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

Statins, lifestyle changes could reduce total cholesterol and cardiovascular risk

WILDPIXEL

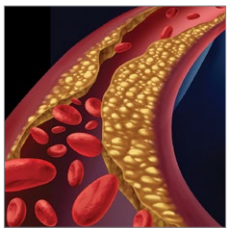
Erik R. Vanderlip, MD, MPH
Assistant Professor
Departments of Psychiatry and Medical Informatics
University of Oklahoma School of Community Medicine
Tulsa, Oklahoma

High serum cholesterol is a leading cause of heart attack and stroke,[1,2] 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 reoccurrence of these events.[1,3,4] 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.[5,6]

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).[7-9] 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

Disclosure
The author reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.



Dyslipidemia

Clinical Point

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

Discuss this article at www.facebook.com/CurrentPsychiatry

Table 1

Clinical data necessary to calculate 10-year CVD risk

Age
Sex
Race: white, African American, other
Smoking status (Yes/No)
HDL cholesterol (mg/dL)
Total cholesterol (mg/dL)
Systolic blood pressure (mm Hg)
Treatment for hypertension (Yes/No)
Diabetes (Yes/No)

CVD: cardiovascular disease; HDL: high-density lipoprotein

receive treatment.[10] Persons with SMI generally do not receive guideline-concordant, systematic quality preventive care, which contributes to a widening mortality gap for this population.[11,12]

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.[1] These guidelines focus on updated 10-year CVD risk assessment models with treatment goals reliant on adherence to statin therapy rather than prespecified cholesterol targets listed in previous guidelines.[13]

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.[14] For adults taking a second-generation antipsychotic that is associated with weight gain and metabolic syndrome, experts generally recommend yearly non-fasting lipid panels.[6,14]

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[15]
- 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 (***Table 1***). Coupled with laboratory testing, which includes a nonfasting total cholesterol, HDL, and hemoglobin A_{1c} (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 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 2

Statin medications by dose and treatment intensity

Intensity class	LDL cholesterol effect	Drug, dosage	Notes
Low	<30% reduction	Simvastatin, 10 mg Pravastatin, 10 to 20 mg Lovastatin, 20 mg Fluvastatin, 20 to 40 mg Pitavastatin, 1 mg	Lower potency is generally better tolerated with fewer side effects
Medium	30% to 50% reduction	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	
High	>50% reduction	Atorvastatin, 40 to 80 mg Rosuvastatin, 20 to 40 mg	Higher potency may have more side effects, may be dosed regardless of time of day

LDL: low-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***).[16]

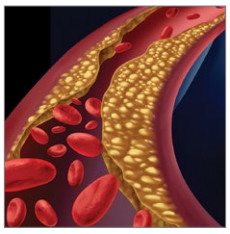
Individuals are eligible for statin therapy based on their level of CVD risk. Persons at higher risk generally benefit from greater intensity statin treatment and cholesterol reduction; highest intensity statin regimens can lower total cholesterol by approximately 50%.

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.[17,18]

Considerations in psychiatric patients. Statins have been associated with depression in case series, but larger analyses have not confirmed this association.[19] Emerging evidence has identified a potential correlation between statin use and accelerated onset of T2DM, but the absolute risk is relatively low and most experts continue to recommend statin therapy despite this potential risk.[13] Many statins, including atorvastatin, are available as a generic and can be taken once daily. Some, such as simvastatin, have notable interactions with commonly prescribed psychotropics including risperidone and quetiapine. Pravastatin is dually excreted by the liver and kidneys and may have

Clinical Point

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



Dyslipidemia

Table 3

Statin eligibility classes

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

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

ASCVD: atherosclerotic cardiovascular disease; HDL: high-density lipoprotein; LDL: low density lipoprotein

Clinical Point

The most notable adverse effects for statins include muscle aches and cramps (myalgia), but generally are not severe

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 recommended. For adults in the general population without liver disease, regular 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.[20] 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.

Box

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/m^2 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 A_{1c} 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 A_{1c} 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%.

Clinical Point

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.[21] Similarly, regular exercise routines can help lower overall cholesterol numbers, but rarely reduce total cholesterol by >10%.

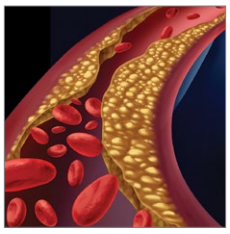
Because individuals with SMI smoke at a higher rate than the general population, it should be noted that smoking cessation is associated with a reduction in total cholesterol and a trial of smoking cessation therapy is warranted before initiating a statin medication for primary prevention of CVD. Many patients would discover that their 10-year ASCVD risk would fall under the level needed for statin therapy if they could successfully stop smoking.

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.[22-24] 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



Dyslipidemia

Related Resources

- American College of Cardiology. Dyslipidemia. www.acc.org/clinical-topics/dyslipidemia.
- Koch J, Thomas CJ. Using lipid guidelines to manage metabolic syndrome for patients taking an antipsychotic. Current Psychiatry. 2016;15(7):59,62-66.

Drug Brand Names

Aripiprazole • Abilify
Atorvastatin • Lipitor
Ezetimibe • Zetia
Fluvastatin • Lescol
Haloperidol • Haldol
Lisinopril • Prinivil, Zestril
Lovastatin • Mevacor, Altoprev
Olanzapine • Zyprexa
Pravastatin • Pravachol
Pitavastatin • Livalo
Pravastatin • Pravachol
Risperidone • Risperdal
Rosuvastatin • Crestor
Simvastatin • Zocor
Tramadol • Ultram
Valproic acid • Depakote, Depakene
Ziprasidone • Geodon

Clinical Point

Cholesterol management is considered part of a program to systematically lower CVD risk

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

1. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 suppl B):S1-S45.
2. LaRosa JC, Hunninghake D, Bush D, et al. The cholesterol facts. A summary of the evidence relating dietary fats, serum cholesterol, and coronary heart disease. A joint statement by the American Heart Association and the National Heart, Lung, and Blood Institute. The Task Force on Cholesterol Issues, American Heart Association. Circulation. 1990;81(5):1721-1733.
3. Albert MA, Glynn RJ, Fonseca FA, et al. Race, ethnicity, and the efficacy of rosuvastatin in primary prevention: the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. Am Heart J. 2011;162(1):106-114.e2.
4. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013;(1):CD004816. doi: 10.1002/14651858.CD004816.pub5.
5. Gaziano JM, Gaziano TA. What's new with measuring cholesterol? JAMA. 2013;310(19):2043-2044.
6. Emerging Risk Factors Collaboration; Di Angelantonio E, Sarwar N, Perry P, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302(18):1993-2000.
7. Crump C, Sundquist K, Winkleby MA, et al. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. JAMA Psychiatry. 2013;70(9):931-939.
8. Crump C, Winkleby MA, Sundquist K, et al. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. Am J Psychiatry. 2013;170(3):324-333.
9. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states [published online March 15, 2006]. Prev Chronic Dis. 2006;3(2):A42.
10. Nasrallah HA, Meyer JM, Goff DC, et al. Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: data from the CATIE schizophrenia trial sample at baseline. Schizophr Res. 2006;86(1-3):15-22.
11. Osby U, Correia N, Brandt L, et al. Time trends in schizophrenia mortality in Stockholm county, Sweden: cohort study. BMJ. 2000;321(7259):483-484.
12. Mitchell AJ, Lord O. Do deficits in cardiac care influence high mortality rates in schizophrenia? A systematic review and pooled analysis. J Psychopharmacol. 2010;24(suppl 4):69-80.
13. Ganda OP. Deciphering cholesterol treatment guidelines: a clinician's perspective. JAMA. 2015;313(10):1009-1010.
14. Vanderlip ER, Chwastiak LA, McCarron RM. Integrated care: nonfasting screening for cardiovascular risk among individuals taking second-generation antipsychotics. Psychiatr Serv. 2014;65(5):573-576.
15. U.S. Preventive Services Task Force. Lipid disorders in adults (cholesterol, dyslipidemia). http://www.uspreventiveservicestaskforce.org/uspstf/uspschol.htm. Published June 2008. Accessed October 12, 2016.

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.

16. Cupp M. Characteristics of the various statins. Pharmacist's Letter. 2012;28(6):280606.
17. Pursnani A, Massaro JM, D'Agostino RB Sr, et al. Guideline-based statin eligibility, coronary artery calcification, and cardiovascular events. JAMA. 2015; 314(2):134-141.
18. Pandya A, Sy S, Cho S, et al. Cost-effectiveness of 10-year risk thresholds for initiation of statin therapy for primary prevention of cardiovascular disease. JAMA. 2015; 314(2):142-150.
19. You H, Lu W, Zhao S, et al. The relationship between statins and depression: a review of the literature. Expert Opin Pharmacother. 2013;14(11):1467-1476.
20. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366(9500):1849-1861.
21. Kelly RB. Diet and exercise in the management of hyperlipidemia. Am Fam Physician. 2010;81(9): 1097-1102.
22. Erhardt L. Cigarette smoking: an undertreated risk factor for cardiovascular disease. Atherosclerosis. 2009;205(1):23-32.
23. Weiden PJ. Switching antipsychotics as a treatment strategy for antipsychotic-induced weight gain and dyslipidemia. J Clin Psychiatry. 2007;68(suppl 4): 34-39.
24. Stroup TS, McEvoy JP, Ring KD, et al; Schizophrenia Trials Network. A randomized trial examining the effectiveness of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk: comparison of antipsychotics for metabolic problems (CAMP). Am J Psychiatry. 2011;168(9): 947-956.

Current PSYCHIATRY
CurrentPsychiatry.com

Clinical Point

Statin therapy usually is indicated for life, or until the age of 75, at which point treatment risks and benefits change