

# Metabolic Side Effects of Antipsychotics: Focus on Hyperglycemia and Diabetes

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Approximately 16 million people in the United States have diabetes, and the World Health Organization has estimated that the worldwide prevalence of diabetes will more than double from 1995 to 2025. Type 2 diabetes, the most common form of diabetes, may be 2 to 4 times more prevalent in patients with severe mental disorders. Within the psychiatric community, there is a great deal of concern about diabetes as a potential side effect of antipsychotic agents. An important population to remember in the context of treatment-emergent hyperglycemia is the 20 million people with impaired glucose tolerance (IGT) (fasting plasma glucose > 110 mg/dL and < 126 mg/dL or 2-hour postload glucose > 140 mg/dL and < 200 mg/dL according to the American Diabetes Association). This prediabetic condition has a 5% to 10% annual risk of converting to diabetes. One hypothesis for antipsychotic treatment-emergent diabetes during double-blind, randomized, controlled trials is that people who develop diabetes soon after the initiation of drug therapy for schizophrenia may have had undiagnosed IGT or diabetes before they started treatment. The emergence of diabetes in clinical practice may be due to an observation effect, but because the incidence of diabetes is greater in people with severe mental illnesses, it is crucial for psychiatrists to be aware of national guidelines for the diagnosis and treatment of type 2 diabetes.

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Within the psychiatric community, there is a great deal of concern about diabetes as a potential side effect of antipsychotic agents. It has been clear since the 1920s that psychiatric illnesses are associated with insulin resistance and glucose dysregulation. The prevalence of type 2 diabetes is greater among patients with schizophrenia or bipolar disorder than in the general population. Further, questions regarding the adverse glycaemic effects of psychotropic agents have existed since well before the introduction of the atypical antipsychotic agents.

Most data on the hyperglycemic effects of antipsychotic agents are from case studies of new-onset diabetes, diabetic ketoacidosis, hyperosmolar coma, or the exacerbation of existing diabetes that have been reported in the literature, to the drug manufacturers, or to the U.S. Food and Drug Administration (FDA). The existing data, which also include a series of epidemiologic studies, can be used to examine the issue of diabetes and antipsychotic agents from the perspective of the endocrinologist, rather than the psychiatrist. In such a context, the magnitude of the problem and how best to manage it do not seem as insurmountable. However, because the incidence of diabetes is greater in people with severe mental illnesses, it is crucial for

psychiatrists to have an awareness of national guidelines for the diagnosis and treatment of type 2 diabetes.

## EPIDEMIOLOGY OF DIABETES

Approximately 16 million people in the United States have diabetes,<sup>2</sup> which equates to about 1 in 17 people. The number of people with diabetes has increased 30% in the last 8 years<sup>2,3</sup> and 6% annually for the last 2 years.<sup>4</sup> The lifetime risk for abnormalities of glucose intolerance is approximately 25%.<sup>5</sup> Overall, about a third of the people with diabetes in the United States are undiagnosed because it is initially an asymptomatic disease.<sup>1</sup> Approximately 800,000 cases of diabetes are diagnosed annually, and diabetes is the leading cause of adult blindness, renal failure requiring dialysis or transplantation, and non-trauma-related amputations. Diabetes is ranked as the sixth leading cause of death by disease. People with diabetes account for 15% of all health care expenditures in the United States, equaling about \$105 billion a year.<sup>2,6</sup> The World Health Organization (WHO) has estimated that the worldwide prevalence of diabetes will more than double from 1995 to 2025.<sup>7</sup>

The prevalence of type 2 diabetes, the most common form of diabetes, may be 2 to 4 times greater in patients with schizophrenia than in reference populations.<sup>8,9</sup> One study<sup>8</sup> examined the prevalence of known diabetes in 95 schizophrenic patients aged 45 to 75 years admitted to a long-term care facility in Italy. The overall prevalence of diabetes was 15.8% (95% confidence interval [CI], 12.1% to 19.5%) and ranged from 0% in those < 50 years old to 12.9% in those 50 to 59 years old, 18.9% in those aged 60 to 69 years, and 16.7% in those aged 70 to 74 years. In that study, diabetes was more common in patients not receiving neuroleptics than in those who were. Additionally, the

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incidence of type 2 diabetes may be 2 to 3 times greater in patients with bipolar disorder than in the general population.<sup>10</sup>

### HYPERGLYCEMIC EFFECTS OF ANTIPSYCHOTIC AGENTS

Since the 1920s, the association of insulin resistance and glucose dysregulation with psychiatric illness has been known.<sup>11</sup> Questions regarding adverse glycemic effects of psychotropic agents have been asked since the 1950s,<sup>12</sup> well before the introduction of atypical antipsychotic agents. Most of the data on the hyperglycemic effects of antipsychotic agents are from case studies<sup>13</sup> of new-onset diabetes. A few cases of diabetic ketoacidosis, hyperosmolar coma, dramatic presentation of new diabetes, or exacerbation of prior diabetes have been reported in the medical literature, to the manufacturers of the various neuroleptic agents, or to the FDA. Studies<sup>12,13</sup> have looked at the development of either hyperglycemia or diabetes in different populations treated with various antipsychotic agents. Though some of these comparisons have suggested statistically significant differences between agents in risk of diabetes, the studies are inconsistent. When the differences exist, they are generally small. This is particularly true of comparisons between olanzapine and risperidone, the most frequently prescribed of the atypical antipsychotic agents.

Allison et al.<sup>14</sup> examined random glucose values associated with the treatment of schizophrenia in controlled clinical trials. In the trials, olanzapine was compared with haloperidol, clozapine, risperidone, and placebo. Consistently through the data sets, about a 4-mg/dL increase in random glucose levels was associated with olanzapine therapy. Compared with glucose levels in patients taking haloperidol and placebo, this increase was statistically significant, although modest (olanzapine, 4.56 vs. haloperidol, 2.45;  $p = .0001$ ; duration [ $t$ ] = 52 weeks; olanzapine, 0.77 vs. placebo, -1.28;  $p = .0004$ ,  $t = 6$  weeks). Compared with glucose levels of risperidone-treated patients, the increase was not statistically significant (olanzapine, 3.98 vs. risperidone, 2.45;  $p = .07$ ;  $t = 26$  weeks). When olanzapine was compared with clozapine, however, clozapine was associated with about a 3 to 4 times greater increase in random glucose levels, resulting in an increase of about 13 mg/dL (olanzapine, 3.17 vs. clozapine, 13.22;  $p = .001$ ;  $t = 18$  weeks).

The first question raised by the Allison data<sup>14</sup> is whether a physiologic explanation exists for increases in glucose levels over time. Because these glucose values were measured randomly, part of the explanation could be meal frequency. Glucose levels would increase if patients were eating meals more frequently. Increases in glucose values could also be related to changes in activity or appetite. There also exists the theoretical possibility that the differences between agents could be related to receptor effects. Dopaminergic and adrenergic receptors are involved in the regulation of insulin secretion and, perhaps to a lesser extent, in the regulation of insulin action.

Another question these data<sup>14</sup> elicit is whether a 3- to 4-mg/dL increase in glucose values translates into adverse

effects. This change in glucose levels might be associated with a 1% increase in absolute risk for developing diabetes in high-risk populations. For example, people with impaired glucose tolerance (IGT) are among the highest risk populations; they have about a 10% chance per year of developing diabetes.<sup>15</sup> A 3- to 4-mg/dL increase in glucose level may be associated with a 2% increase in risk for those with IGT. In a low-risk population, the increased risk of developing diabetes associated with the same increase in glucose levels would be even smaller. For people who already have diabetes but are at high-risk for diabetes-related complications, a 3- to 4-mg/dL increase in glucose would raise the risk for developing eye, kidney, or heart disease by 1%. In people at low-risk for diabetes-related complications, the risk may be 0.1%.

In another study,<sup>16</sup> the annualized incidence of the development of diabetes in groups of patients who were treated with a single typical or atypical antipsychotic agent was examined. After patients began therapy with an antipsychotic agent, their need for an antidiabetic agent was assessed over time by using the Advance PCS (Pharmaceutical Card System) database. Each year, 5% to 8% of patients required therapy with an antidiabetic agent across the spectrum of typical and atypical antipsychotics. The incidence per 1000 patient years of exposure was 84 for patients taking typical antipsychotics (haloperidol, 85), 67 for patients taking atypical antipsychotics (risperidone, 79; olanzapine, 57), and 17 for the unexposed general patient population. Generally, no statistically significant differences were found between the various antipsychotic agents. However, all patients taking the antipsychotics had increased risk of developing diabetes compared with the general patient population in the database.

An important population to remember in the context of treatment-emergent hyperglycemia with antipsychotic agents is the 20 million people with IGT.<sup>17</sup> This prediabetic condition has a 5% to 10% annual risk of converting to diabetes.<sup>15</sup> A review of treatment-emergent diabetes during double-blind, randomized, controlled trials is in process using the criterion of random glucose measurements greater than 200 mg/dL (M. Sowell, M.D., Ph.D.; J.B.B., unpublished data, 2002). The analysis is incomplete; however, based on the observation that many of these patients had baseline random glucose levels of 150 mg/dL, which is above normal, the hypothesis is that people who develop diabetes soon after the initiation of drug therapy for schizophrenia may have had undiagnosed diabetes before they started treatment. Thus, the emergence of diabetes in clinical practice may be due to an observation effect. Patients may have undetected diabetes, or they may be at risk for developing diabetes—for example, patients with IGT—and are diagnosed as having diabetes because they are being seen frequently in the context of a clinical trial or practice. A general review of the literature produces no evidence to suggest that antipsychotic agents cause intrinsic changes in insulin secretion or in insulin action. Certainly, modest changes in diet and activity may result as a behavioral change from better control of a psychiatric illness and could contribute to the development of diabetes. For example, when a patient's schizophrenia or bipolar illness becomes controlled, that person

**Table 1. Criteria for Conducting a Screening Test for Diabetes in Asymptomatic, Undiagnosed Individuals<sup>a</sup>**

Age
45 years and older; repeat at 3-year intervals if normal
Weight
Obesity
Personal history
Family history of diabetes in a first-degree relative
Member of a high-risk ethnic group
Delivered a baby weighing > 9 lb (4.05 kg) at birth
Medical history
Prior diagnosis of gestational diabetes
Hypertension
Dyslipidemia
Prior IGT or IFG

<sup>a</sup>From the American Diabetes Association.<sup>18</sup> Abbreviations: IFG = impaired fasting glucose; IGT = impaired glucose tolerance.

may be able to end a homeless lifestyle, get a job, and earn enough money to eat more. However, the most common reason clinicians see new-onset diabetes in patients being treated with antipsychotics is that many patients with preexisting, undetected diabetes or with a high risk for developing diabetes are now being closely observed during treatment for their mental disorder. Psychiatrists should therefore be aware of national guidelines for the diagnosis and treatment of diabetes.

### DIAGNOSING DIABETES

There are 2 types of tests for diabetes: screening tests and diagnostic tests. Screening tests are useful for those patients at risk for developing diabetes. The American Diabetes Association (ADA) recommends a screening glucose level test every 3 years for anyone 45 years or older (Table 1).<sup>18</sup> For those with concurrent or other diabetes risk factors, the ADA recommends screening patients younger than 45 years and testing more frequently than every 3 years. The risk factors are defined by the ADA as being obese ( $\geq 120\%$  over ideal body weight, or body mass index  $> 27 \text{ kg/m}^2$ ), having a family history of diabetes in a first-degree relative (such as a parent, sibling, or child), being in a high-risk ethnic group (e.g., African American, Hispanic American, Native American, Asian American), having delivered a baby weighing greater than 9 lb (4.05 kg), having a history of gestational diabetes, having hypertension ( $\geq 140/90 \text{ mmHg}$ ), having dyslipidemia (high-density lipoprotein cholesterol level  $\leq 35 \text{ mg/dL}$ , or triglyceride level  $\geq 250 \text{ mg/dL}$ ), and having previously demonstrated IGT or impaired fasting glucose (IFG) ( $\geq 110 \text{ mg/dL}$  and  $< 126 \text{ mg/dL}$ ). Less than  $110 \text{ mg/dL}$  is considered a normal fasting glucose level according to the ADA.

The 3 types of diagnostic tests for diabetes are the casual plasma glucose test, the fasting plasma glucose (FPG) test, and the oral glucose tolerance test (OGTT).<sup>18</sup> To warrant the diagnosis of diabetes, the results of 1 of these tests must be confirmed on a subsequent day by any 1 of the 3 methods shown in Table 2.<sup>18</sup> For example, one instance of symptoms in conjunction with a casual plasma glucose level of greater than or equal to  $200 \text{ mg/dL}$  that is confirmed on a subsequent day by FPG greater

**Table 2. Criteria for the Diagnosis of Diabetes Mellitus<sup>a</sup>**

1. Symptoms of diabetes<sup>b</sup> and casual<sup>c</sup> plasma glucose concentration  $\geq 200 \text{ mg/dL}$
2. Fasting<sup>d</sup> plasma glucose concentration  $\geq 126 \text{ mg/dL}$
3. 2-h PG value  $> 200 \text{ mg/dL}$  during an OGTT<sup>e</sup>

<sup>a</sup>From the American Diabetes Association.<sup>18</sup> Abbreviations: OGTT = oral glucose tolerance test; PG = postload glucose.

<sup>b</sup>The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

<sup>c</sup>Casual is defined as any time of day without regard to time since last meal.

<sup>d</sup>Fasting is defined as no caloric intake for at least 8 hours.

<sup>e</sup>OGTT should be performed as described by the World Health Organization.<sup>19</sup>

than or equal to  $200 \text{ mg/dL}$ , OGTT with a 2-hour postload glucose (PG) value greater than or equal to  $200 \text{ mg/dL}$ , or symptoms in conjunction with a casual plasma glucose greater than or equal to  $200 \text{ mg/dL}$  warrants the diagnosis of diabetes. Also, when using the OGTT, the ADA stipulates that the test be performed as described by WHO,<sup>19</sup> using a glucose load containing the equivalent of  $75 \text{ g}$  anhydrous glucose dissolved in water.

### TREATING DIABETES

A discussion about the advances in diabetes drug therapy that have occurred over the past 6 years is best prefaced by a basic knowledge of the physiology of normal glucose metabolism.

#### Pathophysiology of Diabetes

As a person eats a meal, glucose is produced by the metabolism of starches in the intestinal tract. The glucose is then absorbed from the intestinal tract into the pancreas as well as the rest of the body. In normal glucose metabolism, the pancreas makes insulin in response to the presence of glucose. As the body's glucose level rises, insulin secretion dramatically increases. Every molecule of insulin is sent to the liver, where it suppresses the production of glucose. In the fasting state, the liver produces the brain's glucose supply. The insulin circulates through the liver and then the rest of the body. As the insulin circulates through muscle and fat tissue, it signals the muscle and fat cells to increase glucose transport. After the meal is digested, insulin and glucose levels return to normal. The liver returns to normal glucose production, and muscle and fat cells decrease glucose transport.

In type 1 diabetes, the cells in the body that make insulin are destroyed. In type 2 diabetes, there are multiple defects that can cause the disorder. One is resistance in the liver to the presence of insulin. Another defect is resistance in muscle and fat cells to the presence of insulin. Insulin resistance in the liver and in muscle and fat cells synergistically interacts with a relative and progressive decrease in insulin secretion. At the onset of diabetes, insulin secretion is sufficient for treatment with oral agents. After a decade or more of diabetes, however, insulin secretion becomes poor even in type 2 diabetes. Additionally, the tendency to overeat in patients with type 2 diabetes causes an increase in glucose absorption.

**Table 3. Advantages and Disadvantages of Antihyperglycemic Agents<sup>a</sup>**

Class	Advantages	Disadvantages
Insulin	Efficacy Titratability	Delivery system Weight gain Hypoglycemia
Sulfonylureas	Inexpensive Titratability Once-daily dosing Tolerability	Hypoglycemia Modest weight gain
Meglitinides <sup>b</sup>	Flexibility Fast onset Short duration	Before meal dosing Expensive Modest weight gain Modest hypoglycemia GI complaints
Metformin	No weight gain ? CVD reduction	GI complaints
$\alpha$ -Glucosidase inhibitors	No hypoglycemia No weight gain Well tolerated	Expensive Expensive
TZDs <sup>c</sup>	? CVD reduction Once-daily dosing	Slow onset Weight gain

<sup>a</sup>Abbreviations: CVD = cardiovascular disease; GI = gastrointestinal; TZD = thiazolidinedione. Symbol: ? = probable.

<sup>b</sup>Meglitinides are repaglinide and nateglinide.

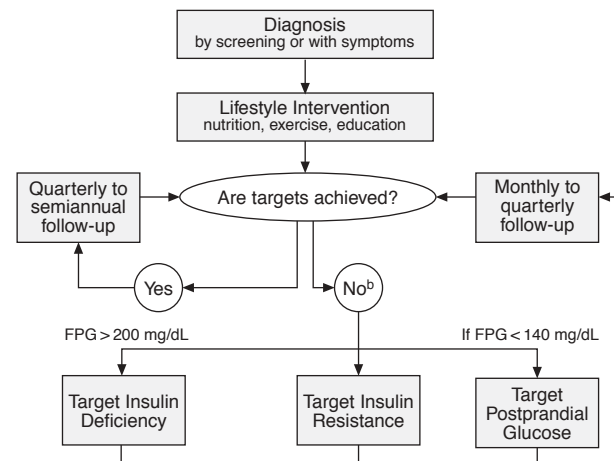
<sup>c</sup>TZDs are pioglitazone and rosiglitazone.

**Drug Therapy for Type 2 Diabetes**

Insulin has been used to treat diabetes since the 1920s, and sulfonylureas have been used since the 1940s. Advances in these older drug classes have given rise to the emergence of 6 new classes of drugs over the last 6 years, and many drugs are now available for the management of diabetes. Insulin therapy works in the pancreas as a substitute for naturally occurring insulin production, and sulfonylureas work in the pancreas as a stimulant for insulin secretion. New insulin analogs have been developed that allow for the more physiologic replacement of insulin, and advances in sulfonylureas have led to the development of newer agents that are better tolerated. Metformin and the thiazolidinediones (TZDs) work in the liver, and they are also active in muscle and fat cells. Metformin is the most liver-active drug, and the TZDs are the most active in muscle and fat.  $\alpha$ -Glucosidase inhibitors slow the absorption of carbohydrates, and meglitinide drugs are rapid-acting stimulants of insulin secretion.

As with any drug, each of the agents used to treat diabetes has advantages and disadvantages (Table 3). The sulfonylureas are inexpensive, and some of the newer agents, such as glimepiride and the glipizide Gastrointestinal Therapeutic System (GITS), can be given once a day and are better tolerated. These newer formulations have a low risk of hypoglycemia and are associated with minimal weight gain. Metformin is a drug that is new to the United States, but it has been available in Europe for 30 years. Metformin is not associated with weight gain, but it can cause gastrointestinal (GI) problems. Clinicians may slowly titrate the dose in an attempt to avoid GI problems, but this results in more complicated instructions for the patient. TZDs are theoretically the best tolerated. They are taken once a day, and side effects are rare, although some patients on monotherapy may develop edema. The TZDs, however, are expensive, require 2 to 6 weeks for onset of action, and are associated with the greatest weight gain.

**Figure 1. Treatment Algorithm for Diabetes Mellitus<sup>a</sup>**



<sup>a</sup>Abbreviation: FPG = fasting plasma glucose.

<sup>b</sup>Keep adding agents until target reached.

**Management of Type 2 Diabetes**

The accepted treatment algorithm (Figure 1) for diabetes begins with early diagnosis through screening and by making patients aware of the symptoms. In many cases, patients have flagrant diabetes that could have been prevented if they had known that polyuria, blurred vision, and fatigue were symptoms of diabetes. Lifestyle intervention is the next step in the algorithm. A healthy diet and exercise can reduce hyperglycemia significantly and should be a part of every patient's therapy. Clinicians and patients need to decide together on targets for glucose management. The ADA recommends that the goal of therapy should be glycated hemoglobin (HbA<sub>1c</sub>) values of 7% or less and that physicians should reevaluate the treatment regimen in patients with HbA<sub>1c</sub> values consistently greater than 8%.<sup>20</sup> However, these specific HbA<sub>1c</sub> values apply only to assay methods that are certified as traceable to the Diabetes Control and Complications Trial (DCCT) reference method. Although the measurement of HbA<sub>1c</sub> is unacceptable for the diagnosis of diabetes, it has become the preferred standard for management of the disease, because a patient's HbA<sub>1c</sub> value most accurately reflects the previous 2 to 3 months of glycemic control. Patients who are meeting their targets should be seen quarterly to semiannually. Patients who are not meeting their targets should be seen monthly to quarterly, and a variety of treatment options exist for these patients. Careful follow-up helps clinicians get diabetes under control rapidly. Currently, most patients diagnosed with diabetes in the United States have the disease reasonably controlled, which would indicate that diabetes can be well controlled in most patients, but this was not the case 5 to 10 years ago. Managing type 2 diabetes is a process in which the physician begins by prescribing one medication and then adding one new medication at a time to the patient's treatment until the disease is controlled.

Treatment of diabetes also involves reducing cardiovascular risk. Patients with diabetes should take 81 to 325 mg/day of enteric-coated aspirin and a tissue angiotensin-converting

Table 4. Screening Tests for Microvascular Complications in Diabetes

Organ	Screening Test
Eye	Annual dilated fundoscopic examination
Kidney	Annual urine sample for microalbuminuria
Nerve	Annual history and physical, including complete foot examination with evaluation of response to a 10-g filament and/or vibration testing

enzyme (ACE) inhibitor. Tissue ACE inhibitors have been demonstrated to reduce cardiovascular risk as well as microvascular complications. Blood pressure and lipid control also reduces cardiovascular risk,<sup>21</sup> and patients should be educated about the benefits of smoking cessation.

The most effective way to reduce the microvascular complications of diabetes, and possibly prevent morbidity, is through early diagnosis. Early diagnosis is achieved by conducting regular screening tests during the asymptomatic stage (Table 4). Early retinopathy can be detected with annual dilated fundoscopic examinations. Kidney disease can be diagnosed with an annual urine test for microalbuminuria. Nerve disease should be screened with an annual history and physical examination concentrating specifically on the foot. A major neuropathic complication is severe peripheral neuropathy, which greatly increases the risk for amputation.

### CONCLUSION

Diabetes and hyperglycemia are common worldwide, particularly so in the United States where the incidence is increasing at the rate of 6% per year.<sup>4</sup> Diabetes and hyperglycemia are more common in psychiatric patients,<sup>8,10</sup> and treatment-emergent diabetes may be found during routine examinations that occur as part of the management of psychiatric disorders. In most case series reports, the incidence of treatment-emergent diabetes with 1 year of antipsychotic therapy is about 1%.<sup>14</sup> Screening for diabetes risk factors in the routine history and physicals of patients with schizophrenia is reasonable, as is taking into consideration ethnicity and history of elevated glucose, hypertension, and obesity. For patients with 1 or more of these risk factors, screening of plasma glucose and/or referral to a primary care doctor or an endocrinologist to assess this risk are recommended. A healthy diet and exercise do prevent the development of diabetes,<sup>22</sup> so clinicians should routinely counsel patients about diet and exercise as well as smoking cessation.

In comparison with psychiatric disorders, diabetes is a much easier disease to treat. There are several highly effective drugs available that prevent or control diabetes. Furthermore, sufficient data do not exist to suggest major differences between commonly prescribed atypical antipsychotic agents with regard to treatment-emergent diabetes, and the mechanism of increased risk is unknown. Therefore, the benefits of controlling psychotic disorders dramatically outweigh the potential risks associated with elevation of glucose.

*Drug names:* aspirin (Easprin, Ecotrin, and others), clozapine (Clozaril and others), glimepiride (Amaryl), glipizide (Glucotrol and others), haloperidol (Hal-

dol and others), insulin (Lantus, Humalog, and others), metformin (Glucophage and others), nateglinide (Starlix), olanzapine (Zyprexa), pioglitazone (Actos), repaglinide (Prandin), risperidone (Risperdal), rosiglitazone (Avandia).

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

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