

Hyperglycemia and Antipsychotic Medications

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Type 2 diabetes mellitus and impaired glucose tolerance are associated with antipsychotic treatment. Risk factors for type 2 diabetes and impaired glucose tolerance include abdominal adiposity, age, ethnic status, and certain neuropsychiatric conditions. While impaired glucose metabolism was first described in psychotic patients prior to the introduction of antipsychotic medications, treatment with antipsychotic medications is associated with impaired glucose metabolism, exacerbation of existing type 1 and 2 diabetes, new-onset type 2 diabetes mellitus, and diabetic ketoacidosis, a severe and potentially fatal metabolic complication. The strength of the association between antipsychotics and diabetes varies across individual medications, with the largest number of reports for chlorpromazine, clozapine, and olanzapine. Recent controlled studies suggest that antipsychotics can impair glucose regulation by decreasing insulin action, although effects on insulin secretion are not ruled out. Antipsychotic medications induce weight gain, and the potential for weight gain varies across individual agents with larger effects observed again for agents like chlorpromazine, clozapine, and olanzapine. Increased abdominal adiposity may explain some treatment-related changes in glucose metabolism. However, case reports and recent controlled studies suggest that clozapine and olanzapine treatment may also be associated with adverse effects on glucose metabolism independent of adiposity. Dyslipidemia is a feature of type 2 diabetes, and antipsychotics such as clozapine and olanzapine have also been associated with hypertriglyceridemia, with agents such as haloperidol, risperidone, and ziprasidone associated with reductions in plasma triglycerides. Diabetes mellitus is associated with increased morbidity and mortality due to both acute (e.g., diabetic ketoacidosis) and long-term (e.g., cardiovascular disease) complications. A progressive relationship between plasma glucose levels and cardiovascular risk (e.g., myocardial infarction, stroke) begins at glucose levels that are well below diabetic or "impaired" thresholds. Increased adiposity and dyslipidemia are additional, independent risk factors for cardiovascular morbidity and mortality. Patients with schizophrenia suffer increased mortality due to cardiovascular disease, with presumed contributions from a number of modifiable risk factors (e.g., smoking, sedentary lifestyle, poor diet, obesity, hyperglycemia, and dyslipidemia). Patients taking antipsychotic medications should undergo regular monitoring of weight and plasma glucose and lipid levels, so that clinicians can individualize treatment decisions and reduce iatrogenic contributions to morbidity and mortality.

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Hyperglycemia is an underrecognized comorbid complication of treatment with antipsychotic medications. This complication may contribute to increases in morbidity and mortality. Abnormalities in peripheral glucose regulation¹ and type 2 diabetes mellitus² occur more commonly in individuals with schizophrenia compared

with the general population. While impaired glucose metabolism was first described in psychotic patients prior to the introduction of antipsychotic medications, treatment with antipsychotic medications is associated with impaired glucose metabolism, exacerbation of existing type 1 and 2 diabetes, new-onset type 2 diabetes mellitus, and diabetic ketoacidosis, a severe and potentially fatal metabolic complication.

Type 2 diabetes mellitus, formerly referred to as non-insulin-dependent diabetes or adult-onset diabetes, is associated with decreased sensitivity to the actions of insulin, sometimes called insulin resistance, along with a variable and usually progressive defect in β -cell function leading to a relative insulin deficiency.³ Type 1 diabetes mellitus, formerly referred to as insulin-dependent or juvenile-onset diabetes, is a primary β -cell defect causing failure to secrete insulin, and this condition has not generally been associated with schizophrenia. Major functions of insulin include stimulation of glucose disposal into

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skeletal muscle, inhibition of hepatic glucose production, and inhibition of lipolysis in adipocytes. The intracellular signal transduction pathway activated by insulin regulates glucose transport as well as lipid synthesis, contributing to disturbances in glucose and lipid metabolism in type 2 diabetes. Dyslipidemia is a feature of type 2 diabetes, and antipsychotics such as clozapine and olanzapine have also been associated with hypertriglyceridemia, with agents such as haloperidol, risperidone, and ziprasidone associated with reductions in plasma triglyceride levels.^{4,5}

Risk factors for type 2 diabetes mellitus include family history, age, adiposity, and ethnicity. In addition, major neuropsychiatric conditions including affective disorders,⁶ Alzheimer's disease,⁷ and schizophrenia² are further associated with diabetes. As age increases, the risk of developing type 2 diabetes mellitus increases, and up to 30% of people over the age of 60 years in the United States have either type 2 diabetes mellitus, of which almost half of the cases are unrecognized, or the lesser diagnosis of impaired glucose tolerance.⁸ Adiposity, especially visceral abdominal adiposity, is strongly associated with skeletal muscle insulin resistance and type 2 diabetes mellitus.⁹ Whites experience a relatively lower risk of developing type 2 diabetes mellitus in comparison to most other ethnic groups, including Africans, Hispanics, Asians (including Indian Asians), Pacific Islanders, and the majority of indigenous peoples.³ Antipsychotic medications induce weight gain and increase adiposity, suggesting that increased abdominal adiposity may explain some or all treatment-related changes in glucose metabolism. However, case reports and recent controlled studies reviewed below suggest that certain antipsychotic treatments may also be associated with adverse effects on glucose metabolism independent of adiposity.

Hyperglycemia and diabetes mellitus are serious public health problems. Type 2 diabetes mellitus accounts for over \$100 billion in annual health care expenditures in the United States.¹⁰ Type 2 diabetes mellitus is associated with both acute complications and chronic complications related to microvascular and macrovascular disease. Microvascular disease accounts for much of the chronic morbidity of type 2 diabetes mellitus, in the form of nephropathy, neuropathy, and retinopathy.¹⁰ For example, diabetic nephropathy currently accounts for approximately 25% of cases of end-stage renal failure in the United States.³ Acute metabolic complications of type 2 diabetes mellitus include diabetic ketoacidosis, an infrequent but potentially fatal metabolic derangement.¹¹ Macrovascular, or atherosclerotic, disease accounts for increased levels of morbidity as well as mortality in type 2 diabetes mellitus. Diabetes mellitus is associated with marked increases in the risk of stroke and myocardial infarction (MI). Moreover, a progressive relationship between hyperglycemia and cardiovascular event risk (e.g., MI, stroke) begins at plasma glucose levels well below the threshold for diabetes mellitus or even the less severe conditions of impaired fasting glu-

case and impaired glucose tolerance. Increased adiposity and dyslipidemia are additional, independent risk factors for cardiovascular morbidity and mortality. Unfortunately, individuals with schizophrenia suffer increased mortality due to cardiovascular disease, with presumed contributions from a number of modifiable risk factors (e.g., smoking, sedentary lifestyle, poor diet, obesity, hyperglycemia, dyslipidemia). Some of these risk factors may be difficult for patients to modify on their own, and potential iatrogenic contributions to cardiovascular risk have understandably come under increasing scrutiny.

SCHIZOPHRENIA AND DIABETES

Abnormalities in glucose regulation were first reported in schizophrenia prior to the introduction of antipsychotic medications, with early reports indicating a pattern of insulin resistance in untreated patients.^{1,12,13} These early reports suggested that patients with psychotic disorders might have some elevated baseline risk for glucoregulatory disturbances, prior to any consideration of adverse medication effects. However, these early studies had a number of weaknesses, including failure to control for or consider age, weight, adiposity, ethnicity, or diet. Nevertheless, a number of early reports of impaired glucose metabolism suggested an association with various psychiatric disorders, independent of medication effects. A recent analysis of prescription claims for patients receiving diabetes-related medications and antipsychotic medications similarly suggests that schizophrenia patients suffer from increased rates of type 2 diabetes mellitus in comparison to the general population, largely independent of which antipsychotic medications patients are treated with.¹⁴ However, the results of this analysis supported by Eli Lilly and Company are in contrast to the results of an earlier claims database analysis supported by Janssen Pharmaceutica which reported that specific medications were associated with elevated risk of diabetes mellitus.¹⁵ The difficulty with interpreting these conflicting results may be related to the serious methodological limitations inherent to analyses involving insurance claims databases. These limitations include, but are not restricted to, the lack of any direct measure of glucose metabolism, high rates of polypharmacy, and the lack of verification of psychiatric diagnosis and whether or not treatment(s) were even received. Most importantly, these studies use the prescription of a hypoglycemic agent as the indicator for the presence of diabetes mellitus, while it is well known that diabetes is routinely underdiagnosed, with up to half the cases in the United States undetected and untreated. This suggests that studies using treatment as an indicator for the presence of disease may seriously underestimate the prevalence of diabetes mellitus and may include a degree of error that undermines the ability to reliably detect differences between medications.

ANTIPSYCHOTIC TREATMENT AND ABNORMAL GLUCOSE METABOLISM

Glucoregulatory disturbances in schizophrenia became more prominent with the introduction of chlorpromazine and subsequent antipsychotic medications. Phenothiazine treatment was quickly observed to contribute to abnormalities in glucose regulation,¹⁶ including reports of aggravation of existing diabetes¹⁷ and new-onset type 2 diabetes mellitus.¹⁸ Phenothiazine treatment has also been associated with increases in plasma lipid levels,¹⁹ weight, and adiposity.²⁰ These reports provided an early indication that patients with schizophrenia taking antipsychotic medications were at increased risk for clinically significant disturbances in glucose metabolism and for potentially related changes in lipid metabolism and adiposity. While low-potency phenothiazine treatment has frequently been associated with abnormalities in glucose regulation, this association is not consistently observed for all older antipsychotics. Higher-potency agents such as haloperidol have not generally been associated with diabetes mellitus, providing an early demonstration that medication effects on glucose regulation may vary in magnitude across individual agents. In addition, the market dominance that haloperidol achieved may have contributed to the decrease in number of reports of antipsychotic-induced glucose disturbances and the low profile that this potential adverse event enjoyed for many years. Recent reports indicate a reemergence of this adverse event in clinical practice and suggest that certain newer antipsychotic medications may have an even greater propensity than chlorpromazine to contribute to the development of diabetes mellitus, dyslipidemia, and increased weight and adiposity.

Newer antipsychotic medications, like older agents, have been associated with the occurrence of clinically significant hyperglycemia. Recent reports indicate that the strength of this association can vary across different medications. Hyperglycemia, exacerbation of existing type 1 and type 2 diabetes, new-onset type 2 diabetes mellitus, and diabetic ketoacidosis have been associated with treatment using clozapine,^{21–41} olanzapine,^{29,38,39,42–54} quetiapine,^{46,48,55,56} and risperidone.^{57–59} A markedly different frequency of reported cases is observed across different antipsychotic agents that cannot be explained by length of time on the market or number of prescriptions. Multiple cases of adverse events such as new-onset diabetes mellitus and diabetic ketoacidosis have been reported for clozapine and olanzapine. A death has been attributed to olanzapine-related diabetic ketoacidosis in the published literature.⁶⁰ Some of the more compelling case reports concern patients in whom glucoregulatory abnormalities were observed to improve, then worsen following removal and reexposure to the putative offending agent. Colli et al.³³ described a 31-year-old man with schizophrenia who

developed severe hyperglycemia, acidosis (pH = 6.9), and ketosis 3 months after starting clozapine therapy. His body mass index (BMI) was 29 kg/m², and he had gained 3 kg (6.7 lb) since starting clozapine. After resolution of his ketoacidosis, clozapine was discontinued. Two months later, his glycosylated hemoglobin (HbA_{1c}) level normalized to 5.9%, with a fasting plasma glucose level of 5.16 mmol/L. Clozapine was restarted, and 72 hours later, the patient's fasting glucose level was 8.49 mmol/L. Discontinuation of clozapine led again to normalization of the patient's glucose levels. Koval et al.²⁷ reported a similar case wherein withdrawal and reexposure to clozapine led to normalization, followed by a repeated elevation, of blood glucose levels.

In contrast, there are relatively few reports describing an association between diabetes mellitus and quetiapine or risperidone, and there are no reports for ziprasidone. The limited reporting for quetiapine and ziprasidone may be related to the relatively limited use of these agents at the present time, with ziprasidone just introduced in March 2001. Risperidone has received extensive use, but has triggered relatively few reports of an association with diabetes mellitus, including 1 report of hyperglycemia⁵⁷ and 1 report of diabetic ketoacidosis in a human immunodeficiency virus (HIV)-infected man.^{58,59} For all of the antipsychotic medications, many of the individual cases provide limited clinical details, preventing the confirmation of specific diagnoses (e.g., diabetic ketoacidosis) or limiting the interpretability of events as drug effects independent of other risk factors. For example, it was not noted in the report of risperidone-associated diabetic ketoacidosis^{58,59} that glucose intolerance, dyslipidemia, and lipodystrophy are associated with HIV infection⁶¹ and potentially increase the risk of diabetes and diabetic complications in those individuals. Other published reports to date concerning risperidone describe uncomplicated use in schizophrenia patients diagnosed with comorbid diabetes, with no similar reports for other agents at this time.^{29,62,63} On the basis of case reports alone, it is not clear whether the relatively higher frequency of reports of hyperglycemic events in association with certain medications reflects more frequent or larger medication effects on glucoregulation and/or adiposity, or merely a reporting bias.

A reasonable hypothesis at this time is that many antipsychotic medications may be capable of disturbing whole-body glucose metabolism to some degree, with some agents associated with a greater potential for clinically significant adverse effects than others. These adverse effects may or may not be restricted to certain vulnerable individuals. Established risk factors for diabetes include older age, greater adiposity, and ethnicity (e.g., African Americans, Hispanic Americans, Asian Americans including Indian Asians, Pacific Islanders, and Native Americans).³ Evidence to date suggests that diabetes-related adverse events can occur during antipsychotic treatment in

young, lean whites, as well as in patients with established risk factors.³⁴ The standard approach to identify the true incidence of diabetes mellitus associated with different medications, and to identify specific groups of individuals who may be at increased or decreased risk, is to conduct an epidemiologic study in a large sample of individuals, using sensitive indicators for the disease under study.

Unfortunately, no methodologically sound population studies have been completed to establish the prevalence of new-onset diabetes in patients treated with antipsychotic medications. Investigators have made estimates of new-onset diabetes during clozapine and olanzapine treatment using smaller samples than the thousands of subjects that one would prefer to include in such studies. The incidence estimates range from 12% to 36% for clozapine^{21,34,49,64} and from 6% to 35% for olanzapine,^{29,65} suggesting that up to approximately 35% of patients treated with these agents might develop comorbid new-onset diabetes. These numbers may seem high to some clinicians and investigators, based on the perception that high rates of diabetes mellitus are not generally observed in clinical practice. However, the underrecognition of diabetes mellitus in the general population (i.e., up to half the cases are missed in the United States³), and the possibility that psychiatrists may be less vigilant than internists and family practice physicians with respect to screening for diabetes, suggest that it may be unwise to dismiss these reports. The strength of the analyses cited above^{21,29,34,49,64,65} is that they have relied on American Diabetes Association (ADA) or World Health Organization (WHO) criteria for the diagnosis of diabetes, using fasting plasma glucose values or the results of oral glucose tolerance tests (OGTTs). The manufacturers of all of the antipsychotic medications have large and potentially valuable databases of several thousand patients taking these agents from the clinical trials conducted to evaluate safety and efficacy for the U.S. Food and Drug Administration (FDA). Unfortunately, none of the companies or the FDA had specific concerns about diabetes mellitus at the time these early studies were launched, so none of these studies included fasting or postload plasma glucose values. Instead, random plasma glucose values were collected. Whether these values are fasting or postprandial is unknown, limiting the value of the data. Random plasma glucose values offer limited reliability and validity for the sensitive detection of diabetes mellitus and are not used for screening purposes by the ADA or WHO. Eli Lilly, the manufacturer of olanzapine, has calculated an incidence of 3.1% for possible new-onset diabetes mellitus in patients taking olanzapine, using a threshold of random plasma glucose value of 160 mg/dL or higher (data on file, Eli Lilly, Indianapolis, Ind., 2000). The methodological differences between the studies make it difficult to reconcile the up-to-10-fold differences in calculated incidence, 3.1% (data on file, Eli Lilly, Indianapolis, Ind., 2000) versus 35%,⁶⁵ leaving

clinicians to guess at the actual incidence and hope for large population studies that can settle the question. In the meantime, increased regulatory interest at the local and national level has been stimulated by the multiple reports concerning hyperglycemia and diabetes mellitus in association with atypical antipsychotics. During the summer of 2000, the FDA requested that manufacturers of all these antipsychotic medications provide the FDA with reports on this topic. Regulatory agencies in other countries, including Japan, have taken the further step of requiring modifications to the package insert for olanzapine to reflect the risk of hyperglycemia and new-onset type 2 diabetes mellitus.

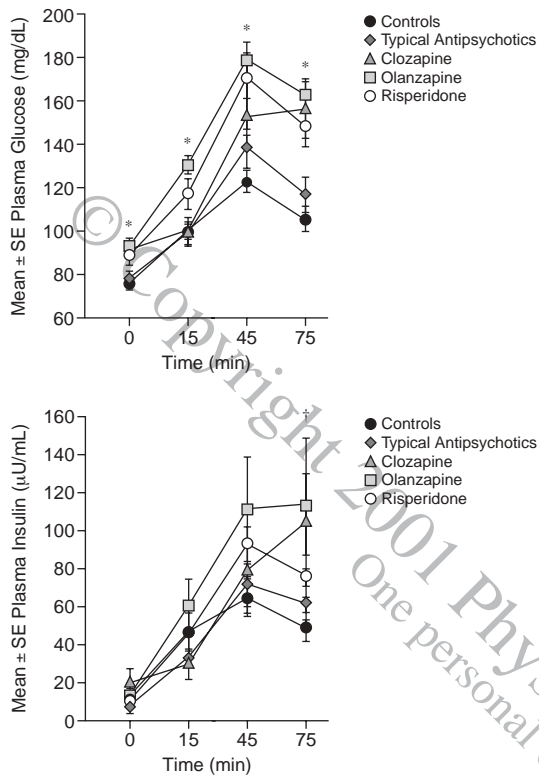
TECHNIQUES FOR STUDYING GLUCOSE METABOLISM

Another approach to understanding the effects of medications on glucose metabolism is through controlled studies that sensitively measure the key parameters of glucose metabolism, insulin secretion, and insulin action. The available measurements of glucose metabolism, generally in order of increasing sensitivity, reliability, and/or validity, are random plasma glucose level, HbA_{1c} level, fasting plasma glucose level, fasting plasma insulin level, homeostatic model assessment (HOMA) calculations of insulin resistance,⁶⁶ OGTTs, intravenous glucose tolerance tests (IVGTTs), frequently sampled IVGTTs with minimal-model measures of insulin sensitivity and other parameters,⁶⁷ and the gold-standard measure of glucose disposal, euglycemic clamps. All of these techniques are now being applied to the study of medication effects on glucose metabolism.

Pharmaceutical companies have large data sets of random glucose values from their clinical trials (e.g., sample from thousands of subjects) that might be used to characterize treatment effects on plasma glucose level. As noted above, however, random glucose testing offers limited sensitivity, reliability, and validity for detecting treatment-related disturbances in glucose metabolism, and these analyses have failed to reject the null hypothesis (i.e., no difference in glucose effects between treatments). The optimistic interpretation of such negative findings is that power was adequate to detect effects if they were really there, and thus the medications tested may not significantly elevate plasma glucose levels. A more conservative interpretation of these negative findings, with unknown treatment effect sizes for random glucose level and power difficult to estimate, is that the results may include type 2 error. We believe it remains difficult to form conclusions about the real effect of treatments on plasma glucose level on the basis of negative findings from analyses of random glucose values.

Fasting plasma glucose values and plasma glucose values following oral glucose loading, unlike random glucose

Figure 1. Fasting and Postload Plasma Glucose and Insulin Level in Patients Treated With Typical Antipsychotics, Clozapine, Olanzapine, or Risperidone and Control Subjects^a



^aData from Newcomer et al.^{50,68} Plasma glucose and insulin values at fasting and postglucose timepoints during a modified oral glucose tolerance test in patients with schizophrenia (N = 48) treated with either typical antipsychotic medication (N = 17), clozapine (N = 9), olanzapine (N = 12), or risperidone (N = 10) and untreated healthy control subjects (N = 31). Significant time × treatment group interactions for both glucose and insulin were accompanied by effects of treatment group at various timepoints.

*p < .05.

†p < .10.

levels, are used by the ADA and WHO to diagnose diabetes mellitus, as well as the less severe conditions of impaired fasting glucose and impaired glucose tolerance. Fasting and postload glucose values have established sensitivity, reliability, and validity for characterizing disturbances in glucose metabolism. Studies with relatively small sample sizes are common in the diabetes literature when sensitive and reliable measures are used, and the effect under study is of sufficient magnitude to produce adequate power to detect effects with that sample size. Newcomer et al.^{50,68} reported on the results of fasting and postload plasma glucose and insulin level in patients treated with newer antipsychotic agents (clozapine, N = 9; olanzapine, N = 12; risperidone, N = 10) compared with patients treated with typical antipsychotics (primarily haloperidol and fluphenazine, N = 17) and untreated healthy control subjects (N = 31; Figure 1).

Subjects with diabetes were excluded in order to observe medication effects on gluoregulation in schizophrenia patients who did not have clinically identifiable gluoregulatory abnormalities, and groups were matched for adiposity and age. Olanzapine-treated patients had significant (SD, 1.0–1.5) glucose elevations at fasting and all postload timepoints during an OGTT, in comparison to untreated healthy controls as well as patients receiving typical antipsychotics. Clozapine-treated patients had significant (SD, 1.0–1.5) glucose elevations at fasting and 75 minutes postload, again in comparison to untreated controls and patients receiving typical antipsychotics. Risperidone-treated patients had similar elevations in fasting and postload glucose levels, but these differences were significant only in comparison to untreated healthy controls. When comparing risperidone-treated patients and those receiving typical antipsychotic medications and when comparing patients receiving typical antipsychotics and untreated healthy controls, no significant differences in plasma glucose values were detected at any timepoint. Treatment-related increases in plasma insulin and C-peptide suggested treatment effects on insulin resistance, rather than a primary defect in insulin secretion. The results of this study indicate that certain newer antipsychotic treatments are associated with adverse effects on glucose regulation, which can vary in severity independent of adiposity. In clinical practice, where patients are not matched for adiposity and patients treated with clozapine and olanzapine can gain more weight and adiposity, observed differences in plasma glucose levels may be larger.

A number of investigators are using other sensitive techniques to evaluate glucose metabolism in recent and ongoing studies. For example, Henderson et al.⁶⁴ reported on the results of frequently sampled IVGTTs with minimal-model analysis, examining adiposity-matched patients treated with clozapine, olanzapine, and risperidone. Higher postload plasma glucose values were observed in clozapine- and olanzapine-treated subjects, as compared with those taking risperidone. In a minimal-model analysis, insulin sensitivity was significantly reduced in the clozapine- and olanzapine-treated subjects, compared with those treated with risperidone. Glick et al.⁶⁹ recently reported HOMA insulin resistance data indicating significant increases in insulin resistance after 6 weeks of olanzapine, but not ziprasidone, treatment in 268 randomly assigned patients. Avram et al.⁴⁰ have published the only report to date describing the use of a euglycemic clamp study, along with OGTT and IVGTT, on the same patient, to investigate glucose regulation in a patient who developed diabetic ketoacidosis while taking clozapine. These techniques indicated increased insulin resistance in this patient. Ongoing studies from this laboratory and others will produce additional results using IVGTT and clamp techniques.

ANTIPSYCHOTIC TREATMENT AND WEIGHT GAIN

Prior to the introduction of newer, atypical antipsychotic medications, patients with schizophrenia were observed to have a higher mean BMI than persons in the general population.⁷⁰ Clinically significant weight gain was first observed during treatment with chlorpromazine,⁷¹ with low-potency typical agents demonstrating more of an effect on weight than higher-potency agents.^{20,72,73} A causal effect of antipsychotic treatment to induce weight gain has been established in double-blind, randomized, placebo-controlled clinical trials submitted to the FDA. Certain newer medications appear to have larger effects on weight gain than older agents, inducing excessive weight gain in up to 50% of adult patients,⁷⁴ with children and adolescents apparently susceptible to still larger effects.⁷⁵ Individual antipsychotic treatments produce weight gain of varying magnitude,^{70,76,77} with the most prominent effects linked to clozapine^{70,78–80} and olanzapine.⁸¹ Among the newer antipsychotic medications, clozapine and olanzapine have the largest effects on short- and longer-term weight gain. Although weight gain tends to plateau between 6 and 12 months, some individuals may continue to gain weight over longer periods, with progressive weight increases reported during 46 months of clozapine treatment in one recent study.^{34,70,78,79,82–85}

With the exception of indirect adiposity estimates using BMI (kg/m²) and waist-hip circumference ratio, few direct data are available on the effects of antipsychotic treatment on whole-body or regional adiposity. These missing data have physiologic and clinical significance. Increased adiposity, and particularly abdominal adiposity, is a predictor of cardiovascular morbidity and mortality in men and women.^{70,86–88} Increased abdominal adiposity, especially visceral abdominal adiposity, is well known to increase insulin resistance and contribute to hyperglycemia and diabetes.^{9,89} A recently identified hormone, resistin, appears to contribute to this association between abdominal adiposity and skeletal muscle insulin resistance.⁹⁰ Clinical experience suggests that weight gain during antipsychotic treatment primarily involves an increase in total body fat, rather than elements of fat-free mass (e.g., water, muscle).

The working hypothesis for many clinicians and researchers has been that treatment-induced increases in abdominal adiposity are primarily responsible for treatment-related hyperglycemia. The hypothesis is supported by the apparently higher frequency of reported cases of diabetes or other glucoregulatory disturbances during treatment with agents that are also associated with more weight gain. Indeed, a wealth of past research supports the concern that increased adiposity will increase insulin resistance and increase the risk for diabetes mellitus. The hopeful view that antipsychotic-induced weight gain will not tend to increase insulin resistance in patients taking these drugs requires

one to hypothesize a protective factor in this population that would reduce the otherwise predictable effect of adiposity on insulin sensitivity. Higher rates of diabetes and cardiovascular mortality in this patient population argue against that view. In addition, it remains possible that weight gain may not always be required for the development of hyperglycemia and its complications. Differences in plasma glucose level and other indices have been observed in the controlled studies^{50,64,68} noted above, even when subjects are matched for adiposity. Examination of previous case reports reinforces the concept that weight gain is not necessary for the development of hyperglycemia and related complications. Notably, more than 25% (8/28) of the cases we counted^{21–59} involving diabetic ketoacidosis were associated with no weight gain or weight loss. Fewer (15% or 4/27) cases of hyperglycemia and new-onset diabetes (not involving ketosis or acidosis) were associated with the absence of weight gain. In general, development of hyperglycemia occurred over a few months, while the onset of symptoms occurred within 1 to 2 weeks in a few of the cases.

COMPLICATIONS OF HYPERGLYCEMIA

Diabetic ketoacidosis is an acute-to-subacute-onset, potentially fatal, severe metabolic disturbance characterized by hyperglycemia, hyperketonemia, and metabolic acidosis. Symptoms of diabetic ketoacidosis include nausea, vomiting, anorexia, lethargy, and altered mental status. Until recently, it had been widely accepted that diabetic ketoacidosis was rare in type 2 diabetes and was usually associated with severe physiologic stressors. However, high rates of diabetic ketoacidosis in type 2 diabetes mellitus have been reported in various ethnic groups.⁹¹ More recently, it has been recognized that not only is diabetic ketoacidosis common in type 2 diabetes, but this complication may not be restricted to higher-risk groups. In a multiethnic population, Balasubramanyam et al.¹¹ observed that nearly 40% of cases of diabetic ketoacidosis were associated with type 2 diabetes mellitus, and that almost half of the patients with type 2 diabetes mellitus who presented with diabetic ketoacidosis had not been previously diagnosed with type 2 diabetes mellitus. Approximately half of these individuals had no identifiable stressor associated with the onset of diabetic ketoacidosis. Mortality rates from diabetic ketoacidosis range from 2% up to 20% or higher.⁹² Factors that influence the outcome of diabetic ketoacidosis include the patient's age and general health, along with the time elapsed between symptom onset and diagnosis and treatment. Clinicians and investigators can reasonably be concerned that patients taking antipsychotic medications may tend to take longer than the general population to identify signs and symptoms of diabetic ketoacidosis and then to work with care providers to initiate treatment. Finally, while monitoring

can diagnose type 2 diabetes mellitus, diabetic ketoacidosis has a sudden and precipitous onset, making monitoring for this complication difficult or impossible. Clinicians, other caregivers, and patients must be educated to recognize the signs and symptoms of this infrequent but serious complication.

While diabetic ketoacidosis is an uncommon complication of diabetes mellitus, common complications of diabetes include microvascular disease (e.g., retinopathy, nephropathy, neuropathies) and macrovascular disease (e.g., cardiovascular and cerebrovascular disease). While diabetes-related microvascular disease produces considerable morbidity, macrovascular disease is associated with morbidity as well as mortality. Even hyperglycemia involving glucose levels below the diagnostic threshold for diabetes has been clearly associated with increased cardiovascular morbidity and mortality. A series of studies^{8,93-98} indicates a progressive relationship between hyperglycemia and cardiovascular event risk (e.g., MI, stroke), and this progressive relationship begins at glucose levels well below diabetic thresholds. The combination of hyperglycemia, dyslipidemia, and abdominal adiposity, often associated with hypertension, is strongly predictive of increased cardiovascular morbidity and mortality.^{99,100} Gerstein et al.⁹³ reported that the odds ratio for MI in patients diagnosed with diabetes mellitus (i.e., fasting plasma glucose level ≥ 126 mg/dL) was 5.49 (95% confidence interval = 3.34 to 9.01), a more than 5-fold increase in risk compared with controls. Subjects with levels of hyperglycemia consistent with impaired fasting or impaired glucose tolerance had increased odds ratios for MI ranging from 3.22 to 4.08, respectively. Excluding diabetics and those with impaired glucose control, and adjusting for smoking, adiposity, and triglyceride levels, an increase in postprandial plasma glucose level as small as 21 mg/dL was sufficient to increase MI risk 1.6 times. Results like these suggest that patients taking antipsychotic medications, like other members of the general population, may not need to reach clinical criteria for diabetes mellitus to be at increased risk for cardiovascular morbidity and mortality.

Well-described independent multivariate risk factors for MI include smoking, hypertension, obesity, sedentary lifestyle, and hyperlipidemia, as well as hyperglycemia. Many patients taking antipsychotic medications are at increased risk for MI based on high rates of smoking and sedentary lifestyles. Additional risk factors like elevations in weight and plasma glucose and lipid levels can further increase risk. The degree to which these "modifiable" risk factors are readily modified by patients with psychotic disorders remains to be seen. To the extent that risk factors like increased weight, adiposity, and plasma glucose and lipid levels can be modified by treatment with specific agents, these risk factors may turn out to be more "modifiable" than other risk factors in this population.

Schizophrenia patients have been shown to have increased rates of cardiac mortality,¹⁰¹ with most studies completed prior to the introduction of newer antipsychotic agents. A further understanding of medication effects on weight and glucose and lipid levels can offer physicians an important opportunity to address potential iatrogenic sources of increased cardiovascular morbidity and mortality. A recent analysis by Fontaine et al.¹⁰² underscores the dilemma faced by psychiatrists when trying to balance antipsychotic effectiveness with adverse reactions such as weight gain. With data from the public use data set of the Framingham Heart Study, an analysis was performed that was designed to estimate the effect of weight gain on the number of deaths and new cases of impaired glucose tolerance and hypertension over a 10-year period beginning in 1999. Fontaine and colleagues¹⁰² calculate that while clozapine might prevent 492 suicide deaths per 100,000 schizophrenia patients, the weight gain associated with treatment is predicted to cause an additional 416 deaths.

POSSIBLE MECHANISMS OF ANTIPSYCHOTIC-INDUCED HYPERGLYCEMIA

Decreased sensitivity (increased resistance) to insulin action as well as decreased insulin secretion due to decreased β -cell function are involved in type 2 diabetes mellitus.¹⁰³ Controlled studies conducted to date suggest treatment effects on insulin resistance, rather than a primary defect in insulin secretion.^{39,64} Insulin resistance during antipsychotic treatment may arise from increased abdominal adiposity, or possibly is a direct effect of antipsychotic medications on glucose transporter function. Dwyer et al.¹⁰⁴ recently reported effects of antipsychotic medications on glucose transporter function, suggesting a structure-function relationship in which similar drugs (e.g., olanzapine and clozapine) that achieve relatively higher intracellular concentrations may similarly bind to, and interfere with the function of, the glucose transporter proteins. This affinity for glucose transporters can be hypothesized to underlie clinical observations of decreased sensitivity to insulin action in vivo, but additional clinical and basic studies are needed.

Serotonin receptor activity has also been hypothesized to be involved in glucose control, with both 5-HT_{1A} and 5-HT₂ receptors implicated. However, the exact roles of these receptors appear complex.¹⁰⁵ Based on current data, the rank order of in vitro affinities of relevant antipsychotics for serotonin receptors does not fit well with the rank order of their effects on glucose regulation. Earlier studies have suggested that phenothiazines decrease insulin secretion¹⁰⁶ or release catecholamines that in turn inhibit insulin secretion,¹⁰⁷ or that chlorpromazine has some other anti-insulin action,¹⁰⁸ but these results have not been replicated.

OTHER PSYCHOACTIVE MEDICATIONS

Schizophrenia patients are commonly treated with multiple psychoactive medications in addition to antipsychotics. Antidepressants and mood stabilizers have also been associated with alterations in glucose metabolism.^{109–118} Some of these agents, such as tricyclic antidepressants and mood stabilizers, may exert some of their effect on plasma glucose levels as a result of the weight gain they can induce. There may also be unknown direct effects of these agents on glucose metabolism. Valproate, for example, has been associated with insulin resistance and elevated plasma insulin levels.¹¹⁹ The combination of multiple agents that exacerbate hyperglycemia may produce additive, or even synergistic, effects on glucose regulation, but no controlled investigations have addressed these issues. With respect to antidepressants, tricyclic antidepressants may worsen glucose regulation,¹¹⁵ while selective serotonin reuptake inhibitors may have a beneficial effect on glucose regulation.¹²⁰ Monoamine oxidase inhibitors have been associated with lowered plasma glucose levels, with the hydrazine monoamine oxidase inhibitors, such as phenelzine, associated with more robust effects.¹²¹

MONITORING RECOMMENDATIONS

Patients taking antipsychotic medications should undergo regular monitoring of weight and plasma glucose and lipid levels, so that clinicians can individualize treatment decisions and reduce risks for morbidity and mortality. The ADA recommends routine screening for diabetes beginning at age 45 years in whites without other risk factors for diabetes. If results are within normal range, repeat testing is recommended every 3 years thereafter. However, the ADA recommends beginning surveillance at an earlier age, and more frequent monitoring, in individuals with any of the following risk factors for diabetes and cardiovascular disease: obesity, a first-degree relative with diabetes, membership in a high-risk ethnic population, previous diagnosis of gestational diabetes or delivery of a baby larger than 9 pounds (4.1 kg), hypertension (> 140/90 mm Hg), a high-density lipoprotein level \leq 35 mg/dL, triglyceride level \geq 250 mg/dL, or previous diagnosis of impaired fasting glucose (fasting plasma glucose level \geq 110 mg/dL but < 126 mg/dL) or impaired glucose tolerance (OGTT revealing 2-hour postload glucose level of \geq 140 mg/dL but < 200 mg/dL).³

Many neuropsychiatric illnesses, including depression, Alzheimer's dementia, and bipolar affective disorder, as well as schizophrenia, are associated with increased rates of diabetes mellitus or impaired glucose regulation.^{2,6,7} As discussed above, many medications taken by patients with these disorders may also have effects on glucose regulation. Therefore, the presence of these neuropsychiatric disorders and the use of certain medications that may interfere with

glucose regulation should, using the logic of the ADA recommendations, justify more frequent monitoring of plasma glucose levels, beginning at a younger age than 45 years. When one considers that many patients with psychiatric disorders already have additional, ADA-defined risk factors such as obesity, nonwhite ethnic status, and dyslipidemia, it seems reasonable that these individuals should certainly be targeted for increased monitoring.

Diabetes screening and monitoring can be accomplished using a variety of clinically available methods, but these vary in sensitivity, convenience, interpretability, and validity. The clinically available methods include assessment of random plasma glucose level, HbA_{1c} level, fasting plasma glucose level, and the 2-hour postload plasma glucose level from an OGTT. Random glucose values are difficult to interpret, far less reliable than other measures, and validated for diagnosis only at higher values associated with poorly controlled disease (e.g., > 200 mg/dL). HbA_{1c} testing has not achieved wide acceptance or standardization of nationwide laboratory standards and remains insensitive at lower values (i.e., an HbA_{1c} level outside normal limits is very likely to indicate disease, whereas an HbA_{1c} level within normal limits cannot exclude disease).

The ADA recommends that fasting and 2-hour postload plasma glucose values be used to screen for and diagnose diabetes mellitus (\geq 126 mg/dL and \geq 200 mg/dL, respectively).³ Similarly, fasting and 2-hour postload plasma glucose values can also be used to diagnose impaired fasting and impaired glucose tolerance (\geq 110 mg/dL and \geq 140 mg/dL, respectively).³ We recommend checking fasting plasma glucose level annually in all patients treated with any antipsychotic medication. We also recommend checking fasting plasma glucose level prior to and after starting or changing antipsychotic therapy. In higher-risk individuals (e.g., African American, obese, smoker, with family history of diabetes mellitus, and with cardiovascular disease), an OGTT could be obtained initially, followed by serial fasting plasma glucose values obtained at 3- to 6-month intervals. In particularly high-risk individuals, one should consider obtaining a second fasting plasma glucose level within the first weeks of treatment when starting or changing antipsychotic medications.

Glucose monitoring should be performed in addition to weight monitoring due to the additional risk that weight gain poses for hyperglycemia and type 2 diabetes. In addition, clinicians should consider monitoring fasting triglyceride levels or lipid profiles in patients treated with antipsychotic medications. While there are currently fewer data available to guide the development of monitoring recommendations for lipids, it is likely that increased risk factors for diabetes mellitus and for cardiovascular disease would also increase the need for monitoring for dyslipidemia.

Patients with plasma glucose and/or lipid values outside, and perhaps nearly outside, the normal range require a referral to a primary care physician and nontrivial efforts

at diet and exercise interventions. As such, it is important for psychiatrists to establish close working collaborations with primary care physicians such as internists or family practice physicians. This collaboration is necessary to integrate difficult decisions about the management of diabetes mellitus and hyperglycemia along with difficult psychiatric treatment decisions.

TREATMENT RECOMMENDATIONS

While a full review of the management of diabetes mellitus is beyond the scope of this review, clinicians need to be aware of their options in the management of hyperglycemia, impaired glucose tolerance, and diabetes mellitus. In patients who are experiencing elevations of blood glucose level, the question of whether to change medications must also be considered. There is no standard approach to these issues, and management must be individualized based on personal and family medical history and other risk factors.

The diagnosis of diabetes mellitus provides clearer treatment guidelines than the diagnoses of hyperglycemia or impaired glucose tolerance. A well-described approach to the treatment of diabetes mellitus includes FDA-approved hypoglycemic agents (i.e., insulin, sulfonylureas such as glipizide, biguanides such as metformin, thiazolidinediones such as rosiglitazone) and nontrivial diet and exercise interventions. Current management of type 2 diabetes mellitus also includes control of triglyceride levels, blood pressure, and adiposity. However, if noncompliance limits the effectiveness of these intensive management schemes, then one must consider the contribution of medications, including antipsychotics, to the presentation and severity of the problem. Even when optimal management of diabetes mellitus is successful, there will always be a question as to whether the patient could be best served by treatment with an equally efficacious antipsychotic that does not require intensive medication and lifestyle interventions to maintain normoglycemia.

If hyperglycemia rises to the level of impaired glucose tolerance or impaired fasting glucose, then nontrivial diet and exercise interventions should be employed, along with control of triglyceride levels, blood pressure, and adiposity. However, there are currently no FDA-approved indications for insulin or hypoglycemic agents in patients with impaired glucose control. The Diabetes Prevention Program, sponsored by the National Institute of Diabetes and Digestive and Kidney Disorders, has addressed the use of pharmacologic approaches for the treatment of impaired glucose control, with early results indicating the importance of diet and exercise goals that may or may not be easy for psychotic patients to achieve.¹²²

The patient who has hyperglycemia that does not rise to the level of impaired glucose tolerance or impaired fasting glucose also has no current indication for pharmacologic

hypoglycemic agents. However, these patients should be targeted for the same nonpharmacologic interventions used in patients with higher levels of hyperglycemia (e.g., diet and exercise), and lipid levels and blood pressure should be appropriately controlled. This is due in part to the concern that progressive and continuously increasing risk for cardiac events is associated with even these lower levels of hyperglycemia. When a frank diagnosis of diabetes mellitus does not necessitate a referral to a primary care physician, it may be even more important for psychiatrists to monitor and modify risk factors like elevations in plasma glucose.

Clinicians have been facing and will continue to face decisions concerning the contribution of specific medications to weight, glucose, and lipid problems and whether a medication switch is indicated. These decisions cannot be made easily, given the risk of psychiatric symptom exacerbation during medication changes. Some patients require ongoing treatment with their current antipsychotic medication (i.e., treatment-resistant patients taking clozapine or patients who have failed treatment with every other available atypical antipsychotic), even when adverse events emerge with those treatments. However, many more patients will experience adverse events such as weight gain without a clear requirement that they remain on treatment with that specific antipsychotic agent versus other agents associated with less weight gain. Psychiatry remains a branch of medicine in which clinicians are constantly evaluating the efficacy and adverse events associated with specific psychiatric medications in the context of the patient's overall medical health. For example, while the high-potency typical antipsychotics such as haloperidol may be associated with relatively smaller effects on glucose levels and weight compared with some atypical antipsychotics, we would agree with most clinicians that this is not an argument for returning most patients to treatment with older, typical agents. The many advantages of atypical antipsychotics with respect to reduced side effects, superior tolerability, improved cognition, and clinical outcomes argue for the continued use of these agents. However, many patients in clinical practice have not been exposed to an adequate trial of all of the various atypical antipsychotics due, for example, to excellent efficacy with their current atypical agent. When these patients experience significant weight gain or are diagnosed with diabetes mellitus, impaired glucose control, or "merely" lower levels of hyperglycemia, we believe that treatment with other atypical antipsychotics should be considered. Obviously, careful informed consent becomes critical during such decision-making.

CONCLUSION

Increased adiposity is an established risk factor for cardiovascular morbidity and mortality. Antipsychotic

medications cause weight gain, with larger effects for certain medications. Hyperglycemia and diabetes are also associated with increased morbidity and mortality due to both acute and long-term complications. Recent reports indicate an association between antipsychotic medications and both hyperglycemia and diabetes mellitus, with some of the same medications associated with more weight gain also associated with larger increases in plasma glucose level. Further research is needed to understand the *in vivo* physiology of antipsychotic treatment effects on glucose and lipid metabolism and adiposity. This information will be particularly important for the numerous patients who already possess one or more additional risk factors for diabetes or cardiovascular disease (e.g., obesity, smoking, hypertension, hyperglycemia, ethnic status, dyslipidemia). The clinical management of diabetes mellitus and cardiovascular disease in psychotic patients will always be a difficult proposition, increasing the need to identify effective prevention strategies and to understand the role of psychiatric medications in contributing to risk. Patients taking antipsychotic medications should undergo regular monitoring of weight, plasma glucose levels, and plasma lipid levels, so that clinicians can individualize treatment decisions and reduce iatrogenic contributions to morbidity and mortality.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), glipizide (Glucotrol and others), haloperidol (Haldol and others), metformin (Glucophage), olanzapine (Zyprexa), phenelzine (Nardil), quetiapine (Seroquel), risperidone (Risperdal), rosiglitazone (Avandia), ziprasidone (Geodon).

Disclosure of off-label usage: The authors have determined that, to the best of their 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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