

Agitated and hallucinating, with a throbbing headache

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Mr. K, age 42, who has a history of schizophrenia, arrives at the emergency room agitated and belligerent. Physical exam reveals type 2 diabetes mellitus. How would you treat him?

CASE Psychotic, and nonadherent

Mr. K, a 42-year-old Fijian man, is brought to the emergency department by his older brother for evaluation of behavioral agitation. Mr. K is belligerent and threatens to kill his family members. Three years earlier, he was given a diagnosis of schizophrenia and treated at an inpatient psychiatric unit.

At that time, Mr. K was stabilized on risperidone, 4 mg/d. However, he did not follow-up with treatment after discharge and has not taken any psychotropic medications since that time.

His brother reports that Mr. K has been slowly deteriorating, talking to himself, staying up at night, and getting into arguments with his family over his delusional beliefs. Although Mr. K once worked as a security guard, he has not worked in 8 years. He has been living with his family, who are no longer willing to accept him into their home because they fear he might harm them.

In the emergency department, Mr. K reports that he has a throbbing headache. Blood pressure is 177/101 mm Hg; heart rate is 103 beats per minute; respiratory rate is 18 breaths per minute; weight is 185 lb; and body mass index (BMI) is 31.8. Physical examination is unremarkable.

Laboratory values show that sodium is 131 mEq/L; potassium, 3.7 mEq/L; bicarbonate, 26 mEq/L; glucose, 420 mg/dL; hemo-

globin A_{1c} 12.7; and urine glucose, 3+. Mr. K denies being told he has diabetes.

What are Mr. K's risk factors for diabetes?

- a) schizophrenia
- b) physical inactivity
- c) obesity
- d) Fijian ethnicity
- e) all of the above

The authors' observations

The prevalence of type 2 diabetes mellitus (T2DM) in persons with schizophrenia or a schizoaffective disorder is twice that of the general population.¹⁻⁴ Multiple variables contribute to the increased prevalence of diabetes in this population, including genetic predisposition, environmental and cultural factors related to diet and physical activity, a high rate of smoking,^{5,6} iatrogenic causes (metabolic dysregulation and weight gain from antipsychotic treat-

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Disclosures

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DAVE OUTLER FOR CURRENT PSYCHIATRY



How would you handle this case?

Answer the **challenge questions** throughout this article

Clinical Point

Diabetes is associated with lower global cognitive functioning among persons with schizophrenia

Table 1

Considerations when treating patients who have comorbid schizophrenia and diabetes

Lifestyle modifications	Patients with severe mental illness often live in a low socioeconomic neighborhood and have difficulty accessing health care and healthy food; they also have fewer opportunities and resources to engage in physical activity
Cognitive function	Patients with severe mental illness might experience cognitive decline, which makes lifestyle interventions such as calorie or carbohydrate counting difficult and which can diminish adherence to a complicated medication regimen
Effects of metabolic regulation	Consider antipsychotics that are less likely to cause metabolic dysregulation and weight gain, such as first-generation antipsychotics or second-generation antipsychotic agents with lower risk of metabolic effects, such as aripiprazole, lurasidone, and asenapine
Adherence	Consider long-acting injectable antipsychotics in patients with poor adherence to oral formulations because symptom remission can lead to improved health maintenance
Risks vs benefits of a specific antipsychotic	Consider the benefits of symptom reduction with antipsychotics vs risks of metabolic side effects. At times, it might be difficult to avoid the latter, such as with use of olanzapine and quetiapine
Risks vs benefits of strict blood sugar control	Consider the necessity of strict blood sugar control with insulin vs the risks of hypoglycemia and overdose with insulin

ment), and socioeconomic factors (poverty, lack of access to health care). In addition, symptoms of psychosis such as thought disorder, delusions, hallucinations, and cognitive decline in persons with chronic schizophrenia and schizoaffective disorder can make basic health maintenance difficult.

In Mr. K's case, premorbid risk of diabetes was elevated because of his Fijian ethnicity.⁷ With a BMI of 31.8, obesity further increased that risk.^{5,6,8} In addition, his untreated chronic mental illness, lack of access to health care, low socioeconomic status, longstanding smoking habit, and previous exposure to antipsychotics also increased his risk of T2DM.

The interaction between diabetes and psychosis contributes to a vicious cycle that makes both conditions worse if either, or both, are untreated. In general, medical comorbidities are associated with depression and neurocognitive impairment in persons with schizophrenia.⁹ Specifically, diabetes is associated with lower global cognitive functioning among persons with

schizophrenia.¹⁰ Poor cognitive functioning can, in turn, decrease the patient's ability to manage his medical illness. Also, persons with schizophrenia are less likely to be treated for diabetes, dyslipidemia, and hypertension, as in Mr. K's case.¹¹

How would you treat Mr. K's newly diagnosed diabetes?

- refer him to a primary care physician
- start an oral agent
- start sliding-scale insulin
- start long-acting insulin
- recommend a carbohydrate-controlled diet

TREATMENT Stabilization

Mr. K is admitted to the medical unit for treatment of hyperglycemia. The team starts him on amlodipine, 5 mg/d, for hypertension; aripiprazole, 10 mg/d, for psychosis; and sliding-scale insulin (lispro) and 20 units of insulin (glargine) nightly for diabetes. Mr. K's blood glucose level is well regulated on this regimen; after being medically cleared, he is transferred to the inpatient psychiatric unit.



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Table 2

Oral agents vs insulin for glycemic control

	Advantages	Disadvantages
Oral agents	<ul style="list-style-type: none"> Low risk for hypoglycemia (metformin, biguanides) Potential for weight loss in the long term (metformin) Concomitant cardiovascular benefits Low cost (biguanides, sulfonylureas) 	<ul style="list-style-type: none"> Slower effect in lowering blood glucose Specific contraindications (eg, renal impairment, heart failure, need for radiographic contrast studies with metformin) Dosage ceiling because of side-effect profiles Increased risk for hypoglycemia (sulfonylureas)
Insulin	<ul style="list-style-type: none"> Immediate effect Dosage can be tightly controlled No dosage ceiling 	<ul style="list-style-type: none"> Moderate to high cost Increased risk of hypoglycemia Increased hunger and appetite Increased weight gain in the long term

Source: Adapted from reference 13

EVALUATION Denies symptoms

Mr. K appears older than his stated age, is poorly groomed, and is dressed in a hospital gown. He is isolated and appears to be internally preoccupied. He repeatedly denies hearing auditory hallucinations, but often is overheard responding to internal stimuli and mumbling indecipherably in a low tone. His speech is decreased and his affect is flat and guarded. He states that he is not “mental” but that he came to the hospital for “tooth pain.” Every day he asks when he can return home and he asks the staff to call his family to take him home. When informed that his family is not able to care for him, Mr. K states that he would live in a house he owns in Fiji, which his family members state is untrue.

How would you treat Mr. K’s psychosis?

- continue aripiprazole
- switch to risperidone, an agent to which he previously responded
- switch to olanzapine because he has not been sleeping well
- switch to haloperidol because of diabetes

The authors’ observations

Pharmacotherapy for patients with comorbid schizophrenia and diabetes requires

consideration of clinical and psychosocial factors unique to this population.

Antipsychotic choice

Selection of an antipsychotic agent to address psychosis requires considering its efficacy, side-effect profile, and adherence rates, as well as its potential effects on metabolic regulation and weight (*Table 1*). Typical antipsychotics are less likely than atypical antipsychotics to cause metabolic dysregulation.¹² When treatment with atypical antipsychotics cannot be avoided—such as when side effects or an allergic reaction develop—consider selecting a relatively weight-neutral drug with a lower potential for metabolic dysregulation, such as aripiprazole. However, many times, using an agent with significant effects on metabolic regulation cannot be avoided, making treating and monitoring the resulting metabolic effects even more significant.

Glycemic control

Initiating an agent for glycemic control in persons with newly diagnosed diabetes requires weighing many factors, including mode of delivery (oral or subcutaneous), level of glycemic control required, comorbid medical illness (such as renal impair-

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When atypicals cannot be avoided, consider selecting a relatively weight-neutral drug with a lower potential for metabolic dysregulation

Table 3

Variables to consider before initiating insulin treatment

Diet and lifestyle	Have dietary and lifestyle modifications been instituted?
Choice of antipsychotics	If possible, have you adjusted the choice of antipsychotic to minimize metabolic risk?
Oral agents	Have metformin or alternative agents been tried?
Degree of glycemic control desired	Is the patient insulin dependent? Can the patient's blood glucose be controlled without using insulin?
Risks of using insulin	Consider the increased risk of hypoglycemic episodes with insulin use
Weight gain	Consider the potential for insulin-related weight gain with weight gain related to antipsychotics
Symptom severity	Does the patient have ongoing hallucinations and delusions that interfere with his ability to administer his insulin? What is the daily insulin requirement? If patient's insulin requirement is low, there's a higher chance that the patient can be managed with dietary interventions and activity and non-insulin treatment modalities
Level of functioning	Does the patient have the insight, cognitive abilities, and executive functioning needed to monitor his blood glucose and administer the correct dose of insulin?
Setting	Where will the patient be placed at discharge? If the patient returns home, will family members be available to help administer insulin? If the patient is placed in a group home, will he (she) have access to a refrigerator to safely store insulin? Is insulin treatment a barrier to finding a placement for the patient?
Safety concerns	Are there safety concerns regarding the patient's access to needles and large amounts of insulin?

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Chronically mentally ill persons might have reduced cognitive functioning that could affect their ability to maintain complicated medication regimens

ment and heart failure), cost, and potential long-term side effects of the medication (*Table 2, page 47*).¹³ Oral agents have a slower effect on lowering the blood glucose level, and each agent carries contraindications, but generally they are more affordable. Many present a low risk of hypoglycemia but sulfonylureas are an exception. In addition, metformin could lead to weight loss over the long term, which further lowers the risk of diabetes.

If, however, tight and immediate glycemic control is needed, subcutaneous insulin injections might be required, although this method is more costly, carries an increased risk of hypoglycemic episodes acutely, and leads to weight gain in the long run because of induced hunger and increased appetite.

Psychosocial factors

In addition to the clinical variables above, treating diabetes in patients with comor-

bid schizophrenia requires considering other psychosocial factors that might not be readily apparent (*Table 3*). For example, patients with schizophrenia might have decreased motivation, self-efficacy, and capacity for self-care when it comes to health maintenance and medication adherence.¹⁴ Chronically mentally ill persons might have reduced cognitive functioning that could affect their ability to maintain complicated medication regimens, such as administering insulin and monitoring blood glucose.

In addition, easy access to hypodermic needles and large amounts of insulin could become a safety concern in patients with ongoing hallucinations, delusions, and thought disorder, despite antipsychotic treatment. For example, a patient with schizophrenia and diabetes who has been maintained on insulin might begin hearing voices that tell her to inject her eyeballs with insulin. Similarly, although the risk of hypo-

Table 4

Weight-neutral hypoglycemic agents

Agent	Effect on weight
Metformin (oral)	Weight loss
Exenatide (injection)	Weight-neutral to some weight loss
Canagliflozin (once-daily injection)	Weight-neutral to some weight loss
Sitagliptin, saxagliptin, linagliptin (oral)	Weight-neutral

glycemic episodes in patients treated with insulin is well known, patients with schizophrenia have a higher risk of acute complications of diabetes than other patients with diabetes.¹⁵

Psychosocial factors, such as placement, support system, and follow-up care need to be considered. In some instances, the need to administer daily subcutaneous insulin could be a barrier to placement if the facility does not have the staff or expertise to monitor blood glucose and administer insulin.

If the patient is returning home, then the patient or a caretaker will need to be trained to monitor blood glucose and administer insulin. This might be difficult for persons with chronic mental illness who have lost the support and care of their family. Also, consider the issue of storing insulin, which requires refrigeration. Because of the potential complications involved in using insulin in patients with schizophrenia, practitioners should consider managing non-insulin dependent diabetes with an oral hypoglycemic agent, when possible, along with lifestyle modifications.

OUTCOME Weight loss, discharge

Mr. K is transitioned from aripiprazole to higher-potency oral risperidone, titrated to 6 mg/d. At this dosage, he continues to maintain a delusion about owning a house in Fiji, but was seen responding to internal stimuli less often. The treatment team places him on a diabetic and low-sodium diet of 1,800 kcal/d. His fasting blood glucose levels range in the 70s to 110s mg/dL during his first week of hospitalization.

The treatment team starts Mr. K on oral metformin, titrated to 1,000 mg twice daily, while tapering him off insulin lispro and glargine over the course of hospitalization. The transition from insulin to metformin also is considered because Mr. K's daily insulin requirement is rather low (<0.5 units/kg).

Mr. K's course is prolonged because his treatment team initiates the process of conservatorship and placement in the community. Approximately 6 months after his admission, Mr. K is discharged to an unlocked facility with support from an intensive outpatient mental health program. At 6 months follow-up with his outpatient provider, Mr. K's hemoglobin A_{1c} is 7.0 and he weighs 155 lb with a BMI of 26.5.

The authors' observations

Despite Mr. K's initial elevated hemoglobin A_{1c} of 12.7 and weight of 185 lb, over approximately 6 months he experiences a 5.7-unit drop in hemoglobin A_{1c} and weight loss of 30 lb with dietary management and metformin—without the need for other agents. Other options for weight-neutral treatment of T2DM include exenatide, which also is available as a once weekly injectable formulation, canagliflozin, and the gliptins (sitagliptin, saxagliptin, and linagliptin) (Table 4).

Mr. K's improved control of his diabetes occurred despite initiation of an atypical antipsychotic, which would have been expected to cause additional weight gain and make his diabetes worse secondary to metabolic effects.¹² Treatment with metformin in particular has been associated with weight loss in patients with¹⁶ and without¹⁷

Clinical Point

Patients with schizophrenia have a higher risk of acute complications of diabetes than other patients with diabetes

Clinical Point

Treatment with metformin has been associated with weight loss in patients with and without comorbid schizophrenia

Related Resources

- Cohn T. The link between schizophrenia and diabetes. *Current Psychiatry*. 2012;11(10):28-34,46.
- Annamalai A, Tek C. An overview of diabetes management in schizophrenia patients: office based strategies for primary care practitioners and endocrinologists [published online March 23, 2015]. *Int J Endocrinol*. 2015;2015:969182. doi: 10.1155/2015/969182.

Drug Brand Names

Amlodipine • Norvasc	Lurasidone • Latuda
Aripiprazole • Abilify	Metformin • Glucophage
Asenapine • Saphris	Olanzapine • Zyprexa
Canagliflozin • Invokana	Quetiapine • Seroquel
Exenatide • Bydureon, Byetta	Risperidone • Risperdal
Glargine • Lantus	Saxagliptin • Onglyza
Linagliptin • Tradjenta	Sitagliptin • Januvia
Lispro • Humalog	

comorbid schizophrenia, including those with antipsychotic-induced weight gain.¹⁸⁻²⁰

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Bottom Line

Persons with schizophrenia are at higher risk of type 2 diabetes mellitus for many reasons, including metabolic effects of antipsychotics, reduced cognitive functioning, poor self-care, and limited access to health care. Typical antipsychotics are less likely to cause metabolic dysregulation but, if an atypical is needed, one that is relatively weight-neutral should be selected. When choosing an agent for glycemic control, consider a patient's or a caretaker's ability to administer medications, monitor blood glucose, and follow dietary recommendations.