorrhea, weight gain, effects on mood, and effects on immune function.⁶ Although these effects may occur with elevations in prolactin, it is unclear whether there is a causal relationship. Prolonged elevation of prolactin levels may have more serious consequences, increasing the risk for diabetes, dyslipidemia, and decreasing bone mineral density.^{12,13}

Symptoms related to hyperprolactinemia, especially sexual adverse events, are often difficult to spontaneously obtain from patients because they may not be aware that such symptoms should be monitored or may be embarrassed to report them. Clinicians need to know that sexual dysfunction commonly occurs in patients with psychotic disorders and should try to elicit this information from them.^{14,15} In an open-label randomized trial, sexual dysfunction (reduced libido and/or orgasm) was reported in 65% of patients (53/82) treated with risperidone, 43% (17/40) treated with conventional antipsychotics, and 18% (7/40) treated with olanzapine.¹⁴ In a separate study comparing sexual functioning in patients treated with risperidone or quetiapine, sexual dysfunction occurred in 50% of patients (12/24) treated with risperidone and 16% of patients (4/25) treated with quetiapine.¹⁵ Thus, soliciting information and warning patients about adverse events that may be related to hyperprolactinemia are necessary to help prevent or combat its consequences.

OBESITY

Classification and Epidemiology

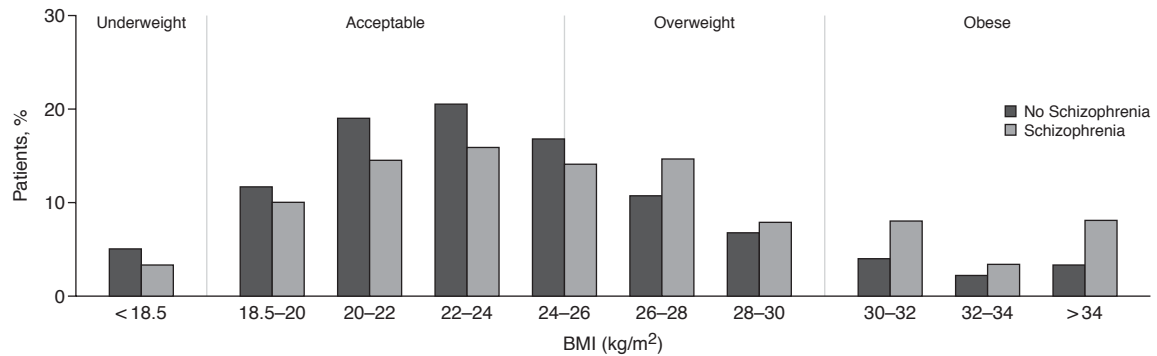
The prevalence of obesity is a serious health concern that continues to increase in the United States.¹⁶ The World Health Organization (WHO) uses body mass index (BMI) to define the concepts of overweight and obesity.¹

The WHO definition of overweight is a BMI of 25 to 29 kg/m^2 , whereas obesity is defined as a BMI of $\geq 30 \text{ kg}/\text{m}^2$. Mokdad et al.¹⁶ reported that in 2001 the prevalence of obesity among adults in the United States was 20.9%, representing 44.3 million obese American adults and an increase of 5.6% from the previous year. The prevalence of morbidly obese (BMI $\geq 40 \text{ kg}/\text{m}^2$) adults in 2001 was 2.3%. Among racial groups, the highest rate of obesity was reported among blacks (31.1%). Data from the 1989 National Health Interview Survey indicate that patients with schizophrenia, especially women, tend to have a higher BMI than the general population,^{17,18} indicating that patients with schizophrenia are particularly vulnerable to weight gain.

Effect of Schizophrenia and Antipsychotics on Body Weight

Both schizophrenia and antipsychotic drugs can contribute to weight gain,^{19,20} although the extent of their involvement is unclear. Work by Allison et al.¹⁸ suggests that noninstitutionalized patients with schizophrenia are overrepresented in the high BMI categories (Figure 1). Inactivity and apathy exhibited by these patients may contribute to weight gain. In addition, many patients with schizophrenia are of a lower socioeconomic status and have poor access to proper nutrition.²⁰ The mechanism of drug-induced weight gain with antipsychotic drugs is not clearly understood; however, several possibilities, including histamine- and serotonin-receptor antagonism, effects on leptin, hyperprolactinemia, and smoking cessation have been proposed.^{17,21–24}

Antagonism of histamine-1 (H_1) and serotonin-2C (5-HT_{2C}) receptors is thought to be one possible underlying mechanism of antipsychotic-induced weight gain.¹⁷ It is postulated that blockade of central H_1 receptors stimulates energy intake, increasing appetite.^{17,23} Sedative effects produced by some atypical antipsychotics through H_1 blockade may also induce weight gain by reducing physical activity, especially if caloric intake is not reduced.²⁴ Animal data indicate that blocking 5-HT_{2C} results in weight gain and insulin resistance.^{21,24,25} Although atypical antipsychotics have some activity at 5-HT_{2C} receptors, several reviews have shown that data regarding the association between 5-HT_{2C} receptor blockade and weight gain with atypical antipsychotics are inconsistent,^{17,23,24} suggesting that 5-HT_{2C} probably plays a synergistic role. Olanzapine, which is associated with greater weight gain than many of the other atypical antipsychotics, possesses high 5-HT_{2C} and H_1 antagonism.¹⁷ In contrast, risperidone and ziprasidone have high 5-HT_{2C} antagonism but do not possess high H_1 antagonism. Although quetiapine has high affinity for H_1 receptors, it has weak antagonistic activity for 5-HT_{2C}, and tolerance to sedative side effects induced by H_1 blockade may develop.^{17,26} Further research is needed to clarify the role that receptor affinity of the atypical

Figure 1. Body Mass Index (BMI) Distribution of Patients With Schizophrenia Versus the General Population^a

^aData from Allison et al.¹⁸

antipsychotics may have in contributing to effects on weight.

Leptin is an adipocyte-derived hormone responsible for regulating insulin secretion and energy metabolism by binding to receptors in the adipocytes, skeletal muscles, and hypothalamus.^{17,22} Leptin secretion may be altered by serotonergic mechanisms and can affect feeding behavior through activating central H₁ receptors.²² Increased levels of circulating leptin have been observed with atypical and conventional antipsychotics.^{21,22}

Elevated prolactin levels may contribute to antipsychotic-induced weight gain by reducing insulin sensitivity or by altering the ratio of androgen to estrogen in the body.²³ Smoking cessation also has been implicated as a potential mechanism for weight gain.²⁴ Several atypical antipsychotics have been shown to reduce cigarette smoking in patients with schizophrenia.^{27,28} However, a clear relationship between smoking cessation and weight gain among these patients has not been established. Pooled data from two 8-week double-blind studies evaluating adult patients with schizophrenia or schizoaffective disorder suggest a positive correlation between weight gain and smoking status with olanzapine, but not with risperidone.²⁹

Clinical Issues

Several factors contribute to the lack of predictability of weight gain with antipsychotics. First, it has been suggested but not confirmed that some patients may not actually gain weight with antipsychotics, but may experience redistribution of body fat leading to increased abdominal obesity. In a study evaluating the effect of antipsychotic therapy on fat distribution in patients with first-episode schizophrenia, treatment was associated with significant increases in intra-abdominal fat in both men and women.³⁰ Second, the weight gain does not appear to be related to dose.²⁴ Third, data are inconsistent regarding the correlation between baseline BMI and weight gain with anti-

psychotic therapy.^{24,31} Concomitant medications, such as mood stabilizers (e.g., lithium, valproic acid derivatives), also may contribute to increased body weight if given together with atypical antipsychotics.³²

Although comparisons of atypical antipsychotics are limited by differences in study design, patient characteristics, duration of therapy, methods of body weight measurement, and the presence of concomitant medications, data show differences in the degree of weight gain caused by various atypical antipsychotics.²⁴ Clozapine and olanzapine produce the largest weight gains, whereas limited data with ziprasidone and aripiprazole suggest minimal effects on weight.^{32–34} In a meta-analysis evaluating 10 weeks of therapy with atypical antipsychotics, the mean increase in weight was 4.50 kg with clozapine, 4.20 kg with olanzapine, 2.10 kg with risperidone, and 0.04 kg with ziprasidone.³³ Quetiapine has been reported to be associated with a 1.58-kg increase in weight following 9 to 13 weeks of therapy.³⁵

In general, increased weight gain is observed during the first 4 to 12 weeks of therapy with most atypical antipsychotics,²⁴ after which the rate of increase appears to stabilize at a lower level. Clozapine and olanzapine reportedly cause weight gain that continues over a prolonged period.²⁴ In a 5-year naturalistic study, records of 82 outpatients with schizophrenia or schizoaffective disorder indicate that weight gain plateaus 46 months after initiating treatment with clozapine.³⁶ For olanzapine, the plateau period for weight gain took 4 to 5 months in one report and approximately 10 months in another.^{31,33} Data from the Intercontinental Schizophrenia Outpatient-Health Outcomes (IC-SOHO) study reported mean weight gain at 1 year of 3.4 kg with olanzapine, 2.2 kg with risperidone, 2.1 kg with haloperidol, and 1.9 kg with quetiapine.³⁷ Switching from olanzapine to ziprasidone therapy results in weight loss and improved serum lipids and glucose tolerance.¹⁹ In a 10-week, open-label, pilot study of 12 psychiatrically stable patients with olanzapine-induced weight gain (> 20% total body

Table 1. Adult Treatment Panel III Classification of Dyslipidemia^a

Parameter (mg/dL)	Classification
Total cholesterol level	
< 200	Normal
200–239	Borderline high
≥ 240	High
LDL cholesterol level	
< 100	Normal
100–129	Near or above optimal
130–159	Borderline high
160–189	High
≥ 190	Very high
HDL cholesterol level ^b	
< 40	Low
≥ 60	High
Triglyceride level	
< 150	Normal
150–199	Borderline high
200–499	High
≥ 500	Very high

^aAdapted with permission from the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.⁴⁴

^bOptimal HDL level is > 40 mg/dL in men and > 50 mg/dL in women. Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

weight; BMI > 25 mg/kg²), switching to quetiapine resulted in a mean weight loss of 2.25 kg ($p = .03$) with no significant changes in glucose or lipid parameters.³⁸ The addition of quetiapine to existing clozapine treatment has been shown to reduce weight and improve glucose metabolism over a 10-month period.³⁹

Consequences of Weight Gain

Obesity has a significant impact on morbidity and mortality and is associated with an increased risk for various diseases. These comorbidities include hypertension, type 2 diabetes mellitus, coronary heart disease, dyslipidemia, stroke, gallbladder disease, osteoarthritis, sleep apnea, respiratory problems, and certain cancers.^{17,19,20,33} Of these, coronary heart disease and atherosclerotic diseases (e.g., stroke) are the most significant problems associated with obesity.²⁰ The risk of death increases as BMI increases: > 80% of the estimated deaths attributable to obesity occur in individuals with a BMI > 30 kg/m².²⁰ One study infers that the magnitude of weight gain related to several atypical antipsychotics may suggest an increased 10-year mortality rate as well as increased rates of hypertension and impaired glucose tolerance.⁴⁰

Anecdotal information suggests that patients who experience weight gain with antipsychotic medications are more likely to be noncompliant with their prescribed therapy, which puts them at an increased risk for relapse.¹⁹ Survey data from the Columbia-St. Luke's Obesity Research Center indicate that patients who experience weight gain are 13 times more likely to request that their current medication be discontinued. These same pa-

tients are 3 times as likely to be noncompliant with their therapy as nonobese patients.¹⁷

Overweight or obese individuals may also face increased social stigmatization and discrimination.²⁰ This is compounded in patients with schizophrenia and may erode their self-image. Given the numerous consequences associated with weight gain, it is important that physicians carefully consider the choice of antipsychotic treatment. Whether the consequences of weight gain significantly affect the benefits of treatment has yet to be determined.

Finally, being overweight or obese also is associated with an increased financial burden.²⁰ Wolf and Colditz⁴¹ determined that the total medical costs in 1995 attributable to obesity within the United States were \$99.2 billion. In this study, direct medical costs accounted for > 50% of this expenditure, and indirect costs accounted for 39.2 million lost workdays, which reflect a \$3 billion loss in productivity. Data from the 1998 Medical Expenditure Panel Survey and the 1996–1997 National Health Interview Survey show that combined annual medical spending attributable to overweight and obesity is estimated at \$51.5 billion and \$78.5 billion, respectively.⁴² In addition, prescription costs are greater for patients with obesity than for patients who are not overweight or obese.²⁰

LIPID ABNORMALITIES

Classification and Epidemiology

Within the general U.S. population, lipid abnormalities are common, with elevated total cholesterol (≥ 200 mg/dL) and low-density lipoprotein (LDL) cholesterol (≥ 130 mg/dL) levels estimated to affect 51% and 46% of adults, respectively.⁴³ High-density lipoprotein (HDL) cholesterol (normal level ≥ 40 mg/dL) is reduced in an estimated 26% of adults. The classification for dyslipidemia according to the National Cholesterol Education Program Adult Treatment Panel III is shown in Table 1.⁴⁴ According to these guidelines, cutoff points for normal triglyceride and LDL cholesterol levels were lowered to < 150 mg/dL and < 100 mg/dL, respectively, and for low HDL cholesterol levels were raised from < 35 mg/dL to < 40 mg/dL. Risk factors for LDL cholesterol, some of which may be modifiable with lifestyle changes, include middle age, smoking, low HDL cholesterol, hypertension, and family history of coronary heart disease.⁴⁴

Effect of Schizophrenia and Antipsychotics on Serum Lipids

Effects on serum lipids in patients with schizophrenia appear to be drug induced and primarily involve hypertriglyceridemia. Phenothiazine derivatives were one of the first groups of antipsychotic drugs noted to cause elevations in triglycerides and total cholesterol.

Table 2. Diagnostic Criteria for Diabetes Mellitus^a

Method ^b	Defining Level, mg/dL
Symptoms ^c plus a random glucose level	≥ 200
Fasting plasma glucose level	≥ 126
Oral glucose tolerance test ^d	≥ 200

^aReprinted with permission from The American Diabetes Association.⁵⁵ Copyright © 2004 American Diabetes Association.

^bDiagnosis is based on using 1 of 3 methods confirmed on 2 separate occasions.

^cClassic symptoms include polyuria, polydipsia, and unexplained weight loss.

^dNo longer routinely used.

Although both lipid parameters were elevated, the increase was greater for triglycerides than for total cholesterol. Since then, atypical antipsychotics classified as dibenzodiazepine (clozapine, olanzapine) and dibenzothiazepine (quetiapine) derivatives have shown an effect on serum triglycerides similar to that of phenothiazines.¹⁷ However, these agents and risperidone vary widely in their effects on triglycerides.^{45–47} The mechanism for the elevation in serum triglyceride levels is unclear; however, dibenzodiazepine derivatives and phenothiazines share a similar 3-ring structure.¹⁷

As with weight gain, the effects on serum lipid levels for the various atypical antipsychotics differ. Increases in serum triglyceride levels appear to be most closely associated with clozapine and olanzapine.³ Quetiapine and risperidone appear to have intermediate effects on lipids. In an analysis of short- and long-term clinical trials in schizophrenia, ziprasidone was not associated with increases in total cholesterol or triglycerides.⁴⁸ The risk for elevated lipids also appears to be low for aripiprazole.³

In 4 patients experiencing hypertriglyceridemia with clozapine, lipid levels were reduced after switching to risperidone.⁴⁹ In a retrospective chart review comparing serum triglyceride levels in patients treated with clozapine or conventional antipsychotics for 1 year, clozapine caused a significant increase in triglycerides compared with conventional antipsychotics (mean value = 264.6 ± 160.5 mg/dL vs. 149.8 ± 78.3 mg/dL). Although total cholesterol levels were slightly elevated, the difference was not statistically significant between the 2 groups. Patients included in this chart review had no history of hyperlipidemia, nor were they administered antihyperlipidemic agents.⁵⁰

In a study of 9 patients treated with olanzapine and observed for an average of 16 months, mean fasting triglyceride levels increased from 170 mg/dL to 240 mg/dL. There were no significant changes in cholesterol values.⁵¹ Fasting triglyceride levels were increased 60 mg/dL from a mean baseline of 162 ± 121 mg/dL in 25 inpatients receiving olanzapine for 12 weeks.⁵² In patients who were switched from olanzapine to ziprasidone, reductions in serum triglyceride and cholesterol levels were observed over 6 weeks.¹⁷

Clinical Issues and Consequences of Dyslipidemia

Five-year outcome data indicate a significant correlation between weight gain and elevated fasting cholesterol and triglyceride levels when data were controlled for time of exposure.³⁶ This correlation is an important finding, because both hypertriglyceridemia and abdominal obesity are risk factors for metabolic syndrome and diabetes.⁴⁴ In addition, elevation in serum lipid levels is an important risk factor for cardiovascular disease.⁵³

IMPAIRED GLUCOSE METABOLISM

Classification and Epidemiology

Diabetes is a metabolic disorder characterized by hyperglycemia. The 2 major categories of diabetes mellitus are type 1 (inability of β cells to secrete insulin) and type 2 (varying degrees of insulin resistance and/or relative insulin secretory deficiency).⁵⁴ In addition to hyperglycemia and defects in insulin secretion and action, patients with type 2 diabetes often have a pattern of dyslipidemia characterized by hypertriglyceridemia and depressed HDL cholesterol levels.⁵³ The diagnosis of diabetes mellitus is explained in Table 2.⁵⁵ Diabetic ketoacidosis (DKA) is an acute metabolic disturbance and complication of diabetes mellitus characterized by hyperglycemia, hyperketonemia, and metabolic acidosis.⁵⁶

In 2001, the prevalence of diabetes was 8%, representing approximately 17 million U.S. adults.¹⁶ The prevalence was found to increase with age, and the highest rate of diabetes by ethnic group was found in blacks (11%). In patients with schizophrenia, an increased prevalence (11%–18%) of type 2 diabetes was first observed in conjunction with antipsychotic use with the introduction of the phenothiazines in the late 1950s.⁵⁷ The lifetime prevalence of type 2 diabetes in patients with schizophrenia is estimated at 13% to 15% in the United States and 9% to 19% in international studies.^{57,58} Unfortunately, population-based studies to determine the incidence and prevalence of new-onset diabetes in patients treated with antipsychotics are limited, and actual rates are therefore uncertain. As a result, precise estimates of diabetes during antipsychotic therapy are unknown. A review by Haupt and Newcomer⁵⁶ reported an estimated prevalence of 12% to 36% for clozapine and 6% to 35% for olanzapine, whereas data from Eli Lilly estimate the prevalence of new-onset diabetes in patients taking olanzapine at 3%.⁵⁶ Many of the studies reporting on the prevalence of new-onset diabetes with antipsychotic therapy are limited by small sample sizes and differences in study design that may strongly influence findings. In a retrospective database study conducted by Gianfrancesco and Wang,⁵⁹ the authors emphasize the importance of using a strong study design (screening for preexisting diabetes at 8 months before the observation/treatment period, identifying diabetes using prescription claims only, inclusion of diagnostic codes for both type 1 and type 2 diabetes, and

treatment with antipsychotic monotherapy only) to accurately determine the diabetes risk associated with antipsychotic treatment. In the study,⁵⁹ treatment with conventional antipsychotics (all dose levels) and olanzapine (medium- and high-dose levels) was associated with the greatest risk of diabetes. Compared with untreated patients, the risk of diabetes for patients treated with risperidone was greater at high doses only, but was not significantly greater with quetiapine at any dose level.

Effect of Schizophrenia and Antipsychotics on Glucose Metabolism

Patients with schizophrenia have an increased risk of abnormal glucose regulation. Even among patients who are not treated with antipsychotics, a pattern of insulin resistance and an elevated baseline risk of gluco-regulatory disturbances are present.⁵⁶ Similar to the general population, patients with schizophrenia are predisposed to an increased risk for diabetes by a number of risk factors,^{60,61} including age, ethnicity, overweight at baseline, duration of obesity, physical activity, and family history of diabetes.

In patients with schizophrenia who are taking atypical antipsychotics, abnormal glucose regulation often presents initially as DKA and is associated with increased age and with clozapine therapy.⁶⁰ It is unclear whether atypical antipsychotics cause impaired glucose metabolism or are a risk factor that precipitates the development of these disorders. Underlying mechanisms possibly involved with the development of impaired glucose metabolism in psychiatric patients include reduced sensitivity to insulin; antagonism of serotonin, histamine, or dopamine receptors; antipsychotic-induced weight gain; effect on glucose transporters; and damage to pancreatic islet cells.^{56,57,62,63}

Clinical Issues

The atypical antipsychotics show differences in their effects on insulin sensitivity and glucose utilization.^{56,64} Various methods, including euglycemic clamp, homeostasis model assessment-insulin resistance (HOMA-IR), oral glucose tolerance test, and minimal model analysis developed by Bergman, have been used to measure insulin sensitivity and glucose utilization in patients treated with antipsychotics. Studies utilizing these methods suggest that clozapine and olanzapine are associated with a greater degree of insulin resistance than other available atypical or conventional antipsychotics.⁶⁴⁻⁶⁷ Pilot data of 10 outpatients with schizophrenia and insulin resistance, presented at the 157th annual American Psychiatric Association meeting, suggest that aripiprazole (mean dose, 21.5 mg) had a positive effect on insulin resistance, as measured by HOMA-IR, with 70% of patients showing improvement at the end of 16 weeks of therapy.⁶⁸

The U.S. prescribing information for all of the commercially available atypical antipsychotics contains the following warning⁶⁹⁻⁷⁴:

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

The manufacturers of these atypical antipsychotics recommend that patients with an established diagnosis of diabetes who are started on atypical antipsychotics be monitored regularly for worsening of glucose control. In addition, any patient treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia, and if it is present, fasting blood glucose testing should be conducted.

Consequences of Impaired Glucose Metabolism

Diabetic ketoacidosis and long-term complications of diabetes are associated with significant morbidity and mortality.^{56,75} DKA is associated with mortality rates of 2% to 20%. Outcomes are influenced by age, general health, and time elapsed between onset of symptoms and treatment.⁵⁶ With diabetes, microvascular complications can lead to blindness, renal failure, and diabetic neuropathy. Of greater concern are the macrovascular complications, which can lead to stroke, myocardial infarction, and coronary artery disease. The risk of myocardial infarction in patients with type 2 diabetes (but without schizophrenia) and no prior history of myocardial infarction is as high as that in nondiabetic patients with a prior history of myocardial infarction.⁷⁶ Diabetes is also associated with reduced gastrointestinal motility and increased lower extremity amputations. Unfortunately, the effect of diabetic complications in patients with schizophrenia has not been adequately studied. There is some suggestion that impaired glucose regulation may be associated with impaired cognition⁷⁷; however, further studies are needed to clarify this potential effect.

METABOLIC SYNDROME

Classification and Epidemiology

Features of metabolic syndrome, as defined by the National Cholesterol Education Program, include abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance with or without glucose intolerance, and pro-

thrombotic and proinflammatory states.⁴⁴ The diagnosis of metabolic syndrome is made when ≥ 3 risk factors listed in Table 3 are present.

In the United States, an estimated 47 million adults have metabolic syndrome.⁷⁸ Data regarding the prevalence of metabolic syndrome in patients with schizophrenia are limited; however, in a cohort of 35 outpatients, the frequency of metabolic syndrome was 37% (13/35).⁷⁹ Data from a 22-week, open-label, multicenter study of patients switched from olanzapine to risperidone suggest that 54% of the patients (65/121) entering the study had metabolic syndrome at baseline.⁸⁰

Effect of Schizophrenia and Antipsychotics on Metabolic Syndrome

The effects of schizophrenia and antipsychotics on metabolic syndrome are just beginning to be investigated. Given that patients with schizophrenia are already at an increased risk for obesity, hyperlipidemia, and diabetes, the risk of metabolic syndrome should be of particular concern in this patient population. In a 22-week, open-label, multicenter study, the prevalence of metabolic syndrome in 71 patients switched from olanzapine to risperidone was reduced from 56% at baseline to 35% at study endpoint.⁸⁰ A post hoc analysis presented at the 157th annual American Psychiatric Association meeting assessed the incidence or worsening of metabolic syndrome in patients receiving aripiprazole (N = 504) or olanzapine (N = 505).⁸¹ Following 26 weeks of therapy, metabolic syndrome was present in 8.5% of patients treated with aripiprazole compared with 14.4% of patients treated with olanzapine. At 1 year, the event rate in patients receiving olanzapine (20%) remained higher than the rate in patients receiving aripiprazole (10%). Overall, the relative risk (RR) for metabolic syndrome was doubled with olanzapine versus aripiprazole treatment (RR = 2.1; $p = .0016$).

Clinical Issues and Consequences of Metabolic Syndrome

Metabolic syndrome is associated with an increased risk for diabetes and, more importantly, cardiovascular disease. According to the National Cholesterol Education Program Adult Treatment Panel III,⁴⁴ metabolic syndrome is considered a secondary target of risk reduction therapy for cardiovascular disease. Schizophrenia without antipsychotic treatment is associated with a pattern of insulin resistance that, when combined with lipid abnormalities and weight gain, predisposes patients with schizophrenia to metabolic syndrome.⁸² As discussed above, treatment with atypical antipsychotics has effects on weight, serum lipids, and glucose metabolism. Collectively, these effects predispose patients with schizophrenia to metabolic syndrome. Early detection and management of metabolic syndrome is critical in helping to prevent the complications (e.g., cardiovascular disease) associated with this disorder.

Table 3. Risk Factors for Metabolic Syndrome^a

Risk Factor	Defining Level
Abdominal obesity (waist circumference), ^b cm (in)	
Men	> 102 (> 40)
Women	> 88 (> 35)
Triglyceride level, mg/dL	≥ 150
High-density lipoprotein cholesterol level, mg/dL	
Men	< 40
Women	< 50
Blood pressure, mm Hg	$\geq 130/\geq 85$
Fasting plasma glucose level, mg/dL	≥ 110

^aAdapted with permission from the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.⁴⁴

^bSome male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94–102 cm (37–40 in).

MONITORING RECOMMENDATIONS AND TREATMENT CHALLENGES

Risk Assessment and Monitoring

A thorough medical history should be taken at the initial evaluation of all patients with schizophrenia and should include a review of all risk factors for diabetes, a history of weight gain and lipid abnormalities with and without psychotropic medications, and other relevant medical history.^{3,83} In all patients receiving antipsychotic medications, weight and glucose and lipid levels should be obtained at baseline and monitored regularly. According to the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes,³ weight should be checked 4, 8, and 12 weeks after initiating or changing antipsychotic therapy and quarterly thereafter. The suggested time frame for monitoring glucose and lipid levels is 3 months after initiating antipsychotic therapy. If normal, blood glucose levels should be monitored at least annually and lipid levels should be reassessed every 5 years or more frequently, if needed.³ Glycosylated hemoglobin A1c (HbA_{1c}) is routinely used to monitor long-term (over 2–3 months) glycemic control. The American Diabetes Association recommends that HbA_{1c} levels be < 7%, and more stringent goals (HbA_{1c} levels < 6%) may be considered for individual patients.⁵⁵

Treatment Strategies

No standard approach exists for managing patients with schizophrenia and comorbid metabolic disorders. In general, management should be individualized, taking into account the risk factors and personal and family history of the patient.⁵⁶

Nonpharmacologic interventions. Prevention of metabolic disorders is critical in minimizing the morbidity and mortality associated with these disorders. An important component of prevention is education. All patients receiving antipsychotic medications and their families and caregivers should be educated from the onset of therapy on nutrition, exercise, symptoms of diabetes, and the results

of neglecting proper medical care.^{3,83} Lifestyle changes, which include proper diet and physical activity, are an essential part of managing obesity, hyperlipidemia, and diabetes. Although managing obesity is challenging in any individual, data indicate that patients with schizophrenia are capable of acquiring skills related to eating behavior.¹⁷

Pharmacologic interventions. In addition to lifestyle interventions, pharmacotherapy should be considered, if appropriate. For weight gain, pharmacologic management should be reserved for patients who fail to lose weight within several months of lifestyle interventions, especially in the presence of other comorbid disorders. Drug options include appetite suppressants, sibutramine, and orlistat.¹⁷ Lipid-lowering agents should be considered in patients with comorbid diabetes, in cases where lifestyle interventions have not been successful, or if triglyceride concentrations are > 500 mg/dL. Management options for hypertriglyceridemia include fish oil, nicotinic acid, fibrates, and ezetimibe that alter cholesterol metabolism. In patients with comorbid diabetes, statins may be a more appropriate option.¹⁷ The management of hyperglycemia due to diabetes and impaired glucose tolerance should include regulating triglyceride levels, blood pressure, and adiposity. For patients diagnosed with diabetes, drug treatment should be considered if lifestyle changes are unsuccessful. Drug options include insulin, sulfonylureas, biguanides, and thiazolidinediones.⁵⁶

Treatment Challenges

It is critical that mental health professionals have a close working relationship with other medical professionals, especially internists and endocrinologists, in order to optimize treatment for their patients.⁸⁴ Mental health professionals should not hesitate to refer their patients to specialized services when needed.³

Switching patients to a different treatment is an important clinical decision. In patients experiencing DKA, discontinuing or switching to another antipsychotic is strongly recommended. If discontinuation of the medication is not possible, adding another antipsychotic that has a lesser effect on glucose metabolism and reducing the dosage of the initial drug should be considered.⁸³ The Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes recommends that a patient who gains $\geq 5\%$ of his or her initial weight at any time during therapy or develops worsening glycemia or dyslipidemia while on antipsychotic therapy consider switching to another antipsychotic.³ In general, switching to another agent should not be at the expense of reduced efficacy.⁸³ When switching antipsychotic therapy, the safest approach is cross-titration, in which the current antipsychotic is discontinued gradually while the new antipsychotic is initiated and the dose gradually escalated.³ In treatment-resistant patients, the decision not to switch to another agent should be discussed with the patient and caregivers,

and they should be educated regarding the long-term risk of continuing to take the offending drug.⁸³ Controlled data regarding the differences among the various atypical antipsychotics are needed to assist physicians in making better treatment decisions.

In patients receiving antipsychotics, strategies that may help prevent metabolic changes include carefully considering the choice of antipsychotic, administering the lowest effective dose, and avoiding ancillary medications that may enhance weight gain.⁸⁴ Minimizing weight gain using weight-reducing agents is another important consideration. For example, many of the available drug treatments for reducing weight have central nervous system (CNS) activity that may exacerbate underlying psychosis. Of the commercially available drugs for treating obesity, orlistat may be the best choice for the chronically mentally ill because of its lack of CNS activity.¹⁷

CONCLUSION

Atypical antipsychotics continue to represent a significant advance over conventional antipsychotics. The use and availability of these agents in the treatment of schizophrenia have offered many positive benefits (e.g., reduced risk of extrapyramidal symptoms, improvement in negative symptoms and, possibly, cognition) and may reduce some of the morbidity and mortality of the disorder. However, it is critical that mental health professionals and general medical physicians work together in identifying and managing patients who are at high risk for metabolic disorders. Proper awareness on the part of the medical community, caregivers, and patients can help offset the detrimental consequences that may result from the metabolic disorders addressed in this article.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), ezetimibe (Zetia and Vytorin), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), orlistat (Xenical), quetiapine (Seroquel), risperidone (Risperdal), sibutramine (Meridia), ziprasidone (Geodon).

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