Statins and Cognitive Side Effects
What Cardiologists Need to Know

Carlos Rojas-Fernandez, BSc (Pharm), PharmD[a,b,c,*],
Zain Hudani, BPharm, MSc Candidate[d],
Vera Bittner, MD, MSPH, FNLA[e]

KEYWORDS

• Statins • Cognition • Memory • Adverse drug effects • Iatrogenesis • Drug safety

KEY POINTS

- Adverse cognitive effects such as amnesia, concentration difficulties, confusion, and other complaints have been reported and attributed to statins in the lay press, the scientific literature, and by the US Food and Drug Administration (FDA) by way of spontaneous reports.
- Spontaneous reports from the FDA's Adverse Event Reporting System do not allow appropriate causality assessment.
- The weight of the evidence to date does not support the position that statins have a propensity to meaningfully or commonly contribute to adverse cognitive effects.
- Clinicians should not dismiss patient-reported cognitive effects. A thorough assessment should be conducted to rule out other potential causes.
- Baseline assessment of cognition before initiating a statin drug is not recommended at this time.

INTRODUCTION

Since the approval of the first statin, lovastatin, on September 1, 1987 by the United States Food Drug Administration (FDA),[1] statins have revolutionized the primary and secondary prevention of atherosclerotic cardiovascular disease. A series of meta-analyses by the Cholesterol Treatment Trialists (CTT) summarizes the clinical trials evidence and documents significant reductions in nonfatal myocardial infarction and coronary death; fatal and nonfatal stroke; coronary revascularizations; coronary mortality; and, importantly, in total mortality with statin therapy.[2] Statin benefits in these trials were proportional to the degree of reduction in low-density lipoprotein cholesterol levels in post-hoc analyses, were seen in patients across the spectrum of cardiovascular risk, and were largely independent of the baseline lipid profile.[2–4] Absolute risk reductions were greater in high-risk versus low-risk subjects.[2] In high-risk subjects with coronary disease, high-intensity

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[a] Schlegel-UW Research Institute for Ageing & School of Pharmacy, University of Waterloo, Waterloo, Ontario, Canada; [b] School of Public Health and Health Systems, Faculty of Applied Health Sciences, University of Waterloo, Waterloo, Ontario, Canada; [c] Michael G. DeGroote School of Medicine, Department of Family Medicine, McMaster University, Hamilton, Ontario, Canada; [d] University of Waterloo School of Pharmacy, 10 Victoria St S, Kitchener, Ontario N2G 1C5, Canada; [e] Division of Cardiovascular Disease, University of Alabama at Birmingham, LHRB 310, 701 19th Street South, Birmingham, AL 35294, USA
* Corresponding author. Schlegel Research Chair in Geriatric Pharmacotherapy, University of Waterloo School of Pharmacy, 10 Victoria St S, Room 7004, Kitchener, ON N2G 1C5.
E-mail address: carlos.rojas-fernandez@uwaterloo.ca

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statin therapy provides incremental benefits compared with moderate-intensity statin therapy.[5]

Despite these well-documented benefits, statins in general and high-intensity statins in particular remain underused. The most recent report based on the National Health and Nutrition Survey reveals that in 2011 to 2012, 29% of individuals with diagnosed cardiovascular disease and 37% of those with diabetes did not report using any lipid level–lowering medications.[6] This underuse is in part driven by concerns among clinicians and patients about statin safety. In the CTT meta-analyses, there was no increase in cancer incidence. Subsequent analyses of the clinical trials database showed an increase in the incidence of diabetes mellitus with statin use.[7] Statin myopathy is also well described, although the true incidence is a matter of controversy.[8,9] Both statin-induced diabetes and statin myopathy seem to be related to the intensity of statin therapy.[8,9]

Statin benefits and risks were carefully considered in the 2013 American College of Cardiology/American Heart Association Cholesterol Treatment Guidelines, which concluded that benefits outweigh risks for the 4 statin benefit groups and individuals with a risk of future cardiovascular events of more than 7.5% over the next 10 years, but the guidelines also emphasize the importance of individual benefit/risk discussions during the clinician-patient encounter.[10]

More recently, data from 2 randomized trials, 1 challenge-dechallenge study, and multiple case reports have suggested a potential association between statins and cognitive impairment.[11,12] In 2012, the FDA extended the warning section of statin labels to include a statement that statin use may contribute to "…notable, but ill defined memory loss or impairment that was reversible upon discontinuation of statin therapy."[13] The FDA stated that the data on which this statement was predicated did not suggest these cognitive changes to be common, or that they lead to clinically significant cognitive decline or impairment. Because statin drugs are widely used, these potential side effects need to be carefully considered and put in the context of available scientific evidence as well as the established benefits of statins.

COGNITIVE IMPAIRMENT DEFINED AND IMPLICATIONS FOR IATROGENESIS

Cognition can be generally described under 4 domains: executive function, memory, language, and visuospatial ability. The risk-benefit profile of statins in relation to cognitive impairment is best considered with knowledge of the spectrum of cognitive disorders. Cognitive impairment can be defined as impairment in any of the aforementioned domains. Mild cognitive impairment (MCI) is a state between normal cognition and dementia, the latter being defined as cognitive impairment involving 2 domains and being sufficiently severe to interfere with daily activities and leading to a progressive loss of independence.[14] Clinically, patients with MCI have difficulties performing objective cognitive tasks, but the difficulties are not severe enough to impair instrumental activities of daily living. The distinction between MCI and dementia is often hazy because the demands of activities of daily living vary considerably depending on age, education, occupation, family situation, and other factors.

When considering potential cognitive effects of statins, clinicians should remember that MCI and dementia are common in individuals more than 65 years of age and can have a variety of causes, including neurodegenerative conditions such as Alzheimer disease, frontotemporal dementia, Parkinson disease, and dementia with Lewy bodies. Cognitive impairment may also be attributable to other conditions, including depression, infections, metabolic disturbances, inflammatory or vascular diseases, and anoxic injury, or may be secondary to various medications, or may occur in conjunction with general anesthesia or cardiopulmonary bypass. In addition, MCI/dementia may be the result of primary and secondary causes combined.[15] Although mixed dementias with primary and secondary causes are frequent, there is no gold standard for diagnosing these disorders.[16] In addition, variability exists in the clinical course of dementing illnesses. Some dementias progress slowly, some more rapidly, whereas others progress in spurts or at intermediate rates. The variable course of illness progression makes it difficult to interpret case reports of putative statin-induced cognitive adverse effects, because the duration and extent of follow-up vary across reports. In contrast, iatrogenic cognitive impairment from drugs that are well known to contribute to, or cause, cognitive impairment (**Table 1**) can be observed soon after the causative drug is started and are easily attributable to these medications from their clinical pharmacology.[17]

Considering the proportion of the population receiving statins, uncommon adverse effects have the potential to affect a large number of people. For example, it was estimated that, in 2002, 7.8% of the Canadian population was taking a statin.[18] If the incidence of statin-associated cognitive impairment were 0.1%, it would currently affect about 2500 people in Canada. In the United States, approximately 41% of adults 45 years of