A growing body of literature examining the putative links among cholesterol, mood disorders, and suicide has produced inconsistent findings and unclear clinical implications that may leave psychiatrists unsure of how to interpret the data. Understanding cholesterol’s role in mood disorders may be relevant to the 2 primary causes of excess deaths in patients with mood disorders: suicide and vascular disease.1

Plausible links
In the early 1990s several studies suggested a link between low cholesterol (<160 mg/dL) and unnatural deaths, including suicide.2-4 Follow-up studies confirmed associations between low cholesterol and suicide attempts, especially violent ones.5 These associations are compelling given the neurobiologic effects of cholesterol, such as a net reduction of serotonergic function (Box 1, page 18). Low cholesterol may predispose an individual to aggression, impulsivity, and violence (Table 1, page 19).6 Many studies have found that patients with mood disorders have lower cholesterol levels;7 however, other research suggests they are at increased risk of hyperlipidemia, typically hypertriglyceridemia rather than hypercholesterolemia.8

Depression. Several studies have shown an association between low cholesterol and depressive symptoms, although this finding has not been replicated in Asian subjects.9,10 Patients with manic or mixed syndromes...
Cholesterol and depression

Clinical Point
Current evidence does not support considering low serum cholesterol a risk factor for suicide

have been found to have lower serum cholesterol, and individuals with major depression and bipolar disorder have lower cholesterol levels in the brain compared with healthy controls. Some studies have observed higher total cholesterol levels after patients receive pharmacotherapy for major depressive symptoms. These findings have led to speculation that low serum cholesterol in patients with mood disorders is partially a state-dependent effect of depressive illness.

Suicide. Cohort, case-control, and cross-sectional studies have linked low cholesterol to an increased risk of suicide. Individuals who attempt suicide by violent means have lower cholesterol compared with those who use less violent methods. A meta-analysis found statistically significant correlations between low cholesterol and future or past suicidal behavior; however, low cholesterol explained <0.01% of suicidal behavior. Studies comparing cholesterol levels of individuals following violent vs nonviolent suicide attempts have demonstrated stronger associations.

Assessing suicide risk. Current evidence does not support considering low serum cholesterol a risk factor for suicide. One study used cholesterol as a clinical predictor of suicide, but this model has not been prospectively validated. As a whole, the evidence does not suggest that cholesterol levels explain a substantial portion of suicidal behaviors.

Effects of lipid-lowering agents
If there is a causal relationship between low cholesterol and mood disorders, then it stands to reason that using cholesterol-lowering drugs would increase the risk of depression and suicide. However, the data do not support that conclusion.

Many case reports have documented adverse psychiatric reactions to statins, including depression, suicidality, emotional lability, agitation, irritability, anxiety, panic, and euphoria. In an early analysis of primary prevention trials, patients receiving cholesterol-lowering treatment—mainly non-statins—were estimated to have twice the risk of death by suicide or violence compared with controls. However, a more recent meta-analysis of larger clinical trials of lipid-lowering agents including statins and observational studies did not reveal an association between lipid-lowering medications and suicide.
In a large case-control study, statin users had a lower risk of depression (adjusted odds ratio [OR] 0.4, 95% confidence interval [CI], 0.2 to 0.9) than patients taking non-statin lipid-lowering drugs (adjusted OR 1.0, 95% CI, 0.5 to 2.1).\(^1\) However, statins reduced cholesterol more (30% to 50%) than non-statin drugs (10% to 20%). A clinical trial of >1,000 patients with stable coronary artery disease treated with pravastatin—an HMG-CoA reductase inhibitor with low lipophilicity that is less likely than other statins to cross the blood-brain barrier—revealed no changes in self-reported anger, impulsiveness, anxiety, or depression.\(^2\)

This study did not exclude patients with psychiatric illness—who are at greatest risk of suicide—but other trials of lipid-lowering drugs did.\(^3\) As a result, the effects of lipid-lowering medications on psychiatric patients are unclear. A clinical trial is underway to assess the effects of pravastatin (low lipophilicity), simvastatin (high lipophilicity), or placebo on mood, sleep, and aggression.\(^4\)

**Low cholesterol: State or trait?**

Much of the research linking low cholesterol, mood disorders, and suicidality could be confounded by depressed mood leading to reduced serum cholesterol. There has been considerable debate about whether low cholesterol predisposes patients to suicide or if depression independently leads to poor nutrition and therefore low cholesterol and increased suicide risk.\(^5\,^6\)

Some researchers have suggested that depression lowers cholesterol and increases risk of suicide,\(^7\) but study designs have limited the ability to discern the directionality of the relationship. Attempts to control for depression-related malnourishment and other potential confounders are needed to better understand these relationships.

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**Clinical Point**

Research linking low cholesterol and suicidality could be confounded by depressed mood leading to reduced serum cholesterol.

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**Table 1**

Psychiatric features associated with low cholesterol\(^2\)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Syndromes</th>
<th>Behaviors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety, depressed mood, emotional lability, euphoria, impulsivity, irritability, suicidal ideation, aggression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia nervosa, bipolar disorder, borderline personality disorder, major depressive disorder, seasonal affective disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide and suicide attempts, violence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^*\)Small studies have suggested possible relationships with dissociative and panic disorders

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Cholesterol and depression

trition and weight loss—which lowers total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)—suggest the association may be independent of these variables. These findings suggest that cholesterol may be considered a trait marker and is not entirely state-dependent. However, multiple, large, long-term randomized controlled trials have not shown increased depression and suicide with use of lipid-lowering agents in healthy populations.

The Figure (page 19) illustrates known epidemiologic associations of low cholesterol, low serotonergic function, and suicide and contrasts conceptual models of cholesterol as a state and a trait marker. A case can be made for cholesterol as both a state and a trait marker, and these models could overlap, with depression-induced decreases in cholesterol further mediating changes in serotonergic function and related behavioral sequelae.

Improving cardiac health

Limited epidemiologic studies suggest that patients with mood disorders may have lower levels of total cholesterol and LDL-C, but higher rates of hypertriglyceridemia compared with the general population. Unfortunately, psychiatric patients—who may be at increased risk of developing cardiovascular disease—may be less likely to be screened and appropriately treated for lipid abnormalities. To address this disparity, consider assuming an active role in assessing and managing hyperlipidemia in your patients with...
mood disorders. Be aware of your patients’ lipid profile and ensure that they follow monitoring recommendations.

The National Cholesterol Education Program recommends screening all adults age >20 for hyperlipidemia every 5 years using measures of total cholesterol, LDL-C, HDL-C, and triglycerides. If LDL-C or triglycerides exceed target values (Table 2), appropriate management includes recommending lifestyle changes and pharmacotherapy (Box 2).

Patients should receive a fasting lipid profile before and 12 weeks after starting any antipsychotic and semiannually thereafter. Consider closely monitoring lipids when patients gain weight with psychotropics. Refer patients with hyperlipidemia to a primary care physician, but in the absence of such a provider, mental health clinicians who are familiar with treatment guidelines can manage these patients.

Closely monitor individuals with mood disorders for changes in behavior or mental status after starting a lipid-lowering agent. Consider discontinuing the drug if a patient develops an adverse reaction. If symptoms return after medication rechallenge, consider other management strategies such as an alternate lipid-lowering agent or re-emphasizing behavioral measures.

References
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Closely monitor individuals with mood disorders for changes in behavior or mental status after starting a lipid-lowering agent.

Low cholesterol has been associated with suicide, but not strongly or consistently enough to warrant routine use in suicide risk assessment. Lipid-lowering therapies do not appear to increase overall suicide risk. Patients with mood disorders are at higher risk of developing cardiovascular disease and should not be deprived of potentially life saving, lipid-lowering treatment, although close monitoring for adverse effects is warranted.

Related Resources


Drug Brand Names

- Ezetimibe - Zetia
- Pravastatin - Pravachol
- Simvastatin - Zocor

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