

Statins, Cholesterol Depletion-and Mood Disorders: What's the Link?

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serotonin-1A receptors may help explain the relationships between cholesterol levels and symptoms of anxiety and depression.

Shrivastava and colleagues¹ explored the effect of chronic cholesterol depletion induced by mevastatin on the function and dynamics of the human serotonin-1A receptors stably expressed in animal cells. Statins are competitive inhibitors of HMG-CoA reductase, the key rate-limiting enzyme in cholesterol biosynthesis.

"Our results show a significant reduction in the level of specific ligand binding and G-protein coupling to serotonin-1A receptors upon chronic cholesterol depletion, although the membrane receptor level is not reduced at all," they wrote. The effect of chronic cholesterol depletion on the ligand binding of serotonin-1A receptors is reversible.

In addition, the researchers found novel changes in receptor dynamics with chronic cholesterol depletion.

These results have broad implications in light of recent reports of anxiety and depression in patients receiving long-term statin therapy. CNS cholesterol levels are abnormally low in many people with mood disorders.

The same researchers had previously demonstrated that maintaining normal cholesterol levels is important for the function of neuronal serotonin receptors.

Cholesterol and psychiatric effects

"It has long been reported that total serum cholesterol levels are consistently lower in more severely depressed and more aggressive patients," said James Lake, MD, chair of the APA's Caucus on Complementary and Integrative Medicine, and visiting assistant professor of medicine at the Center for Integrative Medicine at the University of Arizona School of Medicine in Tucson. "Because of these findings, it has been suggested that total cholesterol might be a clinically useful biological marker for predicting the risk of suicide and that it may be of prognostic value in managing severely depressed patients."

Still, the relationship between serum cholesterol level and mood is complex, and "research findings to date are inconsistent," he added.

Research findings dating back to the 1990s show that serum cholesterol level, especially the HDL fraction, is significantly lower in many patients with major depressive disorder than in matched non-depressed individuals and that clinical improvement following antidepressant therapy is often associated with normalization of serum total cholesterol to higher levels.²⁻⁵ But more recent studies have failed to replicate these findings.⁶⁻⁸

With the emergence of statin drugs in the late 1970s and their widespread use, new questions arose about the possible link between mood and anxiety disorders and statins. In 2009, 211

million prescriptions for lipid- and cholesterol-lowering drugs, including statins, were dispensed in this country, according to IMSHealth Reports. The leading statin drugs include atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor, Altoprev), pravastatin (Pravachol), rosuvastatin calcium (Crestor), and simvastatin (Zocor).

Although statin drugs are generally well tolerated, there are mounting reports of adverse effects related to mood and sleep and cognitive performance; widespread reports of muscle aches, nausea, diarrhea, and constipation; and occasional reports of liver damage.

Individuals who take statins to lower their cholesterol sometimes display symptoms of irritability, anxiety, and depression; these symptoms are reported by their family members, caregivers, and coworkers. Some statin users themselves have reported adverse affects on such Web sites as www.statineffects.com, maintained by Beatrice Golomb, MD, PhD, associate professor of medicine, and her team at the University of California, San Diego, as well as www.askapatient.com, operated by Consumer Health Resource Group, LLC.

For more than a decade, Golomb and her team have researched the effects of statin medications.

"Some individuals taking statins report problems with anxiety and depression, but far more report problems with irritability and changes in personality," Golomb told *Psychiatric Times*.

"An analysis of 324 e-mails of individuals taking statins who reported adverse effects found about 30% reported mood changes (depression, anxiety, irritability)," she said.

In a survey of persons citing statin adverse effects, Golomb reported that nearly two-thirds (65%) of the 843 respondents endorsed increased anxiety or irritability and 32% endorsed an increase in depressive symptoms as part of the adverse-effect complex they attributed to statins.

"In 2004, we published a case series of 6 patients who were referred or self-referred with irritability and short temper on statin cholesterol-lowering drugs," Golomb said.

The patients completed a survey, providing information on the character of behavioral effect, time-course of onset, and recovery and relevant factors.⁹ In each case, the personality disruption, once evident, was sustained until statin use was discontinued, and it resolved promptly with drug cessation. In 4 cases, rechallenge with statins occurred and led to symptom recurrence. Manifestations of severe irritability, according to Golomb, included homicidal impulses, threats to others, and road rage.

Currently, Golomb and her team are preparing another case series involving 12 individuals who experienced problems with irritability, anxiety, or depression during statin therapy.

Lake and Golomb point out that lowering cholesterol levels

reduces morbidity and mortality from heart disease. However, statins fail to improve overall survival, except in middle-aged men with heart disease or high levels of inflammatory markers.

Practical Steps to Reduce Cholesterol and Improve Depressed Mood: Guidelines for Patients
Several modifications in diet and lifestyle can be made to reduce cholesterol and improve depressed mood:

? Exercise more. Exercise is known to increase HDL while lowering LDL levels.

? Stop smoking. The primary effect of smoking is lowering HDL.

? Avoid trans fats. Trans fats raise LDL and lower HDL.

? Follow a Mediterranean diet. Monounsaturated fats (eg, olive oil and avocados) increase HDL and lower LDL. Fruit, vegetable, and nut consumption favorably affect lipids and health.

? Eat foods containing omega-3 fatty acids. Fatty fish, such as sardines and salmon, contain omega-3 fats that raise HDL and lower LDL levels, but attention must be paid to mercury contamination and other chemicals that could reduce health benefits. In some randomized studies, omega-3 fatty acids have been reported to improve mood and reduce irritability/anger expression.

? Eat more whole grains. Whole grains contain dietary fiber and niacin, both of which raise HDL and lower

LDL.

? Increase sun exposure and increase vitamin D levels. Vitamin D increases HDL and increases levels of serotonin in the brain, which may affect depressive symptoms.

Hypotheses advanced

Several hypotheses have been advanced to explain the relationship between cholesterol, mood disorders, and violence, according to Lake.

Some researchers have suggested that dysregulation of normal serotonin activity may help explain a possible relationship between low cholesterol levels and violent death. For example, Steegmans and colleagues¹⁰ found that plasma serotonin concentrations are lower in untreated men with persistently low serum cholesterol concentrations (4 to 5 mmol/L or less) than in a reference group. This finding is consistent with the hypothesis that dysregulation of serotonin activity may explain the observed relationship between low cholesterol concentrations and behavioral changes and violent death, Lake said.

Sarchiapone and colleagues,¹¹ among others, have hypothesized that low cholesterol levels indirectly lead to reduced brain serotonin because of the requirement of adequate cholesterol in nerve cell membranes to maintain the functional integrity of serotonin receptors, Lake added.

Golomb and associates¹² also have extensively researched the issues of low cholesterol levels, serotonin, and violence. "We hypothesized, tested, and found support for a means by which lower cholesterol may, through links to insulin sensitivity and there-by to serotonin, be associated with increased accidents and suicides," she said.

Findings from some human clinical trials, however, raise questions about the hypothesis. Lake cited a literature review involving statins and mental health in which the authors "found no statistically significant effect" of low serum cholesterol concentrations on psychological well-being.¹³ Could the type of statin make a difference regarding varying study results? It could, according to Lake.

Golomb's team, for example, found a difference. They tested 1016 healthy men and women for 6 months in a randomized, double-blind, placebo-controlled trial using 20 mg of the more lipophilic simvastatin, 40 mg of the hydrophilic pravastatin, or placebo.

"A significantly greater number of individuals taking simvastatin reported sleep problems than those taking either pravastatin or the placebo," Golomb said in her report at the American Heart Association meeting in 2007.¹⁴ "Those who reported much worse sleep while taking study medication also showed a significant adverse change in aggression scores," she added.

Some authors, according to Lake, postulate that lipophilic

statins may cause deleterious effects on mental health through an immunomodulatory mechanism. In contrast to non-lipophilic statins, the more lipophilic statins readily penetrate the blood-brain barrier, where they inhibit HMG-CoA reductase and suppress several cytokines (including interferon- γ , and interleukin [IL]-2 and IL-12), which results in lowering of tryptophan availability in the brain and decreased serotonin synthesis.

What are the practical implications? Lake offers this advice:

- Check cholesterol levels of severely depressed patients, especially those who are nonresponsive or only partially responsive to antidepressants.
- Address mental health issues possibly related to the use of certain cholesterol-lowering drugs.
- Have depressed patients being treated for elevated cholesterol levels work with their primary physician or cardiologist to regulate their total serum cholesterol to levels not significantly lower than 160 mg/dL while maintaining a desirable balance between HDL and LDL cholesterol. In some cases, this could involve substituting a different statin.

Lake said many of his depressed patients have low cholesterol levels secondary to statins and do not respond or only partially respond to antidepressants or evidence-based complementary and alternative medicine (CAM) therapies. He has these patients work with their primary physician to adjust

their statin dose or to consider alternatives to statins.

Some patients who take statins complain of GI distress and many other adverse effects, Lake said. Alternatives are niacin, usually as niacinamide, red yeast rice, or garlic extract—all of which are supported by research evidence for lowering cholesterol. Omega-3 essential fatty acids also lower total serum cholesterol, he said.

"I almost always advise exercise and rational dietary changes to address a previously diagnosed elevated cholesterol for which statins were initially prescribed," he said. "Many people who follow a reasonable diet and who exercise can adequately manage their cholesterol without recourse to statins or other conventional or CAM cholesterol-lowering drugs."

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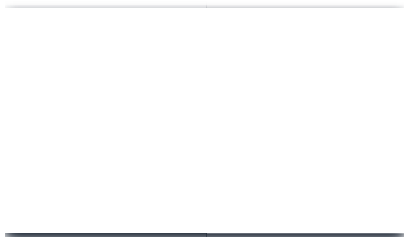
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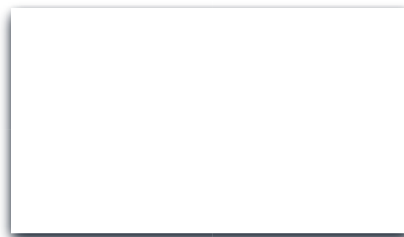
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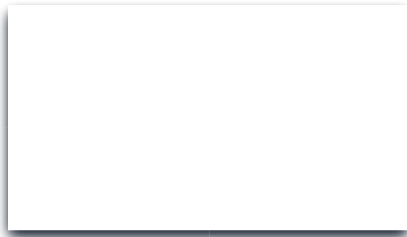


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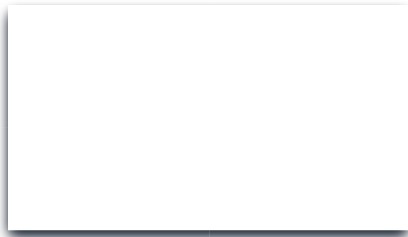


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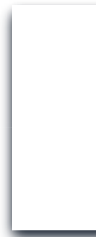
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