

The link between



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SCHIZOPHRENIA and DIABETES

Vigilant metabolic monitoring informs treatment decisions

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Although diabetes and schizophrenia are common companions, it is unclear how this association should influence our practice. What do we need to know about diabetes, and what are the key intervention points for psychiatrists?

This article is informed by my experience monitoring >1,000 patients with schizophrenia in a large urban mental health facility using an electronic metabolic monitoring system and consulting on hundreds of individuals with comorbid schizophrenia and diabetes in a mental health metabolic clinic.

A significant link

The association between schizophrenia and diabetes has been recognized for more than a century.¹ The prevalence of diabetes is increased 2- to 3-fold in patients with schizophrenia.^{2,3} This relationship is specific to type 2 diabetes mellitus (T2DM); type 1 diabetes mellitus, an autoimmune disease, is less common in patients with schizophrenia.⁴ Factors that contribute to comorbidity between schizophrenia and T2DM include:

- illness susceptibility: the mechanisms remain unclear but include the thrifty phenotype hypothesis,⁵ autonomic hyperactivity,⁶ and potential cellular and genetic links^{7,8}
- lifestyle: diet, physical inactivity, and cigarette smoking⁹⁻¹²
- antipsychotic use¹³
- social health determinants, such as income, housing, and food insecurity.¹⁴

The relative contribution of factors underlying this association is unknown; it is likely that they all contribute. Nevertheless, based on



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Table 1

American Diabetes Association diagnostic criteria for diabetes

Test ^a	Threshold	Qualifier
A1C, or	≥6.5%	Lab NGSP certified, standardized DCCT assay
Fasting glucose, or	≥126 mg/dL	No caloric intake for at least 8 hours
2-hour glucose, or	≥200 mg/dL	After 75 g of anhydrous glucose
Random glucose	≥200 mg/dL	Plus classic hyperglycemic symptoms or crisis

^aResults should be confirmed by repeat testing
 DCCT: Diabetes Control and Complications Trial; NGSP: National Glycohemoglobin Standardization Program
 Source: References 21-23

information from our facility’s metabolic monitoring database, depending on demographic variables, such as ethnicity and cigarette smoking, 20% to 30% of patients with schizophrenia will develop diabetes or prediabetes during the course of psychiatric treatment.

When evaluating a patient’s risk for a cardiac event, we consider having a diabetes diagnosis equivalent to having had a myocardial infarction.¹⁵ Likely, the high prevalence of T2DM among schizophrenia patients and challenges in managing diabetes and prediabetes underlies these patients’ reduced life expectancy.¹⁶ Self-care, a cornerstone of diabetes management, is challenging for patients with schizophrenia because of deficits in executive functioning, working memory, and motivation, coupled with negative symptoms and social and economic disadvantages that often accompany schizophrenia.

How diabetes impacts practice

What psychiatrists need to know. Insulin resistance—reduced biologic effectiveness of insulin—is the precursor of T2DM. Insulin is required to move glucose from the blood into cells. Weight gain, particularly abdominal adiposity, is the principal driver of insulin resistance. The body responds by producing more insulin (hyperinsulinemia) to maintain glucose homeostasis. Hyperinsulinemia underlies metabolic syndrome, an important risk marker for developing T2DM. Diabetes usually develops after many years when the pancreas fails to compensate for insulin resistance.

In most cases the development of diabetes in patients with schizophrenia follows this course. Weight gain, a consequence of lifestyle factors as well as antipsychotics and other psychotropics that promote obesity, leads to progressive insulin resistance. Consequently, metabolic syndrome is twice as prevalent among patients with schizophrenia compared with matched controls.^{17,18}

Occasionally patients develop T2DM within a few weeks or months of starting antipsychotic treatment—usually with clozapine or olanzapine—before they gain weight, which suggests a second mechanism may be involved. Animal studies have documented rapid development of insulin resistance after a single subcutaneous injection of antipsychotics that have high metabolic liability, possibly through a direct effect on insulin signaling.¹⁹ This phenomenon has been difficult to demonstrate in humans.²⁰

Psychiatrists need to know how to diagnose diabetes (*Table 1*)²¹⁻²³ and the signs and symptoms of diabetes and diabetic ketoacidosis (*Table 2*).^{24,25} Hemoglobin A1C diagnostic testing often is the preferred test because it does not require fasting.

Managing diabetes is complex and ideally involves a range of health practitioners who work with patients to provide education, promote self-care behaviors, and direct complex health care. These services are outside the scope of psychiatric practice, but given the functional deficits in seriously mentally ill patients, it is important to have an overview of diabetes care (*Table 3, page 32*).

In addition to diagnosing diabetes, psychiatrists should be able to identify patients at risk for developing diabetes and initiate prevention strategies. Interventions are focused on lifestyle—weight reduction, increased physical activity, diet, and smoking cessation—as well as pharmacologic strategies such as metformin.

Diagnostic criteria and strategies to manage prediabetes and metabolic syndrome are outlined in *Table 4* (page 33).^{21,26,27} Prediabetes and metabolic syndrome predict development of T2DM. Additional risk factors include ethnicity (Hispanic, black, Native American, and South Asian), family history, gestational diabetes, and cigarette smoking.²⁸

What patients need to know. Similar to schizophrenia, a diabetes diagnosis may be difficult for patients to accept. Initially, a patient may have no manifestations or symptoms. However, untreated diabetes has serious long-term health consequences—including blindness, amputations, kidney disease, and early death from heart attacks.

Patients should actively participate in treatment that involves learning about the illness, making lifestyle changes, working on self-care, and keeping regular medical appointments. Three components of lifestyle change must be addressed:

- Diet: counseling with a dietician or other health professional to reduce or stabilize body weight and make changes in diet quality, portion size, and meal frequency to improve glucose control and reduce long-term diabetes complications
- Physical activity: increasing physical activity, initially by walking daily, to benefit glucose control and weight maintenance
- Smoking: reducing or stopping cigarette smoking to improve glucose control and reduce diabetes complications.

Metabolic monitoring

Metabolic monitoring is the key to keeping patients with schizophrenia well. Treating metabolic conditions falls outside of psychiatric practice; however, many argue that mental health clinicians should monitor

Table 2

Signs and symptoms of diabetes and diabetic ketoacidosis

Diabetes
Frequent urination
Excessive thirst
Extreme hunger
Unusual weight loss
Increased fatigue
Irritability
Blurry vision
Diabetic ketoacidosis^a
Thirst or very dry mouth
Constantly feeling tired
Dry or flushed skin
Nausea, vomiting, or abdominal pain
Difficulty breathing (short, deep breaths)
Fruity odor on breath
Difficulty paying attention or confusion
^a Vomiting is a sign of escalation
Source: References 24,25

basic metabolic parameters during antipsychotic treatment and advocate medical interventions when indicated because:

- most antipsychotics are associated with weight gain and metabolic side effects
- patients with schizophrenia have cognitive deficits that impact health maintenance
- mental health providers often are the primary health care contacts for patients with serious mental illness.

The goals of metabolic monitoring are to²⁹:

- identify treatable medical conditions such as diabetes, dyslipidemia, and hypertension when treatment delay or no treatment has consequences
- identify individuals with prediabetes and metabolic syndrome for targeted prevention
- determine the association between antipsychotic treatment and metabolic disturbance to evaluate the risk of treatment vs antipsychotic switching.

Although most psychiatrists support published monitoring guidelines such as those of the American Diabetes Association and

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In addition to diagnosing diabetes, psychiatrists should be able to identify patients at risk for diabetes and initiate prevention strategies



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Antipsychotics that many consider most effective—clozapine and olanzapine—also have the greatest metabolic liability and risk for T2DM

Table 3

Components of diabetes care

Self-care tasks	Tests/annual assessments
Self-monitoring of glucose	A1C (2 to 4 times/year)
Medication management	Urinary microalbumin
Meal planning	Fasting lipids
Exercise	Blood pressure
Smoking cessation	Dilated eye exam
Foot self-examination and foot care	Foot exam
Stress management	General health and cardiovascular exam

American Psychiatric Association,³⁰ audits show that monitoring is limited or absent unless an institution has a coordinated structure for collecting data as well as oversight to ensure adherence.³¹ My team has developed a computer-coordinated monitoring system that is integrated within an electronic health record.³² Patients are monitored at least annually throughout antipsychotic treatment with basic measurements—weight, waist circumference, and blood pressure—A1C, fasting glucose, and fasting lipid profile. Early psychosis patients and those switched to antipsychotics with high metabolic liability require more frequent monitoring.

How to intervene

To switch or not to switch? For many psychiatrists, deciding whether or when to switch from a high or intermediate metabolic liability antipsychotic to one with low metabolic liability is difficult. Clinicians must balance potential metabolic benefits against the risk of psychotic decompensation and side effects. Ultimately, patients and their families make the decision, taking into account information provided to them. For medical-legal purposes, document the discussion of potential risks and benefits. These are difficult decisions and there are no clear guidelines. In my clinical experience, the following issues need to be considered:

- The antipsychotics that many clinicians consider to be the most effective—clozapine and olanzapine—also have the greatest metabolic liability and risk for emergent T2DM.

- Patients who are stable and in psychotic remission may risk a relapse of their illness if switched.

- The clearest indication for switching is when a patient who does not have diabetes develops the condition shortly after starting an antipsychotic. This scenario is rare, but evidence suggests that diabetes may resolve or reverse with an antipsychotic switch.³³

- In patients who gain weight while taking a high- or intermediate-liability antipsychotic and are able to tolerate a switch to a low-liability antipsychotic, the effect size of weight reduction can be large and may result in a patient returning to their pretreatment weight.

- To reduce relapse risk, patients switching antipsychotics should be closely monitored at least weekly for ≥ 1 month. A plateau cross-taper—building the new antipsychotic up to therapeutic levels before gradually reducing the first antipsychotic—may be safer than abrupt discontinuation or standard cross-titration.

- Switching from one high or intermediate liability antipsychotic to another (eg, olanzapine to quetiapine or risperidone) often provides little if any metabolic benefit on body weight or diabetes control.

- Established diabetes (type 1 or type 2) should not be a contraindication to antipsychotic treatment, including clozapine, if clinically warranted. Monitor metabolic parameters more closely for 6 to 12 months after the switch. In most cases, patients experience limited, if any, metabolic consequences. If so, diabetes medication can be adjusted.

Table 4

Managing patients at risk for diabetes

Prediabetes ²¹	Management
Impaired fasting glucose (100 to 125 mg/dL)	Weight reduction (7%) Activity (150 minutes/week) At least yearly glucose monitoring
Impaired glucose tolerance (2-hour plasma glucose: 140 to 199 mg/dL)	
Prediabetic A1C (5.7% to 6.4%)	
Metabolic syndrome (any 3) ²⁶	Management
Waist circumference ^a (men >40 inches; women >35 inches)	Weight reduction Reduce consumption of refined carbohydrates Exercise Focused interventions for individual criteria
Fasting triglycerides (≥150 mg/dL)	
Fasting high-density lipoprotein cholesterol (men <40 mg/dL; women <50 mg/dL)	
Fasting glucose (≥100 mg/dL or taking medication)	
Blood pressure (≥130/85 mm Hg or taking medication)	

^aWaist circumference guidelines are ethnicity specific. The International Diabetes Federation²⁷ has published specific cutoffs for those of Asian background (men: ≥90 cm [35 inches] and women: ≥80 cm [31 inches])

- Patients who have experienced significant weight gain on an atypical antipsychotic often do not gain more weight when switched to clozapine. A patient may reach a “ceiling” in terms of weight gain and medication-related metabolic effects.

Data from metabolic monitoring informs the decision to switch and metabolic consequences of switching. Conducting monitoring at baseline, when starting an antipsychotic, when switching to a high-liability agent, 3 months after the switch, and then annually provides data needed to consider switching or initiating medical and behavioral or lifestyle interventions.

Facilitate early diabetes treatment.

Clinicians who are most closely involved in caring for patients with schizophrenia often are best situated to screen for diabetes. I have found that without a close working relationship with my patients’ primary care practitioners, patients may experience a long delay in receiving care. After your patient is diagnosed with diabetes, establish a relationship with diabetes treatment providers and work with your patient to ensure they engage in diabetes care.

Contribute to diabetes chronic disease management.

Mental health practitioners can complement diabetes care in patients with serious mental illness by:

- navigating the health system and ne-

gotiating for service on patients’ behalf

- promoting positive relationships among diabetes and mental health treatment teams
- evaluating and treating depression that may be comorbid with diabetes
- assessing treatment capacity, self-care deficits, cognitive functioning, psychotic symptoms, negative symptoms, etc., that impact diabetes self-care and collaborating with diabetes care providers to support patients.

Start with a low-liability agent

Patients who are early in the course of psychotic illness are most susceptible to the metabolic effects of antipsychotics.¹³ The average weight gain observed with olanzapine was 34 lbs at 2 years in first episode psychosis patients (mean age 24 ± 4.9).³⁴ Metabolic consequences with medium-liability second-generation antipsychotics—such as quetiapine and risperidone—are extreme, particularly in children, adolescents, and young adults (age <30).^{35,36} Although frank diabetes is uncommon in early psychosis because patients are, to a certain extent, protected by insulin compensation—increased insulin secretion maintains glucose levels within a therapeutic range—diabetes risk is increased, and hyperinsulinemia and hypertriglyceridemia are early markers of

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Data from metabolic monitoring informs the decision to switch antipsychotics and metabolic consequences of switching



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Related Resources

- American Diabetes Association. www.diabetes.org.
- International Diabetes Federation. www.idf.org.
- Framingham Heart Study. Coronary heart disease (10-year risk). www.framinghamheartstudy.org/risk/coronary.html.
- National Cholesterol Education Program. Risk assessment tool for estimating your 10-year risk of having a heart attack. <http://hp2010.nhlbi.nih.net/atp/iii/calculator.asp>.

Drug Brand Names

Clozapine • Clozaril	Quetiapine • Seroquel
Metformin • Glucophage	Risperidone • Risperdal
Olanzapine • Zyprexa	

Disclosure

Dr. Cohn is a speaker for Pfizer Canada.

metabolic strain. Also, response to initial antipsychotic treatment—possibly independent of the agent selected—is robust in early psychosis.³⁷

For these reasons, it is important to initiate schizophrenia treatment with low metabolic liability agents and reserve more potent agents with high metabolic liability for patients who do not respond adequately.

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Bottom Line

Comorbidity between schizophrenia and type 2 diabetes mellitus is common and clinically relevant. Psychiatrists are well situated to monitor metabolic consequences of antipsychotic treatment, including screening for diabetes and promoting medical care when indicated. Metabolic monitoring informs decisions related to antipsychotic switching and measures the effectiveness of metabolic interventions.

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