How to assess and manage high cholesterol in patients with mental illness

Statins, lifestyle changes could reduce total cholesterol and cardiovascular risk

High serum cholesterol is a leading cause of heart attack and stroke, yet remains one of the most under-screened and undertreated modifiable risk factors in persons with mental illness. Well tolerated and effective treatments can considerably lower the risk of cardiovascular events, and should be offered to psychiatric patients who are at high risk, while considering possible adverse effects and potential interactions between psychotropics and medications used to lower cholesterol.

Systematic lowering of total cholesterol and, particularly, atherogenic low-density lipoprotein (LDL) and non-high density lipoprotein (HDL) cholesterol, results in consistent and significant reduction in risk of cardiovascular events in persons at risk for developing cardiovascular disease (CVD) and in preventing recurrence of these events. Even individuals who have relatively lower levels of total cholesterol but are at high risk (such as if a cardiovascular event has occurred) could reduce their CVD risk (known as secondary prevention) through lipid lowering therapies.

Adults with psychiatric illness shoulder a disproportionate burden of CVD morbidity and mortality, especially those with severe mental illness (SMI, schizophrenia, schizoaffective disorder, bipolar disorder, treatment-resistant depression). Among modifiable CVD risk factors, dyslipidemia has the highest rates of missed screenings and treatment within psychiatric populations. In one analysis, up to 90% of adults with SMI and identified lipid disorders did not...
Dyslipidemia

**Clinical Point**

Many adults receiving care in behavioral health settings qualify for screening at least every 5 years, if not more frequently.

receive treatment. Persons with SMI generally do not receive guideline-concordant, systematic quality preventive care, which contributes to a widening mortality gap for this population.

This review aims to provide clinicians with practical guidance on the assessment and management of high cholesterol to improve recognition and treatment, lower CVD risk, and reduce this observed mortality gap.

**Screening and diagnosis**

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) released updated guidelines on diagnosing and managing high cholesterol to reduce CVD risk. These guidelines focus on updated 10-year CVD risk assessment models with treatment goals reliant on adherence to statin therapy rather than pre-specified cholesterol targets listed in previous guidelines.

Updates to assessment and treatment guidelines have removed some barriers to screening and diagnosing high cholesterol—namely, fasting lipid panels are no longer required to determine 10-year CVD risk and initiate treatment. For adults taking a second-generation antipsychotic that is associated with weight gain and metabolic syndrome, experts generally recommend yearly non-fasting lipid panels.

The United States Preventive Services Task Force recommends screening:

- men age ≥35 at average risk for CVD every 5 years
- women age ≥45 every 5 years
- adults as young as age 20 who have accelerated risk factors, such as cigarette smoking and hypertension
- adults with a family history of heart attack or stroke in male first-degree relative age ≥50 and female first-degree relatives age ≥60.

Many adults receiving care in behavioral health settings, regardless of their medication regimen, qualify for screening at least every 5 years, if not more frequently. Although statin treatment before age 40 is less beneficial and likely not necessary for primary prevention, monitoring could help identify alternative therapies and prioritize more intensive diet and lifestyle modifications.

At a routine office visit, clinicians can collect vital signs, record smoking status, and reconcile all medications, which provides the data needed to calculate a patient’s 10-year CVD risk. Coupled with laboratory testing, which includes a non-fasting total cholesterol, HDL, and hemoglobin A1c (representative of a 3-month blood sugar average, ≥6.5% is diagnostic of type 2 diabetes mellitus [T2DM]), all data points can be entered into online risk calculators (search “ASCVD risk calculator” or visit [http://tools.acc.org/ASCVD-Risk-Estimator](http://tools.acc.org/ASCVD-Risk-Estimator) to access the ACC/AHA risk calculator). Persons scoring >20% 10-year risk are considered at extremely high risk, and are in the same risk category as adults with existing CVD or who have had a cardiovascular event. Persons at <5% 10-year risk generally are considered low risk, and primary prevention with a statin medication is not indicated.

**Treatment and management**

Dietary modification and lifestyle changes (exercise, quitting smoking), lowering

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td>Clinical data necessary to calculate 10-year CVD risk</td>
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<tr>
<td>---</td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td><strong>Race: white, African American, other</strong></td>
</tr>
<tr>
<td><strong>Smoking status (Yes/No)</strong></td>
</tr>
<tr>
<td><strong>HDL cholesterol (mg/dL)</strong></td>
</tr>
<tr>
<td><strong>Total cholesterol (mg/dL)</strong></td>
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<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
</tr>
<tr>
<td><strong>Treatment for hypertension (Yes/No)</strong></td>
</tr>
<tr>
<td><strong>Diabetes (Yes/No)</strong></td>
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</table>

CVD: cardiovascular disease; HDL: high-density lipoprotein
high cholesterol with medications, and switching from highly metabolically active drugs to less metabolically active ones can help lower total cholesterol in patients at risk of CVD.

**Statins**
HMG-CoA reductase inhibitors (statins) consistently reduce total cholesterol and non-HDL cholesterol by 30% to 50%, depending on drug and dosage (potency, listed as low, medium, and high). Not all statins are equally effective at lowering cholesterol; some are more potent than others (Table 2).

Individuals are eligible for statin therapy based on their level of CVD risk. Persons at higher risk generally benefit from greater intensity statin treatment and cholesterol reduction; highest intensity statin regimens can lower total cholesterol by approximately 50%.

There are 4 statin eligibility classes (Table 3, page 56). Most adults fall into category 4: 10-year risk of >7.5% and needing primary prevention. In addition to removing specific LDL targets as therapy goals, calculation of this risk percentage and the specific cut-off values have been the most controversial aspects of the new cholesterol guidelines. Most experts agree that, in adults age 40 to 75, 10-year risk >10% indicates daily statin use as tolerated for primary prevention, and 10-year risk <5% does not warrant statin use. Recent large studies have validated these new techniques for calculating risk, and found them to be beneficial in potential for cost savings and risk classification.

**Clinical Point**
Statins have been associated with depression in case series, but larger analyses have not confirmed this association.

<table>
<thead>
<tr>
<th>Intensity class</th>
<th>LDL cholesterol effect</th>
<th>Drug, dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;30% reduction</td>
<td>Simvastatin, 10 mg, Pravastatin, 10 to 20 mg, Lovastatin, 20 mg, Fluvastatin, 20 to 40 mg, Pitavastatin, 1 mg</td>
<td>Lower potency is generally better tolerated with fewer side effects</td>
</tr>
<tr>
<td>Medium</td>
<td>30% to 50% reduction</td>
<td>Atorvastatin, 10 mg, Rosuvastatin, 5 to 10 mg, Simvastatin, 20 to 40 mg, Pravastatin, 40 to 80 mg, Lovastatin, 40 mg bid, Pitavastatin, 2 to 4 mg</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>&gt;50% reduction</td>
<td>Atorvastatin, 40 to 80 mg, Rosuvastatin, 20 to 40 mg</td>
<td>Higher potency may have more side effects, may be dosed regardless of time of day</td>
</tr>
</tbody>
</table>

LDL: low-density lipoprotein
fewer drug-drug interactions in patients with psychiatric illness taking common psychotropic therapies, but is not considered a high-potency statin and might not confer adequate benefits in CVD risk reduction.

Contraindications. Statins are pregnancy category X, and generally should not be prescribed for women of childbearing age without intensive counseling. The most notable adverse effects for statins include muscle aches and cramps (myalgia), but generally are not severe. If encountered, consider checking a serum creatinine kinase (CK) level, and if significantly elevated above 10 times the upper limit, stopping statin therapy would be advised. If the CK is only mildly elevated, consider lowering the dosage or switching to a lower potency agent. Lovastatin and pravastatin generally are better tolerated than atorvastatin and are considered lower potency (Table 2, page 55).

Statins can be safely used in the presence of liver conditions, such as hepatitis C and alcohol use, although periodic monitoring of transaminase levels is not necessary.

Alternate lipid-lowering pharmacotherapies unfortunately have fallen out of favor. Fibrates, niacin, ezetimibe, and omega-3 fatty acids once were recommended to lower triglycerides or raise HDL cholesterol levels, but since have been shown to have little effect on cardiovascular morbidity or mortality. Adding further medications, other than statins, to lower cholesterol values to pre-defined targets is not the current standard of care.

High triglyceride concentrations traditionally have been addressed directly, but failure to improve CVD mortality or morbidity by treating triglycerides alone has resulted in refocusing clinical efforts in dyslipidemia management on atherogenic cholesterol, including LDL and non-HDL fractions. Non-fasting triglycerides >500 mg/dL should be retested when fasting, and levels that remain >500 mg/dL could place the patient at risk for pancreatitis and might warrant intervention with fibrates at that time. This scenario is not common, and referral to a primary care physician or endocrinologist may be warranted.

<table>
<thead>
<tr>
<th>Category</th>
<th>Clinical characteristic</th>
<th>Prevention type</th>
<th>Age range</th>
<th>Statin intensity</th>
<th>Follow-up/notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Presence of ASCVD a</td>
<td>Secondary</td>
<td>21 to 75</td>
<td>High, 50% reduction</td>
<td>Observe for reduction of 50%, ideally LDL &lt;100 mg/dL</td>
</tr>
<tr>
<td>2</td>
<td>Serum LDL &gt;190 mg/dL, non-HDL &gt;220 mg/dL</td>
<td>Primary</td>
<td>21 to 75</td>
<td>High</td>
<td>Workup secondary causes</td>
</tr>
<tr>
<td>3</td>
<td>Type 2 diabetes mellitus</td>
<td>Primary</td>
<td>40 to 75</td>
<td>Moderate to high b</td>
<td>Monitor A1c, intensify diabetes management</td>
</tr>
<tr>
<td>4</td>
<td>10-year ASCVD risk &gt;7.5%</td>
<td>Primary</td>
<td>40 to 75</td>
<td>Moderate</td>
<td>Ensure adherence, start with low-potency potentially</td>
</tr>
</tbody>
</table>

aAtherosclerotic cardiovascular disease: abdominal aortic aneurysm, peripheral arterial disease, symptomatic carotid artery stenosis, prior evidence of coronary artery disease (myocardial infarction, ischemic stroke)
bHigh intensity if 10-year risk >7.5%; moderate otherwise

ASCVD: atherosclerotic cardiovascular disease; HDL: high-density lipoprotein; LDL: low density lipoprotein
Many patients would discover that their 10-year ASCVD risk would fall under the level needed for statin therapy if they could stop smoking.

Lifestyle changes
With or without statin therapies, diet and lifestyle changes are the cornerstone of healthy living and should be encouraged in all patients. Most overweight or obese patients will benefit from exercise and dietary modifications. Such interventions have shown potential for reducing total cholesterol and non-HDL and HDL cholesterol, but rarely are these interventions sustained long enough to produce meaningful reduction in CVD risk through lipid lowering. Diets rich in isocaloric tree nuts and red-yeast rice extract—a form of a statin—have shown promise in reducing cholesterol, but typically take excessive personal resources and are not sustained to the degree necessary to reduce CVD risk over time. Non-fasting laboratory tests reveal hemoglobin A1c of 5.9%, total cholesterol of 235 mg/dL, low high-density lipoprotein (HDL) cholesterol (35 mg/dL), elevated triglycerides (268 mg/dL), and elevated low-density lipoprotein cholesterol (143 mg/dL; which might be low due to non-fasting testing). His hemoglobin A1c is elevated, but not in the diabetic range of >6.5%. Mr. R has no history of heart attack or stroke.

Switching pharmacotherapies
Switching antipsychotic agents from highly metabolically risky compounds, such as risperidone and olanzapine, to less metabolically active compounds, such as aripiprazole, ziprasidone, or haloperidol, have been associated with improvements in lipid profiles. Clinicians must weigh the potential benefits of switching therapies against the risk of psychiatric destabilization and long-term adherence, keeping in mind that changes in lipids seen with switching could be mild (approximately 10% reduction in total cholesterol).

Summing up
Cholesterol management is considered part of a program to systematically lower CVD risk. Statin therapy usually is indicated for life, or until the age of 75, at which point treatment risks and benefits change because of life expectancy. Other components of CVD risk reduction

CASE: Reducing risk, but challenges remain
Mr. R age 43, is a single, white male with a history of schizoaffective disorder, bipolar subtype, obesity, hypertension, and chronic low-back pain. He has been stable on a long-acting injectable risperidone, 25 mg every 2 weeks, and valproic acid, 1,250 mg/d, and takes lisinopril, 20 mg/d, and tramadol, 50 mg, as needed. His body mass index is 36.8 kg/m² and blood pressure is 148/93 mm Hg. He has nicotine stains on his fingers and beard from smoking 2 packs of cigarettes a day.

Non-fasting laboratory tests reveal hemoglobin A1c of 5.9%, total cholesterol of 235 mg/dL, low high-density lipoprotein (HDL) cholesterol (35 mg/dL), elevated triglycerides (268 mg/dL), and elevated low-density lipoprotein cholesterol (143 mg/dL; which might be low due to non-fasting testing). His hemoglobin A1c is elevated, but not in the diabetic range of >6.5%. Mr. R has no history of heart attack or stroke.

An online tool estimates his 10-year risk of cardiovascular events to be 13.8%, indicating statin category 4 (Table 3). At the next visit, you discuss the need to reduce dietary intake of saturated fats and cholesterol, increase his intake of fiber, establish a regular exercise routine, and stop smoking. He starts taking pravastatin, 10 mg/d.

In 3 months, Mr. R’s total cholesterol is 188 mg/dL, a 20% reduction. He is tolerating the statin well, therefore pravastatin is increased to 20 mg/d to achieve approximately a 30% overall reduction in cholesterol. The next month, his total cholesterol is 155 mg/dL and he has cut back on smoking and fried foods, which has reduced his CVD risk by 50%, to 6.7% (his HDL did not change considerably). You discuss the need to continue pravastatin unless he can lose a significant amount of weight, stop smoking, and reduce his overall 10-year risk of cardiovascular events to <5%.
include a focus on blood pressure control, smoking cessation, T2DM management, and weight loss. Tracking lipid profiles over time to ensure broad targets of 30% to 50% reduction in total cholesterol, approximately 3 months after initiation and yearly thereafter, can help ensure adherence to therapy. With systematic lowering of modifiable CVD risk factors, we can hope to gradually improve the quality of life for our patients with mental illnesses (see the Box, page 57, for a case example illustrating successful use of these strategies).

References


Bottom Line

High cholesterol is a leading risk factor for cardiovascular disease, including heart attack and stroke, which contribute to increased morbidity in psychiatric patients. Consider using online tools to evaluate your patients’ 10-year risk of cardiovascular events. Reducing total cholesterol, often with the help of statin medications, significantly reduces the risk of subsequent events in adults at extremely high risk of cardiovascular disease.

Clinical Point
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