Is Statin-Associated Cognitive Impairment Clinically Relevant? A Narrative Review and Clinical Recommendations

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OBJECTIVE: To explore the impact of statin use on cognition.

DATA SOURCES: A literature search was performed using MEDLINE (1950-November 2011), EMBASE (1980-November 2011), and the Cochrane Library (1960-November 2011) using the search terms "cognition/drug effects," "delirium, dementia, amnestic, cognitive disorders/chemically induced," "memory disorders/chemically induced," "hydroxymethylglutaryl-CoA reductase inhibitors/adverse effects," and "hydroxymethylglutaryl-CoA reductase inhibitors." A bibliographic search on included references was also conducted.

STUDY SELECTION AND DATA EXTRACTION: Studies were included for analysis if they were conducted in humans and examined the impact of statin use on cognition as either a primary or secondary endpoint; case reports and case series were also included for analysis.

DATA SYNTHESIS: Reports of statin-associated cognitive impairment were found primarily in observational studies (eg, case reports/series). One randomized controlled trial demonstrated that simvastatin impaired some measures of cognition compared to placebo. Conversely, in the majority of randomized controlled trials and observational studies, statins were found to have either a neutral or beneficial effect on cognition. Preliminary data suggest that statins that are less lipophilic (ie, pravastatin and rosuvastatin) may be less likely to contribute to cognitive impairment due to limited penetration across the blood-brain barrier. These drugs would be a logical alternative in cases where cognitive impairment secondary to another statin is suspected.

CONCLUSIONS: Despite several reports of statin-associated cognitive impairment, this adverse effect remains a rare occurrence among the totality of the literature. If statin-associated cognitive impairment is suspected, a trial discontinuation can reveal a temporal relationship. Switching from lipophilic to hydrophilic statins may resolve cognitive impairment. The vascular benefits and putative cognitive benefits outweigh the risk of cognitive impairment associated with statin use; therefore, the current evidence does not support changing practice with respect to statin use, given this adverse effect.

KEY WORDS: clinical relevance, cognitive impairment, statins.

Ann Pharmacother 2012;46:549-57.

Published Online, 3 Apr 2012, *theannals.com*, DOI 10.1345/aph.1Q620

Since their introduction in 1987, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have become the most commonly prescribed agents for the treatment of dyslipidemia.[1] Statins are the most effective and widely used medicines to reduce low-density lipoprotein cholesterol and reduce cardiovascular events.[2] Statins are well tolerated and have minimal adverse effects, most commonly myopathies, effects on liver enzymes, diarrhea, and rarely rhabdomyolysis.[3] As with all drugs, some adverse effects do not manifest in clinical trials but become evident after use in larger samples and broader patient populations. For example, several case reports and case series have suggested a potential association between statins and cognitive impairment.[4-9] This possible adverse effect warrants further investigation, as it is contradictory to several studies that demonstrate a potential benefit on cognition with the use of statins.[10-13] Cognitive impairment can also be considered a severe adverse effect with the potential to cause other adverse outcomes such as functional impairment.

Furthermore, the incidence of statin-associated cognitive impairment has not been clearly defined, and considering the number of patients receiving statins, even uncommon adverse effects have the potential to impact a large number of people.[9] For example, in 2002, an estimated 7.8% of the Canadian population was taking statins, which accounts for 2,447,062 Canadians.[14,15] If the incidence of statin-associated cognitive impairment were only 0.1%, it would affect nearly 2500 people in Canada. Since cognitive impairment is a potentially debilitating adverse effect, it is important to better understand this risk to adequately assess the appropriateness of statins for individual patients. Additionally, although recent reports have highlighted

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the risk of cognitive impairment with the use of statins, few have provided a balanced discussion of this risk with the beneficial effects of these agents on both cardiovascular outcomes and possibly cognition. It is important to present the benefits and risks of these medications so that clinicians and their patients can make informed decisions.

This article explores the potential adverse effect of statins on cognition, and considers the established vascular and putative cognitive benefits of these drugs as a balance to the risk of adverse effects.

Data Sources

A comprehensive literature search was conducted to identify relevant literature regarding statins and any potential adverse impact on cognition. The databases included in the search were MEDLINE (PubMed; 1950-November 2011), EMBASE (Ovid; 1980-November 2011), and the Cochrane Library (1960-November 2011). All languages were included. The following search terms were used: "cognition/drug effects," "delirium, dementia, amnestic, cognitive disorders/chemically induced," "memory disorders/chemically induced," "hydroxymethylglutaryl-CoA reductase inhibitors/adverse effects," "statin/adverse effects," and "hydroxymethylglutaryl-CoA reductase inhibitors" [Pharmacological Action]. Keywords, exploded terms, and controlled terminology were used for each of the databases searched. Additional references were identified through a bibliographic search. Studies were included for analysis if they were conducted in humans (all patient populations were considered), reported an association between statin use and incident cognitive impairment either as a primary or secondary endpoint, and were available in abstract or full text form. Given the relative paucity of data, case reports, case series, case-control, cohort, and clinical trials were all considered for analysis.

The search strategy yielded 29 references that ultimately met the criteria for inclusion in this analysis. Outcomes attributed to statins in these studies included cognitive impairment, cognitive improvement/protection, and a neutral effect on cognition.

Case Reports and Series

Several case reports described cognitive impairment associated with statin use.[4-8] Medications implicated include simvastatin, atorvastatin, and rosuvastatin. Symptoms reported by patients in these case reports include short- and long-term memory loss, behavioral changes, impaired concentration and attention, paranoia, and anxiety. Symptoms were noted as early as 5 days after initiation of statin therapy; however, in 1 case, symptoms did not occur until after 9 months of therapy. In all cases the offending drugs were discontinued and patients experienced full recovery of cognition, with recovery times varying from a few days to 4 weeks after drug discontinuation.

An analysis of the MedWatch drug surveillance system of the Food and Drug Administration (FDA) over a 5-year period revealed 60 reports of memory loss associated with statins.[9] The majority of reported cases involved simvastatin (36 cases) or atorvastatin (23 cases); 1 case involved pravastatin. Reported symptoms included short-term memory loss, amnesia, or unspecified memory loss. Symptoms developed within 2 months of therapy for approximately half the cases. Thirty-three cases had documented statin discontinuation and, of these, 14 patients had resolution or improvement in memory. Four reports of rechallenge with the same statin were documented, and all 4 resulted in reappearance of memory loss. No formal neuropsychological testing was conducted in any of the reported cases.

Clinical Trials

The association between statin use (specifically pravastatin, lovastatin, atorvastatin, and simvastatin) and cognition has been assessed in various clinical trials as either a primary or secondary endpoint. These studies are summarized in Table 1.

COGNITION AS PRIMARY ENDPOINT

Eleven placebo-controlled clinical trials were identified that investigated the impact of statins on cognition as a primary endpoint. The majority of these trials (7) found no significant difference between statins and placebo on measures of cognition.[16-22] In one randomized, double-blind, placebo-controlled trial, simvastatin had a deleterious effect on some measures of cognition compared to placebo.[23] Detrimental effects were found when tests previously observed to be sensitive to statins were administered ($p = 0.008$; difference in summary z scores = 0.18; 95% CI 0.07 to 0.29) and on tests not previously administered by the researchers ($p = 0.04$; difference in summary z scores = 0.7; 95% CI 0.05 to 0.29).

Another study demonstrated cognitive improvement in attention, psychomotor speed, mental flexibility, working memory, and memory recall with placebo, whereas lovastatin demonstrated improvements only in memory recall.[24] No cognitive decline was noted for either treatment group. In a 4-week crossover study with lovastatin and pravastatin, no difference between treatments was found on cognitive assessments, with the exception of the Digit Symbol Substitution test, which demonstrated improvements with statins over placebo.[25] Similarly, a 6-month before and after comparison study with placebo controls found that those receiving atorvastatin scored significantly higher on all domains of cognition assessed compared to placebo.[26] The domains measured

included attention, psychomotor speed, mental flexibility, working memory, and memory retrieval.

COGNITION AS SECONDARY ENDPOINT

Three studies examined the cognitive effects of statins as a secondary endpoint. A post hoc analysis assessed cognitive performance endpoints in the DALI (Diabetes Atorvastatin Lipid Intervention) study.[27] Although verbal memory was improved in the atorvastatin groups (80 and 10 mg), there were no other significant differences noted in cognitive function among the patients. PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) included cognitive function tests among its secondary endpoints.[28] A detailed summary of the results on cognition from this study was published separately.[29] In general, cognitive function declined among all neurocognitive tests administered over a mean follow-up period of 42 months; however, pravastatin use was not associated with any difference in changes among any of the cognitive domains compared to placebo.[28,29] In a randomized controlled trial, 20,536 patients were randomized to receive either simvastatin or placebo.[30] Cognitive function was assessed as a secondary endpoint using the modified Telephone Interview for Cognitive Status questionnaire. After mean follow-up of 5.3 years, no significant difference was noted in cognition between the simvastatin and placebo groups.

Observational Studies

Several observational studies have been conducted to assess the association between statin use and cognitive function. Study protocols utilized different definitions of cognitive impairment or dementia and included various neurocognitive assessment tools. Of the 9 observational studies identified, 4 suggested potential protective or beneficial effects of statins, 3 found no difference on cognition with statin use, and 1 found an increased risk of delirium. A summary of these studies can be found in Table 2. Three studies selected patients with dementia at the time of analysis and compared statin exposure with controls without dementia.[12,13,31] These studies showed a beneficial effect of statins on dementia in study subjects. Hajjar et al. found that patients receiving statins were significantly less likely to have dementia based on a composite definition (OR 0.23; 95% CI 0.1 to 0.56); Alzheimer disease (OR 0.37; 95% CI 0.19 to 0.74); or vascular dementia subtypes (OR 0.25; 95% CI 0.08 to 0.85).[31] This study also noted improved Mini-Mental State Examination (MMSE) scores among statin users, compared to a decline in controls (OR for no change or improvement: 2.81; 95% CI 1.02 to 8.43; p = 0.045) and higher scores on the Clock Drawing Test (difference of 1.5 ± 0.1; p = 0.036).[31] In a nested case-control study, 284 patients with dementia were compared to 1080 controls without dementia with regard to statin use.[12] Statin users were found to have a lower risk of developing dementia compared to nonusers (adjusted relative risk 0.29; 95% CI 0.13 to 0.63; p = 0.002). Rockwood et al. conducted a case-control study and observed a protective effect of statins for all types of dementia in patients younger than 80 (OR 0.24; 95% CI 0.07 to 0.80), but this protective effect was not significant in those older than 80 (OR 0.43; 95% CI 0.11 to 1.58).[13]

Other studies have likewise observed improvement among various groups. A cohort study found that statin use was associated with significant improvements on the Trail Making B Test of cognitive performance compared to statin nonusers (11.0 seconds difference; p = 0.05).[32] In a second cohort study, it was observed that modified MMSE scores were significantly higher among postmenopausal women with coronary disease taking statins compared to nonusers (93.7 ± 6.1 vs 92.7 ± 7.1, respectively; p = 0.02); statin users also had a trend toward a lower likelihood of cognitive impairment (OR 0.67; 95% CI 0.42 to 1.05).[33] In a third retrospective cohort study, statins were found to have a beneficial effect on lifelong cognitive change (F = 5.78; p = 0.017; partial $\eta^2 = 0.013$).[34] This was measured as significant improvements in IQ between ages 11 and 80 years among statin users compared to nonusers. A cross-sectional study found that statin users performed better on verbal fluency (animals and fruits), naming test, immediate free recall, and word accentuation test compared to nonuser controls (p = 0.002, p = 0.014, p = 0.040, p = 0.013, p = 0.030, respectively); however, when adjusted for potential confounders, no differences were found between statin users and nonusers on these neuropsychological tests.[35]

Conversely, 2 observational studies have found potential cognitive impairment associated with statin use. In a large, retrospective cohort study, Redelmeier et al. found that patients taking statins prior to elective surgery had an approximately 30% higher risk of postoperative delirium (95% CI 15% to 47%; 14 per 1000) compared to those not taking statins prior to surgery (11 per 1000; p < 0.001).[36] A population-based, national cohort study in the US assessed cognition in 7191 participants receiving statins and 17,404 participants not using statins.[37] Cognitive impairment was observed in 8.6% of statin users compared to 7.7% of nonusers (p = 0.014); however, after adjustment for potential confounders the association was not significant (OR 0.98; 95% CI 0.87 to 1.10).

Lastly, in the University of California San Diego Statin Effects Study, patients were administered a survey regarding statin-associated cognitive-specific adverse drug reactions (ADRs).[38] Using the Naranjo probability scale criteria, patient-reported ADRs for cognitive symptoms were classified as definite in 12% of the cases, probable in 63%, and possible in 25%. Onset of cognitive symptoms ranged from 1 day to about 10 years. Discontinuation of statins led to improvement of symptoms in 90% of patients and complete resolution in 32% of patients.

Table 1. Summary of Placebo-Controlled Clinical Trials

Reference	Drug	Pts.	Duration	Cognitive Endpoint	Cognitive Assessment	Results
Harrison (1994)[16]	Simvastatin 40 mg/day; pravastatin 40 mg/day	N = 25; age 20-31.5 years (mean 23.8); healthy	4 weeks	Primary (composite CNS endpoints)	Digit Symbol Substitution Test	Simvastatin and pravastatin had no significant differences vs placebo on cognitive performance
Kostis (1994)[17]	Lovastatin 40 mg/day; pravastatin 40 mg/day	N = 22; age 36-65 years; dyslipidemia	6 weeks	Primary (with sleep and wakefulness; all assessments included in primary analysis)	Reaction Time, Rey Auditory Learning Test, Trail-Making Test A/B, Embedded Figures Test, Benton Visual Retention Test, Verbal Fluency Test	No effects on cognitive performance with either lovastatin or pravastatin
Cutler (1995)[18]	Simvastatin 20 mg/day; pravastatin 40 mg/day	N = 24/arm (crossover); age 40-60 years (mean 51); dyslipidemia	4 weeks	Primary (powered for Digit Symbol Substitution and Visual Analogue Scales)	Digit Symbol Substitution, Bond and Lader Visual Analogue Scales, Auditory Vigilance, Selective Reminding Word Recall, Finger Tapping, Choice Reaction Time, Profile of Mood States	Neither of the statins differed significantly from placebo on any cognitive measure; no effects on cognitive performance
Gengo (1995)[25]	Lovastatin 40 mg/day; pravastatin 40 mg/day	N = 24/arm (crossover); age 40-60 years (mean 50.2); dyslipidemia, no CVD	4 weeks	Primary (powered for Digit Symbol Substitution and Visual Analogue Scales)	Digit Symbol Substitution, Visual Analogue Scales, Choice Reaction Time, Auditory Vigilance, Selective Reminding Word Recall, Finger Tapping, Mood	No significant difference between treatments on any cognitive parameters with the exception of Digit Symbol Substitution, for which both statins were better than placebo
Santanello (1997)[19]	Lovastatin 20 and 40 mg/day	N = 431; age ≥65 years; MMSE score >24, LDL-C 159-221 mg/dL	6 months	Primary (composite health-related quality of life)	3 global change questions	No difference in health-related quality-of-life measures (including cognitive function) between lovastatin and placebo
Muldoon (2000)[24]	Lovastatin 20 mg/day	N = 209; age 24-60 years (mean 46); dyslipidemia, healthy	6 months	Primary (all assessments were included in primary analysis)	Digit Vigilance, Letter Rotation, Digit Span, Recurring Words, Grooved Pegboard, Elithorn Maze, Digit Symbol, Stroop Interference, Trail Making, Associative Learning, Controlled Oral Word Association, Digit Symbol Recall, Verbal Recall, Complex Figure	Placebo improved cognition for all 5 domains; lovastatin improved cognition only in memory recall; no decline in cognition for either group
Gibellato (2001)[20]	Lovastatin 40 mg/day; pravastatin 40 mg/day	N = 80; age ≤59 years; dyslipidemia	4 weeks	Primary	CogScreen–Aeromedical Edition	Cognitive performance not affected by either statin and did not differ significantly from placebo
Muldoon (2004)[23]	Simvastatin 10 and 40 mg/day	N = 308; age 35-70 years (mean ~53); mild-moderate dyslipidemia	6 months	Primary (all assessments were included in primary analysis)	Elithorn Mazes, Digit Vigilance, Recurring Words, Grooved Pegboard, Digit Symbol, Stroop Interference, Trail Making B, Digit Span, Complex Figure, Letter Rotation, Mirror Tracing, 4-Word Short-Term Memory	Placebo improved cognition on Elithorn mazes and Recurrent Words, while simvastatin did not; no significant difference on Grooved Pegboard, Digit Vigilance, Mirror tracing; 4-Word Memory test showed detrimental effects with simvastatin
Golomb (2006)[21]	Pravastatin 40 mg/day; simvastatin 20 mg/day	N = 1016; age >20 years; no CVD or DM	6 months	Primary (all assessments were included in primary analysis)	Recurrent Words, Elithron Maze, Digit Vigilance, Grooved Pegboard	No significant impact on cognition with either pravastatin, simvastatin, or placebo
Parale (2006)[26]	Atorvastatin 10 mg/day	N = 55; age ≥40 years (mean ~56); CV indications, MMSE score >24	6 months	Primary (all assessments were included in primary analysis)	MMSE, Digit Span, Picture Test, Trail Making Test, Controlled Oral Word Association Test, Digit Symbol Substitution Test, Auditory Vigilance and Digit Vigilance Test	Atorvastatin group scored significantly higher than placebo in all neurocognitive tests
Summers (2007)[22]	Atorvastatin 10 mg/day	N = 57; age 25-83 years (mean ~61); CKD	12 weeks	Primary (substudy of LORD trial; all assessments were included in primary analysis)	National Adult Reading Test, Digit Symbol Coding, Trail Making Test, 100-Item Stroop Color-Word Test	Atorvastatin did not cause any decline in cognition; use of atorvastatin did not predict cognitive functioning

Berk-Planken (2002)[27]	Atorvastatin 10 and 80 mg/day	N = 30; age 45-75 years; no CVD	30 weeks	Cognition as secondary endpoint	Auditory-Verbal Memory Test, Orientation, Attention, Psychomotor Speed, Executive Functioning	Modest increase in verbal memory with atorvastatin; overall, no significant effect on cognitive function
Shepherd (2002)[28]	Pravastatin 40 mg/day	N = 5804; age 70-82 years; existing CVD or risk factors	3.2 years	Cognition as secondary endpoint	MMSE, Stroop, Letter-Digit Coding Test, 15-Picture Learning Test	No significant difference in cognitive decline with pravastatin vs placebo
Collins (2004)[30]	Simvastatin 40 mg/day	N = 20,536; age 40-80 years (mean ~64); cerebrovascular disease, CAD, DM, HTN	5.3 years	Cognition as secondary endpoint	The Modified Telephone Interview for Cognitive Status	No significant difference in cognitive decline with simvastatin vs placebo

CAD = coronary artery disease; CKD = chronic kidney disease; CNS = central nervous system; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; HTN = hypertension; LDL-C = low-density lipoprotein cholesterol; MMSE = Mini-Mental State Examination.

Discussion

Several reports have documented cognitive impairment associated with the use of statins, yet most other studies have noted discordant results. Indeed, in many observational studies and clinical trials, statins were found to have a neutral or modestly beneficial effect on cognitive performance; thus, the bulk of the evidence suggests that statins do not have a clinically meaningful effect on cognition, at least for the great majority of the patients who take these drugs. Indeed, the majority of the "evidence" is derived almost exclusively from case reports and case series. While these case reports are useful in reporting novel and potentially important clinical occurrences, they are limited by their observational nature and thus it is vital to interpret these reports accordingly.[39,40] Likewise, the study by Redelmeier et al., while informative and intriguing, may not necessarily be generalizable to the broader population of statin users, given its focus on a postoperative setting.[36]

Potential mechanisms for cognitive impairment should nevertheless be considered. The most widely accepted theory is based on the relationship between cholesterol and myelin.[41] The brain contains high concentrations of cholesterol; unlike other areas of the body, cholesterol in the brain is produced through de novo synthetic processes.[42] Cholesterol is a key component of myelin, which is integral in regulating myelin membrane permeability and fluidity. Treatment with statins may thus reduce de novo cholesterol synthesis and interfere with myelin formation and function.[42] Along these lines, in vitro and mouse models have demonstrated that following chemical demyelination, treatment with simvastatin may impair remyelination processes.[43,44] Impaired myelination may lead to neural conduction deficits and subsequent cognitive impairment.

Another potential toxic mechanism relates to the impact of statins on oxidative stress and mitochondrial function.[45] Statins have been demonstrated to inhibit synthesis of mevalonate, which is a precursor in the biosynthesis of both cholesterol and coenzyme-Q_{10}. Coenzyme-Q_{10} is an essential component for proper mitochondrial function and cellular adenosine triphosphate production and also exhibits antioxidant properties. Statins are thought to reduce coenzyme-Q_{10} levels, which may lead to impaired mitochondrial functioning and increased oxidative stress.[45] Through this mechanism, statins may have an indirect adverse effect on cognition.

It is noteworthy that the cardiovascular benefits of statins have been well established in several large, methodologically sound trials that demonstrate a clear reduction in cardiovascular events, particularly when used for secondary prevention.[2,30,46,47] Conversely, the cognitive benefits of statins are far less well established, but data from animal models and limited human data suggest these drugs may possess cognitive benefits.[10,11] The mechanism for such a benefit has not been

fully elucidated, but several theories exist. Increased cholesterol levels have been associated with increased risk of Alzheimer disease[48]; therefore, the reduction of cholesterol with statins may help to prevent development of Alzheimer disease or other types of dementia. Other proposed mechanisms of cognitive protection involve processes unrelated to cholesterol-lowering effects, such as attenuating endothelial dysfunction, increasing endothelial nitric oxide production, antiinflammatory effects, antioxidant effects, antithrombotic properties, angiogenic effects, and other vasculoprotective properties.[49] It is therefore not surprising that several observational studies examined here found statistically significant improvements in cognition.[12,13,31-33] Nevertheless, there are 2 factors that need to be

Table 2. Summary of Observational Studies

Reference	Design	Drug	Pts.	Cognitive Assessment	Results
Jick (2000)[12]	Nested case-control	Atorvastatin, cerivastatin, fluvastatin, pravastatin, simvastatin	N = 1364; age 50-89 years; dementia pts. and controls	Diagnosis of dementia	Statin users had lower risk of developing dementia vs nonusers (adjusted relative risk 0.29; 95% CI 0.13 to 0.63; p = 0.002)
Hajjar (2002)[31]	Case-control and retrospective	Not specified	N = 655; age 52-98 years (mean 78.7); 74% women; dyslipidemia or dementia pts. and controls	MMSE, Clock Drawing Test, Geriatric Depression Scale	Pts. on statins were less likely to have dementia (OR composite dementia: 0.23; 95% CI 0.1 to 0.56; p = 0.001; OR Alzheimer disease: 0.37; 95% CI 0.19 to 0.74; p = 0.005; OR vascular dementia: 0.25; 95% CI 0.08 to 0.85; p = 0.027); pts. on statins also had improved MMSE score vs decline in controls (OR for no change or improvement: 2.81; 95% CI 1.02 to 8.43; p = 0.045) and scored higher on the Clock Drawing Test (difference of 1.5 ± 0.1; p = 0.036)
Rockwood (2002)[13]	Cohort and case-control	Not specified	N = 1315; age ≥65 years; dementia pts. and controls	MMSE	Adjusted analysis found that the protective effect of statin (or other lipid-lowering agent) was observed for dementia in those <80 years (OR 0.24; 95% CI 0.07 to 0.80), but not for those >80 years (OR 0.43; 95% CI 0.11 to 1.58)
Yaffe (2002)[33]	Cohort subanalysis	Simvastatin, atorvastatin, pravastatin, lovastatin, fluvastatin	N = 1037; age <80 years; postmenopausal women, CAD	Modified MMSE	Statin users had higher mean modified MMSE scores vs nonusers (93.7 ± 6.1 vs 92.7 ± 7.1; p = 0.02) and a trend toward lower likelihood of cognitive impairment (OR 0.67; 95% CI 0.42 to 1.05)
Starr (2004)[34]	Retrospective cohort	Not specified	N = 478; no dementia; tested at age 11 and 80 years	Moray House Test of Intelligence	A relative improvement in IQ was observed among statin users at age 11 and 80 years vs nonusers; statins had a beneficial effect on lifelong cognitive change (F = 5.78; p = 0.017; partial η^2 = 0.013)
Agostini (2007)[32]	Observational cohort	Atorvastatin, lovastatin, pravastatin, simvastatin	N = 756; age ≥65 years	Trail Making B	Statin nonusers performed worse on the Trail Making B outcome (11.0 seconds difference; p = 0.05)
Redelmeier (2008)[36]	Cohort analysis	Atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, rosuvastatin, cerivastatin	N = 284,158; age ≥65 years; admitted for elective surgery	International Classification of Disease codes 293.0-293.9 (delirium)	Pts. on statins prior to elective surgery had ~30% higher risk of postoperative delirium (95% CI 15% to 47%; 14 per 1000) vs those not taking statins (11 per 1000; p < 0.001)
Glasser (2010)[37]	Cohort	Atorvastatin, simvastatin, lovastatin	N = 24,595; age ≥45 years	Six-Item Screener	Cognitive impairment in 8.6% of statin users vs 7.7% of nonusers (p = 0.014); after adjustment for confounders, impairment no longer found (OR 0.98; 95% CI 0.87 to 1.10); no association between statin type and cognition (OR 1.03; 95% CI 0.86 to 1.24)
Benito-León (2010)[35]	Cross-sectional cohort	Pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin	N = 5278; age ≥65 years	37-Item MMSE, Trail Making Test A, Verbal Fluency, Six Objects Test, Story Recall Task, Word Accentuation Test	After adjustment for confounders, no significant difference between statin users and nonusers on neuro-psychological test scores

CAD = coronary artery disease; MMSE = Mini-Mental State Examination.

taken into consideration when interpreting these results. The first is the clinical significance of the findings. For example, modified MMSE scores of 93.7 were found for statin users compared to 92.7 for nonusers in one study, and while these results were statistically significant, this difference would not be clinically relevant in practice.[33] The second element to consider is the quality of the evidence. A recent systematic review found that while several observational studies found protective or beneficial effects on dementia with statins, randomized controlled trials and more robust evidence has thus far failed to establish a clear benefit.[50] In addition, statins are not FDA- or Health Canada–approved for the prevention or treatment of cognitive impairment.

Clinical Considerations

Statins are a commonly used group of drugs, especially in older patients (>65 years), who are at higher risk for cognitive impairment. Clinicians should therefore be able to properly assess, however unlikely, potential adverse cognitive effects of statins, and be able to manage patients who might experience such adverse effects. That said, routine neurologic monitoring is not necessarily recommended.

If statin-associated cognitive impairment is suspected, a thorough neurologic examination should be performed.[51] If no other cause of cognitive impairment can be identified, then the first step would be to discontinue the offending agent and observe the patient for 1-3 months for an improvement in cognition.[51] Note that in all case reports, the patients' cognitive symptoms resolved after discontinuation of the statins. Full resolution occurred within a few days for some patients, but took up to 1 month for others. In a sub-analysis of the Treating to New Target study, short-term withdrawal of statin therapy (ie, up to 6 weeks) in patients with stable cardiac disease was not associated with increased risk of acute coronary syndromes, which is a reassuring finding in the context of withholding these drugs.[52] As the patient will still likely require lipid-lowering therapy, it is important to consider that statins exhibit varying degrees of lipophilicity; this will aid in selecting another statin. Specifically, atorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin, and pitavastatin are relatively lipophilic and are able to cross the blood-brain barrier, whereas pravastatin and rosuvastatin are less lipophilic and are less likely to penetrate into the brain.[53] In this light, it is informative to note that from the 66 cases in the literature, the implicated statins were simvastatin (n = 39), atorvastatin (n = 25), pravastatin (n = 1), and rosuvastatin (n = 1).[4-9] Given the predominance of cases in which lipophilic statins were associated with cognitive impairment, there may be contributing pharmacokinetic and pharmacodynamic factors. This pharmacokinetic consideration suggests that there may be a theoretical basis to switch from a lipophilic statin to a hydrophilic statin in the face of suspected statin-associated cognitive impairment. This strategy proved effective in one case report in which simvastatin-associated cognitive impairment was successfully managed by switching to pravastatin.[8] Conversely, in another case, a patient was switched to simvastatin after 2 failed attempts with atorvastatin; the cognitive symptoms recurred after the change to simvastatin.[7] This may be explained by the fact that atorvastatin and simvastatin are lipophilic agents.[53] Interestingly, pravastatin and rosuvastatin were implicated in 1 case each, suggesting other, as of yet undefined, mechanisms. Rechallenge with a lower dose of the same statin may be an option, but in some cases this has resulted in a return of symptoms; furthermore, it may be difficult to observe therapeutic gains of sufficient magnitude with lower doses.[6]

In patients with persistent cognitive symptoms (while taking various statins), it may be possible to try lipid-lowering agents from different therapeutic classes, although the impact of these agents on cognition may be similar to that of statins, given the proposed mechanisms of cognitive impairment. If lipid-lowering therapy is not an acceptable option, treatment approaches should focus on lifestyle modifications.

Summary

At this time there is insufficient evidence to confidently conclude that statins can cause or contribute to clinically meaningful cognitive impairment. The current evidence demonstrating an association between statins and cognitive impairment has several limitations, including: failure to establish a cause-effect relationship, inability to account for all confounders, lack of controls, inconsistent assessments of cognition, and generally healthy study populations that do not necessarily reflect typical statin users in practice. When balanced with the established vascular benefits of statins and the evidence demonstrating either neutral or possibly beneficial effects on cognition (note that statins are not FDA- or Health Canada–approved for treatment or prevention of cognitive impairment), the risk of cognitive impairment should not change current practice with respect to statin use.

The aforementioned facts notwithstanding, if statin-associated cognitive impairment is suspected, confounding factors, such as concomitant medications, medical conditions, or risk factors for cognitive impairment, should first be assessed. If the statin is still suspected, a trial withdrawal period of 1-3 months is recommended and the patient can be reassessed for symptom resolution. Switching to a hydrophilic agent (eg, pravastatin or rosuvastatin) may be an option for patients who experience cognitive adverse effects while receiving a lipophilic statin. Other lipid-lowering agents may also be considered as viable alternatives in persistent statin-associated cognitive impairment. Routine neurocognitive testing is not recommended for patients taking statins, nor are changes to current practice with respect to statin use.

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Conflict of interest: Authors reported none

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EXTRACTO

¿Es Relevante Clínicamente el Daño Cognitivo Asociado a las Estatinas? Un Repaso Narrativo y Recomendaciones Clínicas

CH Rojas-Fernandez y J-C F Cameron

Ann Pharmacother 2012;46:549-57.

OBJETIVO: El objetivo de este artículo es explorar el impacto de las estatinas en la cognición.

FUENTES DE DATOS: Una búsqueda en la literatura fue llevada a cabo usando MEDLINE (1950 a nov de 2011), EMBASE (1980 a nov de 2011), y Cochrane Library (1960 a nov de 2011) con los términos: "cognición/efectos de fármacos", "delirio, demencia, amnésico, desórdenes cognitivos/inducidos químicamente", "desórdenes de la memoria/inducidos químicamente", "inhibidores de la reductasa hidroximetilglutaril–CoA/efectos adversos", e "inhibidores de la reductasa de hidroximetilglutaril-CoA". Una búsqueda bibliográfica de las referencias incluidas también fue llevada a cabo.

SELECCION DE ESTUDIOS Y EXTRACCION DE DATOS: Los estudios fueron incluidos si examinaban el impacto del uso de las estatinas en la cognición como objetivo primario o secundario; reportes de casos y series de casos también fueron incluidos para el análisis.

SINTESIS DE DATOS: Reportes de daño cognitivo asociados a estatinas fueron encontrados primariamente en estudios observacionales (ej. reportes de casos/series). Hubo un estudio aleatorio y controlado (RCT) que demostró este efecto adverso. Por el contrario, en la mayoría de los RCT y estudios observacionales, se encontró que las estatinas tenían un efecto neutral o beneficioso en la cognición. Datos preliminares suguieren que las estatinas que son menos lipofílicas (ej. pravastatina y rosuvastatina) pueden contribuir menos a daño cognitivo dado la limitada penetración de la barrera hematoencefálica. Estos fármacos pueden ser alternativas lógicas en casos donde se sospeche daño cognitivo secundario por otra estatina.

CONCLUSIONES: A pesar de varios reportes de daño cognitivo asociado a las estatinas, este efecto adverso es de ocurrencia rara en la totalidad de la literatura. Si se sospecha de daño cognitivo asociado a las estatinas, descontinuar el medicamento puede revelar una relación temporal. Cambiar de estatina lipofílica a una hidrofílica puede resolver el daño cognitivo. Los beneficio vasculares y el beneficio cognitivo putativo superan el riesgo de daño cognitivo asociado al uso de estatinas, por lo tanto, la evidencia actual no apoya la práctica de cambiar medicamentos con respecto al uso de estatinas dado este efecto adverso.

Traducido por Sonia I Lugo

RÉSUMÉ

L'Altération de la Cognition Associée aux Statines est-elle Cliniquement Importante? Revue narrative et recommandations cliniques

CH Rojas-Fernandez et J-C F Cameron

Ann Pharmacother 2012;46:549-57.

OBJECTIFS: L'objectif de cet article est d'explorer l'impact de l'utilisation des statines sur la cognition.

SOURCES DE DONNEES: Une recherche documentaire a été effectuée sur MEDLINE (1950 à nov 2011), EMBASE (1980 à nov 2011), et Cochrane Library (1960 à nov 2011) à l'aide des termes: "cognition/effets des médicaments", "délirium", "démence", "troubles amnésiques et cognitifs/induits chimiquement", "troubles de la mémoire/induits chimiquement", "inhibiteurs de l'hydroxyméthylglutaryl-CoA réductase/effets indésirables", et "inhibiteurs de l'hydroxyméthylglutaryl-CoA réductase". Une recherche bibliographique à partir des références retrouvées a également été réalisée.

SELECTION DES ETUDES ET EXTRACTION DES DONNEES: Les études ont été retenues pour l'analyse si elles examinaient l'impact de l'utilisation des statines tant comme critère d'évaluation primaire que secondaire; les rapports de cas et de séries ont également été pris en compte pour l'analyse.

SYNTHESE DES DONNEES: Les rapports d'altération de la cognition associés aux statines ont d'abord été prouvés dans des études observationnelles (ex: rapport de cas/séries). Un essai contrôlé randomisé (RCT) a démontré cet effet indésirable. En revanche, dans la majorité des RCT et des études observationnelles, les statines ont montré un effet soit neutre soit bénéfique sur la cognition. Des données préliminaires suggèrent que les statines moins lipophiles (c-à-d, pravastatine et rosuvastatine) pourraient être moins susceptibles de favoriser l'altération cognitive en raison de leur faible passage de la barrière hémato-encéphalique. Ces médicaments pourraient constituer une alternative logique dans les cas où une altération cognitive liée à une autre statine est suspectée.

CONCLUSIONS: Malgré plusieurs rapports sur l'altération de la cognition associée aux statines, cet effet indésirable reste d'une occurrence rare dans l'ensemble de la littérature. Si une altération de la cognition associée à une statine est suspectée, un test d'interruption peut révéler une relation temporelle. Passer d'une statine lipophile à une statine hydrophile peut également corriger l'altération cognitive. Les bénéfices vasculaires et les bénéfices cognitifs potentiels surpassent le risque d'altération cognitive associée aux statines; de ce fait, les preuves actuelles quant à cet effet indésirable ne sont pas en faveur d'un changement de pratique par rapport à l'utilisation des statines.

Traduit par Michel Le Duff