Reducing morbidity and mortality



Dr. Khan discusses strategies for addressing smoking and obesity in patients with schizophrenia

from common medical conditions in schizophrenia

You play a vital role in systematic screening, initiating treatment, and maintaining follow-up

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Disclosures

Dr. Khan is a speaker for Janssen, Alkermes, and Lundbeck/Otsuka. Drs. Zaidi, Salaria, and Bhattacharyya report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products. ife expectancy for both males and females has been increasing over the past several decades to an average of 76 years. However, the life expectancy among individuals with schizophrenia in the United States is 61 years—a 20% reduction.¹ Patients with schizophrenia are known to be at increased risk of several comorbid medical conditions, such as type 2 diabetes mellitus (T2DM), coronary artery disease, and digestive and liver disorders, compared with healthy people (*Figure, page 32*).²⁻⁵ This risk may be heightened by several factors, including sedentary lifestyle, a high rate of cigarette use, poor self-management skills, homelessness, and poor diet.

Although substantial attention is paid to the psychiatric and behavioral management of schizophrenia, many barriers impede the detection and treatment of patients' medical conditions, which have been implicated in excess unforeseen deaths. Patients with schizophrenia might experience delays in diagnosis, leading to more acute comorbidity at time of diagnosis and premature mortality.

Cardiovascular disease is the leading cause of death among psychiatric patients.⁶ Key risk factors for cardiovascular disease include smoking, obesity, hypertension, dyslipidemia, diabetes, and lack of physical activity, all of which are more prevalent among patients with schizophrenia.⁷ In addition, antipsychotics are associated with adverse metabolic effects.⁸ In general, smoking and obesity are the most modifiable and preventable risk factors for many medical conditions, such as cardiovascular disease, hyperlipidemia, diabetes, and many forms of cancer (*Table 1, page 34*).

In this article, we discuss how to manage common medical comorbidities in patients with schizophrenia. Comprehensive management for all these medical conditions in this population is beyond the scope of this article; we limit ourselves to discussing (1) how common these conditions are in patients with schizophrenia compared with the general population



Clinical Point

Metformin has modest potential for offsetting weight gain and providing some metabolic control in overweight patients with schizophrenia

Figure

Prevalence of cardiovascular disease, HIV, metabolic syndrome, obesity, and diabetes among the general U.S. population and patients with schizophrenia in 2011



^aPrevalence of cardiovascular disease among patients with schizophrenia was calculated to be 3 times that of adult U.S. population²; the average prevalence rate in the general population is 38.3%.³

^bHIV prevalence among patients with schizophrenia ranged from 1.3% to 23.9%, therefore an average of 12.6% is indicated.² The prevalence of HIV of 0.3% is used for the general population.⁴ ^cMetabolic syndrome prevalence among patients with schizophrenia ranged from 19.4% to 68%, therefore an average of 43.7% is indicated.² The prevalence rate of 34.7% in general U.S. population was used for metabolic syndrome.⁵ ^dObesity, defined as a body mass index of >30, prevalence among patients with schizophrenia ranged from (42% to 60%)

average of 51% is indicated, which is on average 3 times higher than the general adult population.² •Diabetes prevalence among patients with schizophrenia was calculated to be 5 times that of general adult U.S. population.²

and (2) what can be done in psychiatric practice to manage these medical comorbidities (*Box, page 35*).

Obesity

Obesity—defined as body mass index (BMI) of >30—is common among patients with schizophrenia. The condition leads to poor self-image, decreased treatment adherence, and an increased risk of many chronic medical conditions (*Table 1, page 34*). Being overweight or obese can increase stigma and social discrimination, which will undermine self-esteem and, in turn, affect adherence with medications, leading to relapse.

The prevalence of obesity among patients with schizophrenia is almost double that of the general population⁹ (*Figure*²⁻⁵). Several factors predispose these patients to overweight or obese, including sedentary lifestyle, lack of exercise, a high-fat diet, medications side effects, and genetic factors. Recent studies report the incidence of weight gain among patients treated with antipsychotics is as high as $80\%^{10}$ (*Table 2, page 36*).

Mechanisms involved in antipsychoticinduced weight gain are not completely understood, but antagonism of serotonergic (5-HT2C, 5-HT1A), histamine (H1), dopamine (D2), muscarinic, and other receptors are involved in modulation of food intake. Decreased energy expenditure also has been blamed for antipsychotic-induced weight gain.¹⁰

Pharmacotherapy and bariatric surgery can be as effective among patients with schizophrenia as they are among the general population. Maintaining a BMI of <25 kg/m² lowers the risk of cardiovascular disease by 35% to 55%.⁶ Metformin has modest potential for offsetting weight gain and continued on page 34





Clinical Point

Mechanisms that increase the risk of T2DM include genetic and environmental factors, such as family history, lack of physical activity, and poor diet continued from page 32

Table 1

Many medical conditions are associated with smoking and obesity

Condition	Smoking	Obesity
Coronary artery disease	v	 ✓
Aortic aneurysm	v	
Hypertension	v	 ✓
Hyperlipidemia		 ✓
Stroke	v	 ✓
Peripheral vascular disease	v	
Teratogenic effects	v	
Type 2 diabetes mellitus		 ✓
Rheumatoid arthritis	v	Associated with osteoarthritis
Respiratory illnesses	v	 ✓
Ectopic pregnancy	v	
Cancer of oropharynx, larynx, esophagus, trachea, bronchus, lung, stomach, pancreas, kidney, ureter, cervix, bladder, and colorectal	~	Associated with endometrial, breast, and colon cancers
Male sexual dysfunction	v	 ✓
Periodontitis	v	

providing some metabolic control in overweight outpatients with schizophrenia,¹¹ and should be considered early when treating at-risk patients.

Managing obesity. Clinicians can apply several measures to manage obesity in a patient with schizophrenia:

• Educate the patient, and the family, about the risks of being overweight or obese.

• Monitor weight and BMI at each visit.

• Advise smoking cessation.

• When clinically appropriate, switch to an antipsychotic with a lower risk of weight gain—eg, from olanzapine or high-dose quetiapine to a high- or medium-potency typical antipsychotic (eg, haloperidol, perphenazine), ziprasidone, aripiprazole, iloperidone, and lurasidone (*Table 2, page 36*).

• Consider prophylactic use of metformin with an antipsychotic; the drug has modest potential for offsetting weight gain and providing better metabolic control in an overweight patient with schizophrenia.¹¹

• Encourage the patient to engage in modest physical activity; for example, a 20-minute walk, every day, reduces the risk of cardiovascular disease by 35% to 55%.⁶

• Recommend a formal lifestyle modification program, such as behavioral groupbased treatment for weight reduction.¹²

• Refer the patient and family to a dietitian.

Type 2 diabetes mellitus

There is strong association between T2DM and schizophrenia that is related to abnormal glucose regulation independent of any adverse medication effect.13 Ryan et al14 reported that first-episode, drug-naïve patients with schizophrenia had a higher level of intra-abdominal fat than age- and BMI-matched healthy controls, suggesting that schizophrenia could be associated with changes in adiposity that might increase the risk of insulin resistance, hyperlipidemia, and dyslipidemia. Mechanisms that increase the risk of T2DM in schizophrenia include genetic and environmental factors, such as family history, lack of physical activity, and poor diet.

Diagnosis. All patients with schizophrenia should be evaluated for undiagnosed diabetes. The diagnosis of T2DM is made by documenting:

• a fasting plasma glucose reading of \geq 126 mg/dL

Key points: Managing medical comorbidity in schizophrenia

 Screening for, and detection of, medical comorbidities can be done adequately in any psychiatric practice. Doing so can lead to timely management for those conditions, thus preventing premature mortality in patients with schizophrenia

Box

- Baseline screening and follow-up monitoring of weight, body mass index, blood glucose, smoking, substance abuse, lipid profile, and other metabolic parameters should be mandatory in patients with schizophrenia, especially those taking a second-generation antipsychotic (*Table 2, page 36*)
- Consider yourself responsible for implementing needed screening assessments; when necessary, closely collaborate with general practitioners and

• symptoms of T2DM, along with a random plasma glucose reading of ≥200 mg/dL

• 2-hour reading of a plasma glucose level >200 mg/dL on an oral glucose tolerance test.

Recent guidelines also suggest using a hemoglobin A_{lc} value cutoff of $\ge 6.5\%$ to diagnose T2DM.

In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, 38% of patients with schizophrenia and diabetes were not receiving any treatment for T2DM.¹⁵

Risk factors for T2DM are:

• BMI >25

- a first-degree relative with diabetes
- lack of physical activity

• being a member of a high-risk ethnic group (African American, Hispanic American, Native American, Asian American, or Pacific Islander)

• having delivered a baby >9 lb or having had gestational diabetes

• hypertension

• high-density lipoprotein (HDL) cholesterol level of ≤35 mg/dL

• triglyceride level of $\geq 250 \text{ mg/dL}$

• history of an abnormal glucose tolerance test

• history of abnormal findings on a fasting plasma glucose test

history of vascular disease.

other specialists to treat hypertension, hyperglycemia and diabetes, and dvslipidemia

- Don't overlook the importance of educating the patient, family, and the mental health team
- Healthy lifestyle interventions should be offered and promoted by psychiatric treatment facilities
- Smoking and obesity are the 2 main risk factors for many medical problems in the general population—more so in patients with schizophrenia. Screening and treating these 2 conditions could prevent many medical comorbidities in these patients. Long-term prospective research on these 2 risk factors, in the form of a controlled trial, is needed

Early detection and management.

• Educate the patient and family about signs and symptoms of T2DM, such as polyuria, nocturia, polydipsia, fatigue, visual disturbances, and (in women) vulvitis. Also, psychiatrists should be aware of, and inquire about, symptoms of diabetic ketoacidosis.

• At the start of therapy with any antipsychotic, particularly a second-generation antipsychotic (SGA), ask patients about a family history of diabetes and measure the hemoglobin A_{1e} value.

• Monitor the hemoglobin A_{1c} level 4 months after starting an antipsychotic, then annually, in a patient with significant risk factors for diabetes.

• Monitor blood glucose every 6 months in patients with no change from initial results and more frequently in those with significant risk factors for diabetes and those who gain weight.

• Order a lipid panel and measure the serum glucose level to rule out dyslipidemia and diabetes, because a patient with high lipid levels and diabetes is at higher risk of developing cardiovascular conditions.

• Advocate for smoking cessation.

• Switch to an antipsychotic with a lower risk of diabetes when clinically appropriate, such as switching a patient from olanzapine or high-dose quetiapine to a high- or



Clinical Point

In the CATIE study, 38% of patients with schizophrenia and diabetes were not receiving any treatment for T2DM



Clinical Point

A comprehensive review suggested that clozapine, olanzapine, and quetiapine are associated with a higher risk of dyslipidemia

Table 2

Risk of metabolic adverse effects with second-generation antipsychotics

Antipsychotic	Weight gain	Risk of diabetes	Hyperlipidemia
Clozapine	+++	+++	+++
Olanzapine	+++	+++	+++
Risperidone	++	++	++
Quetiapine	++	++	++
lloperidone	++	+/-	+/-
Aripiprazole	+	+	+
Ziprasidone	+	+	+
Paliperidone	+	+/-	+/-
Asenapine	+	+/-	+/-
Lurasidone	+	+/-	+/-

+++: High; ++: Moderate; +: Low; +/-: Low or not reported

medium-potency typical antipsychotic (such as haloperidol or perphenazine), ziprasidone, aripiprazole, iloperidone, and lurasidone (*Table 2*).

• Consider prophylactic use of metformin along with antipsychotics. Metformin has been used to improve insulin sensitivity and can lead to weight loss in diabetic and non-diabetic patients. The drug has modest potential for offsetting weight gain and providing better metabolic control in overweight outpatients with schizophrenia.¹¹ Metformin is simple to use, does not lead to hypoglycemia, does not require serum glucose monitoring, and has a favorable safety profile.¹¹

• Educate the patient about modest physical activity. For example, a 20-minute walk every day reduces the risk of cardiovascular disease by 35% to 55%.⁶

• Refer the patient to a dietitian to develop an appropriate diet plan.

• When diabetes is diagnosed, ensure appropriate follow-up and initiation or continuation of therapy with a general practitioner or an endocrinologist.

• Reinforce the need for ongoing followup and compliance with therapy for diabetes.

Hyperlipidemia and dyslipidemia

Elevated cholesterol and triglyceride levels are associated with cardiovascular diseases, such as ischemic heart disease and myocardial infarction. A 10% increase in cholesterol levels is associated with a 20% to 30% increase in the risk of coronary artery disease; lowering cholesterol by 10% decreases the risk by 20% to 30%.¹⁶ Triglyceride levels \geq 250 mg/dL are associated with 2-fold higher risk of cardiovascular disease.¹⁶

The incidence of dyslipidemia is not as well studied as diabetes in patients with schizophrenia. There is increased prevalence of dyslipidemia in patients with schizophrenia compared with the general population because of obesity, lack of physical activity, and poor dietary habits.¹⁶

Data regarding the effects of firstgeneration antipsychotics (FGAs) on lipid levels are limited, but high-potency drugs, such as haloperidol, seem to carry a lower risk of hyperlipidemia than low-potency drugs, such as chlorpromazine and thioridazine.¹⁷ A comprehensive review on the effects of SGAs on plasma lipid levels suggested that clozapine, olanzapine, and quetiapine are associated with a higher risk of dyslipidemia¹⁷ (*Table 2*).

In the CATIE study, olanzapine and clozapine were associated with a greater increase in the serum level of cholesterol and triglycerides compared with other antipsychotics, even after adjusting for treatment duration. Furthermore, a retrospective chart review of patients who switched to aripiprazole from other SGAs showed a decrease in levels of total cholesterol and low-density lipoprotein cholesterol¹⁵ (*Table 2*).

continued from page 36

Patients with schizophrenia are more likely to have dyslipidemia go undiagnosed, and therefore are less likely to be treated for the disorder. In the CATIE study, 88% of patients with dyslipidemia were not receiving any treatment.¹⁵

Management for dyslipidemia.

• Educate the patient and family about risks involved with dyslipidemia.

• Monitor weight and BMI at each visit.

• Monitor lipids to rule out dyslipidemia. Obtain a pretreatment fasting or random lipid profile for any patient receiving an antipsychotic; repeat at least every 6 months after starting the antipsychotic.

• Counsel the patient to quit smoking.

• Switch to an antipsychotic with lower risk of weight gain and dyslipidemia, such as switching from olanzapine or high-dose quetiapine to high- or mediumpotency typical antipsychotics (such as, haloperidol or perphenazine), ziprasidone, aripiprazole, iloperidone, and lurasidone (*Table 2*).

• Educate and encourage the patient about modest physical activity. For example, a 20-minute walk everyday will reduce cardiovascular disease risk by 35% to 55%.⁶

• Refer to a dietitian if indicated.

• Ensure follow-up and initiation of treatment with a general practitioner.

Metabolic syndrome

Metabolic syndrome is cluster of cardiovascular risk factors, including central adiposity, hyperglycemia, dyslipidemia, and hypertension. The National Cholesterol Education Program's Adult Treatment Panel III report defines metabolic syndrome as the presence of 3 of 5 of the following factors:

- abdominal obesity (waist circumference of >40 inches in men, or >35 inches in women)
- triglyceride level, >150 mg/dL
- HDL cholesterol, <40 mg/dL in men and <50 mg/dL in women
- blood pressure, >130/85 mm Hg

• fasting plasma glucose level, >110 mg/dL.

The presence of metabolic syndrome in the general population is a strong predictor

of cardiovascular diseases and diabetes.¹⁸ The adverse effects of metabolic syndrome are thought to relate to atherogenic dyslipidemia, higher blood pressure, insulin resistance with or without glucose intolerance, a proinflammatory state, and a prothrombotic state.

The prevalence of metabolic syndrome in patients with schizophrenia is 2- to 3-fold higher than the general population.¹⁹ In the CATIE study, approximately one-third of patients met criteria for metabolic syndrome at baseline.¹⁵ In a prospective study, De Hert et al²⁰ reported that patients who were started on a SGA had more than twice the rate of developing metabolic syndrome compared with those treated with a FGA (*Table 2*). Other possible causes of metabolic syndrome are visceral adiposity and insulin resistance.¹⁶

Management of the metabolic syndrome involves addressing the individual components that have been described in the preceding sections on T2DM and dyslipidemia.

Hepatitis C

Hepatitis C virus (HCV) infection is thought to be the most common blood-borne illness, with an estimated prevalence of 1% of the U.S. population. Some studies suggest that as many as 16% of people with schizophrenia have HCV infection.⁴ Risk factors for HCV infection include unsafe sexual practices, prostitution, homosexuality, homelessness, and IV drug use.

HCV treatments typically have involved regimens with interferon alfa, which is associated with significant neuropsychiatric side effects, including depression and suicide. There is a dearth of research on treatment of HCV in patients with schizophrenia; however, at least 1 study suggests that there was no increase in psychiatric symptoms in patients treated with interferon-containing regimens.²¹ There is even less evidence to guide the use of newer, non-interferon-based HCV treatment regimens that are better tolerated and have a higher response rate in the general population; there is reason, however, to be hopeful about their potential in patients with schizophrenia and HCV infection.



Clinical Point

Interferon alfa, which is used to treat HCV, is associated with significant neuropsychiatric side effects, including depression and suicide



Clinical Point

When HIV infection is diagnosed, facilitate referral to a HIV or infectious disease specialist for treatment

Managing HCV infection.

• Educate the patients and family about risk factors associated with contracting HCV.

• Screen for HCV infection in patients with schizophrenia because there is higher prevalence of HCV in these patients compared with the general population.

• When HCV infection is diagnosed, educate the patients and family about available treatments.

• Facilitate referral to an HCV specialist for appropriate treatment.

HIV/AIDS

HIV infection is highly prevalent among people suffering from severe mental illness such as schizophrenia. The incidence of HIV/AIDS in patients with schizophrenia is estimated to be 4% to 23%, compared with 0.6% in the general population.²² Risk factors associated with a higher incidence of HIV/AIDS in patients with schizophrenia are lack of knowledge about contracting HIV, unsafe sexual practices, prostitution, homosexuality, homelessness, and IV drug use.²²

Managing HIV/AIDS.

• Educate the patient and family about risk factors associated with contracting HIV/AIDS.

• Educate patients about safe sex practices.

• All patients with schizophrenia should be screened for HIV because there is 10-fold higher HIV prevalence in schizophrenia compared with the general population.

• When HIV infection is diagnosed, facilitate referral to a HIV or infectious disease specialist for treatment.

• Educate the patient in whom HIV/AIDS has been diagnosed about the importance of (1) adherence to his (her) HIV medication regimen and (2) follow-up visits with an infectious disease practitioner and appropriate laboratory tests.

• Educate the patient's family and significant other about the illness.

• Screen for and treat substance use.

• At each visit, inquire about the patient's adherence to HIV medical therapy, viral load, and CD4 cell count.

Chronic obstructive pulmonary disease

Patients with schizophrenia are more likely to suffer from respiratory disease, such as chronic obstructive pulmonary disease (COPD) and asthma, compared with the general population.²³ Smoking is a major risk factor for COPD. In a study by Dickerson et al,²⁴ 64% of people with schizophrenia were current smokers, compared with 19% of those without mental illness.

A high rate of smoking rate among people with schizophrenia suggests a "self-medication" hypothesis: That is, stimulation of CNS nicotinic cholinergic receptors treats the negative symptoms of schizophrenia and overcomes the dopamine blocking effects of antipsychotics.²⁵ Among SGAs, only clozapine has a substantial body of evidence to support its association with decreased smoking behavior.

Managing COPD.

• Educate the patient and family about risk factors associated with COPD and smoking.

• Screen for tobacco use at each visit; try to increase motivation to quit smoking.

• Educate the patients and family about the value and availability of smoking cessation programs.

• Prescribe medication to help with smoking cessation when needed. Bupropion and varenicline have been shown to be effective in patients with schizophrenia; nicotine replacement therapies are safe and can be helpful.

• When treating a patient who is in the process of quitting, encourage and help him to maintain his commitment and enlist support from his family.

• Refer to an appropriate medical provider (primary care provider or pulmonologist) for a patient with an established or suspected diagnosis of COPD.

Cancer

Since 1909, when the Board of Control of the Commissioners in Lunacy for England and Wales noted the possibility of a decreased incidence in cancer among psychiatric patients, this connection has been a matter continued on page 40



Clinical Point

Managing cancer in a patient with schizophrenia poses a significant challenge; he might lack capacity to make decisions about treatment continued from page 38

Related Resources

- Rao S, Raney L, Xiong GL. Reducing medical comorbidity and mortality in severe mental illness. Current Psychiatry. 2015;14(7):14-20.
- Razzano LA, Cook JA, Yost C, et al. Factors associated with co-occurring medical conditions among adults with serious mental disorders. Schizophr Res. 2015;161(2-3):458-464.

Drug Brand Names

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    Aripiprazole - Abilify
    Met

    Asenapine - Saphris
    Ola

    Bupropion - Wellbutrin,
    Pali

    Zyban
    Per

    Chlorpromazine - Thorazine
    Que

    Clozapine - Clozaril
    Risg

    Haloperidol - Haldol
    Thir

    Iloperidone - Fanapt
    Vare

    Lurasidone - Latuda
    Zipr
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Metformin • Glucophage Olanzapine • Zyprexa Paliperidone • Invega Perphenazine • Trilafon Quetiapine • Seroquel Risperidone • Risperdal Thioridazine • Mellaril Varenicline • Chantix Ziprasidone • Geodon

of controversy.²⁶ Subsequent research has been equivocal; the prevalence of cancer has been reported to be either increased, similar, or decreased compared with the general population.²⁶⁻²⁸ Risk factors for cancer, including smoking, obesity, poor diet, sedentary lifestyle, and hyperprolactinemia, are more common among patients with schizophrenia.

Genetic factors and a possible protective effect from antipsychotics have been cited as potential causes of decreased prevalence. Clozapine is associated with an increased risk of leukemia. No conclusion can be drawn about the overall prevalence of cancer in schizophrenia.

Managing cancer in a patient with schizophrenia, however, poses a significant challenge²⁹; he might lack capacity to make decisions about cancer treatment. The patient—or his surrogate decision-makers—need to carefully weigh current quality of life against potential benefits of treatment and

risks of side effects. Adherence to complex, often toxic, therapies can be challenging for the patient with psychosis. Successful cancer treatment often requires close collaboration between the cancer treatment team and the patient's support system, including the treating psychiatrist and case management teams.

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Bottom Line

Patients with schizophrenia are at higher risk of developing comorbid medical conditions because of the illness itself, lifestyle behaviors, genetics, and adverse effects of medications. Because mental health clinicians focus attention on the psychiatric and behavioral aspect of treatment, often there is delay in screening, detecting, and treating medical comorbidities. This screening can be done in any psychiatric practice, which can lead to timely management for those conditions and preventing premature mortality in patients with schizophrenia.

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