Using lipid guidelines to manage metabolic syndrome for patients taking an antipsychotic

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Your patient who has schizophrenia, Mr. W, age 48, requests that you switch him from olanzapine, 10 mg/d, to another antipsychotic because he gained 25 lb over 1 month taking the drug. He now weighs 275 lb. Mr. W reports smoking at least 2 packs of cigarettes a day and takes lisinopril, 20 mg/d, for hypertension.

You decide to start risperidone, 1 mg/d. First, however, your initial work-up includes:

- high-density lipoprotein (HDL), 24 mg/dL
- total cholesterol, 220 mg/dL
- blood pressure, 154/80 mm Hg
- waist circumference, 39 in
- body mass index (BMI), 29
- hemoglobin A_{1c}, of 5.6%.

A prolactin level is pending.

How do you interpret these values?

The impact of statin medications on risk of metabolic syndrome

Metabolic syndrome is defined as the cluster of central obesity, insulin resistance, hypertension, and dyslipidemia. Metabolic syndrome increases a patient's risk of diabetes 5-fold and cardiovascular disease 3-fold.[1] Physical inactivity and eating high-fat foods typically precede weight gain and obesity that, in turn, develop into insulin resistance, hypertension, and dyslipidemia.[1]

Patients with severe psychiatric illness have an increased rate of mortality from cardiovascular disease, compared with the general population.[2-4] The cause of this phenomenon is multifactorial: In general, patients with severe mental illness receive insufficient preventive health care, do not eat a balanced diet, and are more likely to smoke cigarettes than other people.[2-4]

Also, compared with the general population, the diet of men with schizophrenia contains less vegetables and grains and women with schizophrenia consume less grains. An estimated 70% of patients with schizophrenia smoke.[4] As measured by BMI, 86% of women with schizophrenia and 70% of men with schizophrenia are overweight or obese.[4]

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Practice Points

- Many patients with severe mental illness who are being treated with an antipsychotic (and even those who are untreated), are at **high risk of cardiovascular disease**.
- **By using the Pooled Cohort Equation and the treatment algorithm from the lipid guidelines**, you likely will identify many patients who meet criteria for a regimen of statin medication.
- **Initiate statin therapy case by case** to provide secondary prevention for atherosclerotic cardiovascular disease risk in this already high-risk population.

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Antipsychotics used to treat severe mental illness also have been implicated in metabolic syndrome, specifically second-generation antipsychotics (SGAs).[5] Several theories aim to explain how antipsychotics lead to metabolic alterations.

Oxidative stress. One theory centers on the production of oxidative stress and the consequent reactive oxygen species that form after SGA treatment.[6]

Mitochondrial function. Another theory assesses the impact of antipsychotic treatment on mitochondrial function. Mitochondrial dysfunction causes decreased fatty acid oxidation, leading to lipid accumulation.[7]

The culminating affect of severe mental illness alone as well as treatment-emergent side effects of antipsychotics raises the question of how to best treat the dyslipidemia component of metabolic syndrome. This article will:

- review which antipsychotics impact lipids the most
- provide an overview of the most recent lipid guidelines
- describe how to best manage patients to prevent and treat dyslipidemia.

Impact of antipsychotics on lipids

Antipsychotic treatment can lead to metabolic syndrome; SGAs are implicated in most cases.[8] A study by Liao et al[9] investigated the risk of developing type 2 diabetes mellitus, hypertension, and hyperlipidemia in patients with schizophrenia who received treatment with a first-generation antipsychotic (FGA) compared with patients who received a SGA. The significance-adjusted hazard ratio for the development of hyperlipidemia in patients treated with a SGA was statistically significant compared with the general population (1.41; 95% CI, 1.09–1.83). The risk of hyperlipidemia in patients treated with a FGA was not significant.

Studies have aimed to describe which SGAs carry the greatest risk of hyperlipidemia.[10,11] To summarize findings, in 2004 the American Diabetes Association (ADA) and American Psychiatric Association released a consensus statement on the impact of antipsychotic medications on obesity and diabetes.[12] The statement listed the following antipsychotics in order of greatest to least impact on hyperlipidemia:

- clozapine
- olanzapine
- quetiapine
- risperidone
- ziprasidone
- aripiprazole.

To evaluate newer SGAs, a systematic review and meta-analysis by De Hert et al[13] aimed to assess the metabolic risks associated with asenapine, iloperidone, lurasidone, and paliperidone. In general, the studies included in the meta-analysis showed little or no clinically meaningful differences among these newer agents in terms of total cholesterol in short-term trials, except for asenapine and iloperidone.

Asenapine was found to increase the total cholesterol level in long-term trials (>12 weeks) by an average of 6.53 mg/dL. These trials also demonstrated a decrease in HDL cholesterol (−0.13 mg/dL) and a decrease in low-density lipoprotein cholesterol (LDL-C) (−1.72 mg/dL to −0.86 mg/dL). The impact of asenapine on these lab results does not appear to be clinically significant.[13,14]

Iloperidone. A study evaluating the impact iloperidone on lipid values showed a statistically significant increase in total cholesterol, HDL, and LDL-C levels after 12 weeks.[13,15]

Overview: Latest lipid guidelines

Current literature lacks information regarding statin use for overall prevention of metabolic syndrome. However, the most recent update to the American Heart Association's guideline on treating blood cholesterol to reduce atherosclerotic cardiovascular risk in adults describes the role of statin therapy

Clinical Point

Antipsychotics used to treat severe mental illness—specifically SGAs—have been implicated in metabolic syndrome

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Table 1

Statin benefit groups

Group	Statin-therapy options
Clinical ASCVD (history of myocardial infarction, acute coronary syndrome, transient ischemic attack, or peripheral artery disease)	Age <75: High-intensity therapy
	Age >75 or unable to tolerate high-intensity therapy: Moderate-intensity therapy
LDL-C >190 mg/dL	High-intensity therapy
Type 1 or 2 diabetes mellitus, age 40 to 75	Moderate-intensity therapy
	10-year ASCVD risk is ≥7.5%: High-intensity therapy
Estimated 10-year ASCVD risk ≥7.5% using the Pooled Cohort Equation	Moderate-intensity or high-intensity therapy

ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol

to address dyslipidemia, which is one component of metabolic syndrome.[16,17]

Some of the greatest changes seen with the latest blood cholesterol guidelines include:

- focus on atherosclerotic cardiovascular disease (ASCVD) risk reduction to identify 4 statin benefit groups
- transition away from treating to a target LDL value

Clinical Point

Current literature lacks information regarding statin use for overall prevention of metabolic syndrome

Table 2

Levels of intensity of statin therapy

Intensity	Expected LDL-C-lowering capacity	Statin
Low	LDL-C expected to decrease <30% from baseline	Fluvastatin, 20 to 40 mg/d Lovastatin, 20 mg/d Pitavastatin, 1 mg/d Pravastatin, 10 to 20 mg/d Simvastatin, 10 mg/d
Moderate	LDL-C expected to decrease 30% to <50%	Atorvastatin, 10 to 20 mg/d Fluvastatin, 80 mg/d Fluvastatin XL, 80 mg/d Lovastatin, 40 mg/d Pitavastatin, 2 to 4 mg/d Pravastatin, 40 to 80 mg/d Rosuvastatin, 5 to 10 mg/d Simvastatin, 20 to 40 mg/d
High	LDL-C expected to decrease >50%	Atorvastatin, 40 to 80 mg/d Rosuvastatin, 20 to 40 mg/d

LDL-C: low-density lipoprotein cholesterol

Clinical Point

Whenever a patient is started on statin therapy, order a liver function test and lipid profile at baseline

- use of the Pooled Cohort Equation to estimate 10-year ASCVD risk, rather than the Framingham Risk Score.

Placing patients in 1 of 4 statin benefit groups

Unlike the 2002 National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines, the latest guidelines have identified 4 statin treatment benefit groups:

- patients with clinical ASCVD (including those who have had acute coronary syndrome, stroke, or myocardial infarction, or who have stable or unstable angina, transient ischemic attacks, or peripheral artery disease, or a combination of these findings)
- patients with LDL-C >190 mg/dL
- patients age 40 to 75 with type 1 or type 2 diabetes mellitus
- patients with an estimated 10-year ASCVD risk of ≥7.5% that was estimated using the Pooled Cohort Equation.[16,17]

Table 1 (***page 63***) represents each statin benefit group and recommended treatment options.

Selected statin therapy for each statin benefit group is further delineated into low-, moderate-, and high-intensity therapy. Intensity of statin therapy represents the expected LDL lowering capacity of selected statins. Low-intensity statin therapy, on average, is expected to lower LDL-C by <30%. Moderate-intensity statin therapy is expected to lower LDL-C by 30% to <50%. High-intensity statin therapy is expected to lower LDL-C by >50%.

When selecting treatment for patients, it is important to first determine the statin benefit group that the patient falls under, and then select the appropriate statin intensity. The categorization of the different statins based on LDL-C lowering capacity is described in ***Table 2***.

Whenever a patient is started on statin therapy, order a liver function test and lipid profile at baseline. Repeat these tests 4 to 12 weeks after statin initiation, then every 3 to 12 months.

Transition away from treating to a target LDL-C goal

ATP III guidelines suggested that elevated LDL was the leading cause of coronary heart disease and recommended therapy with LDL-lowering medications.[18] The

panel that developed the 2013 lipid guideline concluded that there was no evidence that showed benefit in treating to a designated LDL-C goal.[16,17] Arguably, treating to a target may lead to overtreatment in some patients and under-treatment in others. Treatment is now recommended based on statin intensity.

Using the Pooled Cohort Equation

In moving away from the Framingham Risk Score, the latest lipid guidelines established a new calculation to assess cardiovascular disease. The Pooled Cohort Equation estimates the 10-year ASCVD risk for patients based on selected risk factors: age, sex, race, lipids, diabetes, smoking status, and blood pressure. Although other potential cardiovascular disease risk factors have been identified, the Pooled Cohort Equation focused on those risk factors that have been correlated with cardiovascular disease since the 1960s.[16,17,19] The Pooled Cohort Equation is intended to (1) more accurately identify higher-risk patients and (2) assess who would best benefit from statin therapy.

Recommended lab tests and subsequent treatment

With the new lipid guidelines in place to direct dyslipidemia treatment and a better understanding of how certain antipsychotics impact lipid values, the next step is monitoring parameters for patients. Before initiating antipsychotic treatment and in accordance with the 2014 National Institute for Health and Care Excellence (NICE) guidelines, baseline measurements should include weight, waist circumference, pulse, blood pressure, fasting blood glucose, hemoglobin A_{1c}, blood lipid profile, and, if risperidone or paliperidone is initiated, prolactin level.[20] Additionally, patients should be assessed at baseline for any movement disorders as well as current nutritional status, diet, and level of physical activity.

Once treatment is selected on a patient-specific basis, weight should be measured weekly for the first 6 weeks, again at 12 weeks and 1 year, and then annually. Pulse and blood pressure should be obtained 12 weeks after treatment initiation and at 1 year. Fasting blood glucose, hemoglobin A_{1c}, and blood lipid levels should be collected 12 weeks after treatment onset, then at the 1-year mark.[20] These laboratory parameters should be measured annually while the patient is receiving antipsychotic treatment.

Alternately, you can follow the monitoring parameters in the more dated 2004 ADA consensus statement:

- **baseline assessment** to include BMI, waist circumference, blood pressure, fasting plasma glucose, fasting lipid profile, and personal and family history
- **BMI measured again** at 4 weeks, 8 weeks, 12 weeks, and then quarterly
- **12-week follow-up** measurement of fasting plasma glucose, fasting lipids, and blood pressure
- **annual measurement** of fasting blood glucose, blood pressure, and waist circumference.[12]

In addition to the NICE guidelines and the ADA consensus statement, use of the current lipid guidelines and the Pooled Cohort Equation to assess 10-year ASCVD risk should be obtained at baseline and throughout antipsychotic treatment. If you identify an abnormality in the lipid profile, you have several options:

Related Resource

- AHA/ACC 2013 Prevention Guidelines Tools CV Risk Calculator. https://professional.heart.org/professional/GuidelinesStatements/PreventionGuidelines/UCM_457698_Prevention-Guidelines.jsp.

Drug Brand Names

Aripiprazole • Abilify	Paliperidone • Invega
Asenapine • Saphris	Pitavastatin • Livalo
Atorvastatin • Lipitor	Pravastatin • Pravachol
Clozapine • Clozaril	Quetiapine • Seroquel
Fluvastatin • Lescol	Risperidone • Risperdal
Iloperidone • Fanapt	Rosuvastatin • Crestor
Lovastatin • Mevacor	Simvastatin • Zocor
Lurasidone • Latuda	Ziprasidone • Geodon
Olanzapine • Zyprexa	

Clinical Point

The Pooled Cohort Equation is intended to (1) more accurately identify higher-risk patients and (2) assess who would best benefit from a statin

- Decrease the antipsychotic dosage
- Switch to an antipsychotic considered to be less risky
- Discontinue therapy
- Implement diet and exercise
- Refer the patient to a dietitian or other clinician skilled in managing overweight or obesity and hyperlipidemia.[21]

Furthermore, patients identified as being in 1 of the 4 statin benefit groups should be started on appropriate pharmacotherapy. Non-statin therapy as adjunct or in lieu of statin therapy is not considered to be first-line.[16]

Clinical Point

Patients identified as being in 1 of the 4 statin benefit groups should be started on appropriate pharmacotherapy

CASE CONTINUED

After reviewing Mr. W's lab results, you calculate that he has a 24% ten-year ASCVD risk, using the Pooled Cohort Equation. Following the treatment algorithm for statin benefit groups, you see that Mr. W meets criteria for high-intensity statin therapy. You stop olanzapine, switch to risperidone, 1 mg/d, and initiate atorvastatin, 40 mg/d. You plan to assess Mr. W's weight weekly over the next 6 weeks and order a liver profile and lipid profile in 6 weeks.

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