Statin-Associated Memory Loss: Analysis of 60 Case Reports and Review of the Literature

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Objective. To review case reports of statin-associated memory loss as well as the available published evidence for and against such a link.

Methods. We searched the MedWatch drug surveillance system of the Food and Drug Administration (FDA) from November 1997–February 2002 for reports of statin-associated memory loss. We also reviewed the published literature (using MEDLINE) and prescribing information for these drugs.

Results. Of the 60 patients identified who had memory loss associated with statins, 36 received simvastatin, 23 atorvastatin, and 1 pravastatin. About 50% of the patients noted cognitive adverse effects within 2 months of therapy. Fourteen (56%) of 25 patients noted improvement when the statin was discontinued. Memory loss recurred in four patients who were rechallenged with the drug. None of the 60 reported cognitive test results. Two placebo-controlled trials found no benefits for statins on cognition or disability. One randomized controlled trial of simvastatin found no effects on cerebrospinal amyloid levels. In one small, randomized study, patients receiving statins showed a trend toward lower cognitive performance than those receiving placebo. Five observational studies found a lower risk of dementia among patients receiving statins.

Conclusion. Current literature is conflicting with regard to the effects of statins on memory loss. Experimental studies support links between cholesterol intake and amyloid synthesis; observational studies indicate that patients receiving statins have a reduced risk of dementia. However, available prospective studies show no cognitive or antiamyloid benefits for any statin. In addition, case reports raise the possibility that statins, in rare cases, may be associated with cognitive impairment, though causality is not certain.

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OUTLINE

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The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, also known as statins (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin), are the most widely prescribed drug class for treatment of dyslipidemias because of their convincingly

proven benefits. With more aggressive guidelines and an aging population, statins will be increasingly prescribed, more statins will be developed, and the trend will be toward earlier treatment and higher dosage.

The patient population receiving statins is already at risk for memory loss because of cardiac risk factors, advancing age, and amyloidosis. However, in contrast to the cardiovascular benefits, the effects of statins on cognition and neuronal function are not as well studied. Since cerebrovascular disease is known to cause memory loss, there is growing interest in examining whether statins have cognitive benefits. Experimental studies have shown that cholesterol-fed wild-type rabbits develop brain pathology similar to that of Alzheimer's disease.[1] Transgenic mouse models of Alzheimer's disease exhibited increased amyloid plaques when mice were fed a cholesterol diet.[1] Cell culture and in vivo animal studies have shown that reducing cholesterol can inhibit β-amyloid synthesis.[1]

Consistent with these preclinical findings, observational studies have found that patients receiving statins have a lower risk of dementia.[2–6] Paradoxically, published case reports[7, 8] and an increasing number of anecdotal stories in the lay media have linked statin intake to adverse effects of memory loss or amnesia. Because cholesterol synthesis is essential for neurons to function normally, it is theoretically possible that excessive inhibition of cholesterol synthetic pathways may occasionally result in neurocognitive adverse effects. To gain further insight into links between statins and memory loss, we systematically reviewed a sample of adverse events reported to MedWatch, the drug surveillance system of the Food and Drug Administration (FDA) as well as the current literature.

Methods

We searched the MedWatch data from November 1997–February 2002 for spontaneous adverse events of cognitive impairment associated with simvastatin, pravastatin, and atorvastatin. Simvastatin and pravastatin were selected based on the large amount of data supporting these agents in primary and secondary prevention of coronary events. Atorvastatin was chosen because of its large market share and because it is being studied for its antidementia benefits. Other statins, such as lovastatin, cerivastatin, and fluvastatin, were not included in our MedWatch search due to research time constraints.

Our request was submitted according to the Freedom of Information Act, and we were sent electronic files. The FDA as well as pharmaceutical companies have dedicated proprietary software for analyzing and conducting searches of adverse event reports. The dictionary used to code MedWatch adverse event terms is also proprietary; neither the software nor the dictionary was available to us.

Our initial searches were conducted on a personal computer using a word search, and we later reviewed selected reports manually. Approximately 25,000 adverse events (~13,500 with atorvastatin, ~ 8500 with simvastatin, ~3000 with pravastatin) were reported to MedWatch during this period. All three drug files were searched, using the following as preferred terms: memory, confusion, Alzheimer, think, cognition, attention, and mental. Using other search terms (e.g., those used by the FDA) may have yielded additional cases; however, we wished simply to identify a selection of representative cases rather than all of them. We chose those in which the statin was considered the primary suspect as the cause of mental status changes. About 2% of statin-associated adverse events had a cognitive identifier (cognitive, attentional, or amnestic disorder). The complete MedWatch reports were ordered from the FDA and were then reviewed to eliminate duplicates as well as adverse events that did not clearly involve memory loss or cognitive impairment. This resulted in 60 cognitive adverse events associated with pravastatin, simvastatin, and atorvastatin.

Documentation of statin type, reporter status, mean age, age range, sex, type of memory loss, time to memory loss, statin dosage, and effects of drug discontinuation and rechallenge were reviewed. Reporter status (person who submitted the report) was classified according to the checked box on the report form. As such, this was a descriptive study, and no statistical analyses were performed. Because individual MedWatch reports vary in completeness of demographics and clinical data provided, we have specified where such data were missing. Because reporters' names are deleted from MedWatch reports sent under the Freedom of Information Act, we could not contact the reporters to verify or clarify any information.

Using MEDLINE, we reviewed the published literature from January 1980–September 2002. Search terms used were HMG-CoA reductase inhibitors and statins, which were cross-

referenced with each of the following terms: memory, brain, amnesia, cognition, mental, dementia, and Alzheimer's disease. We also used the prescribing information for atorvastatin, simvastatin, and pravastatin (dated April, May, and October 2002, respectively) as part of our review.

Results

Review of MedWatch Reports

Patient Data

For the 60 case reports of statin-associated memory loss identified, the patients' mean age was 62 years (range 30–84 yrs). Age was not documented for 14 patients. Four were in the 30–45-year age range, 22 in the 46–65-year age range, and 20 in the 66–85-year age range. Thirty-two patients were women, 25 men; three reports did not document sex. Twenty-four (40%) reports were submitted by health care professionals and 36 (60%) by patients receiving statin therapy.

Nature of Memory Impairment

Seventeen patients had short-term memory loss, six had amnesia, and 37 had unspecified memory loss. For the 30 patients with documented time to onset of memory loss after the start of statin therapy, median time was 60 days; approximately 50% of these patients experienced memory impairment within the first 2 months of the start of statin therapy. Two cases illustrate the nature of these reports.

Case No. 1. This case was reported by a 53-year-old woman who experienced "serious brain fog and cognitive impairment" after a few days of atorvastatin therapy. She couldn't function effectively enough to perform her daily work tasks at her office. On her own accord, she stopped taking the drug after 5 days of therapy, and 3 days later her memory had returned to normal. She said she had not been warned of the possibility of this adverse effect, and apparently she had not consulted her health care provider about it. She also reported being in "very good health except for high cholesterol and mild osteoporosis." She took hormones and bisoprolol-hydrochlorothiazide.

Case No. 2. This report, submitted by a nurse practitioner, described a 49-year-old man who was treated with simvastatin 10 mg/day for hypercholesterolemia; he received no concomitant drugs. About 40 days later, he developed "memory loss, anger, aggression, and crankiness." These symptoms lasted 3 weeks. Simvastatin was discontinued, and 2 weeks later the patient's "personality" returned to normal. No further details were provided.

Type of Statin and Medical History

Our case reports involved simvastatin (36 patients), atorvastatin (23 patients), and pravastatin (1 patient). Mean daily doses reported were simvastatin 18 mg and atorvastatin 25 mg; pravastatin dose was not specified. The reports did not contain adequate information regarding lipid levels at baseline or at the time of the memory complaint to examine as a variable.

No specific memory test results were documented in any of the 60 reports. Four reports documented tests such as computed tomography, magnetic resonance imaging (MRI), intelligence quotient (IQ), and an unidentified cognitive test. Test results were normal for three of the four patients; MRI results were unknown for one patient.

Concomitant disorders commonly documented in MedWatch reports were hypercholesterolemia (32 patients), hypertension (6), other cognitive disorders (4), history of stroke (3), history of myocardial infarction or other heart problems (3), osteoporosis (3), and head trauma (1). Concomitant drugs commonly documented were over-the-counter (10 patients), thyroid replacement (8), hormone replacement (7), β-blockers (7), angiotensin-converting enzyme inhibitors (4), calcium channel blockers (4), anticoagulants (4), and steroids (4).

Statin Withdrawal and Rechallenge

Thirty-three reports documented withdrawal of statin therapy after the appearance of memory loss (17 patients were taking simvastatin, 16 atorvastatin). Statin therapy was continued in 11 patients; statin withdrawal was not documented for 16. Of the 33 patients, memory loss resolved or improved in 14 when the statin was withdrawn. Eleven reports indicated no improvement in memory loss, and eight indicated unknown cognitive function after statin withdrawal. Of the four reports (three patients taking atorvastatin, one simvastatin) documenting the effects of rechallenge with the statin, all four reported reappearance of memory loss symptoms.

Overall details were sparse in these reports.

Table 1. Published Prospective, Randomized, Controlled Studies of Effects of Statins or Diet on Cognition

Treatment	No. of Patients	Age Range (yrs)	Results
Simvastatin[9]	20,536	40–80	No statistically significant difference in cognition between statin and placebo groups.
Pravastatin[10]	2891 (pravastatin) 2913 (placebo)	70–82	No statistically significant effects on MMSE, word recall, or performance time.
Lovastatin[11]	98 (lovastatin) 96 (placebo)	24–60	Placebo group improved from baseline on all neuropsychological tests ($p<0.04$); lovastatin group improved from baseline only on memory recall test ($p=0.03$).
Simvastatin, pravastatin[12] (crossover study)	36	40–60	No statistically significant effects on word recall test, profile of mood states, choice reaction time test, symbol substitution, or drowsiness rating.
Simvastatin, pravastatin[13] (crossover study)	25	20–31	No statistically significant effects on EEG potential, mood, sleep, or cognitive performance.
Simvastatin[14]	24 (simvastatin) 20 (placebo)	59–77	No statistically significant effects on CSF levels, AB40, or AB42.
Low-fat diet, low-cholesterol diet[15]	52 (low-fat diet) 53 (low-cholesterol diet) 50 (control)	41–65	At 12 wks, results of the sustained attention task differed significantly ($p<0.001$) in groups with reduced cholesterol.

MMSE = Mini-Mental State Examination; EEG = electroencephalogram; CSF = cerebrospinal fluid.

Memory loss resolved within 1 week of statin withdrawal for one of the three patients receiving atorvastatin; memory loss occurred after 2 weeks of the start of statin therapy in another. In the third patient, memory loss occurred 6 weeks after the start of therapy and 6 weeks after rechallenge, with amnesia lasting 6–12 hours each time. For the patient receiving simvastatin, memory loss resolved within 1 month after drug discontinuation. No other details were available.

Published Reports of Statin-Associated Memory Loss

We identified two published case reports of statin-associated memory loss by searching MEDLINE. One report described a 51-year-old man who experienced delayed-onset, progressive memory loss after approximately 12 months of receiving simvastatin 40 mg at bedtime for hypercholesterolemia. His memory continued to worsen over the next 3 months. The memory loss was attributed to simvastatin, which was discontinued, and pravastatin 40 mg at bedtime was initiated. The patient's short-term memory loss resolved after 1 month.[7]

The second report described a 67-year-old woman who had been treated with atorvastatin 10 mg/day for hypercholesterolemia for the past year with no reported adverse effects. Two months after the patient's atorvastatin dosage was increased to 20 mg/day, she experienced short-term memory loss, mood alterations, and social impairment. After discontinuation of atorvastatin, she experienced a marked improvement in short-term memory.[8]

Neither patient in these two case reports was rechallenged with the suspected drug. No cognitive tests were noted for the patient receiving simvastatin; the report of the patient receiving atorvastatin described repeated tests of mental status but provided no specific details.

Cognitive Outcomes in Randomized Trials of Statins

We identified several randomized studies of statins in which objective neuropsychological testing or brain amyloid levels were examined as a primary or secondary outcome.[9–14] One study also examined cognitive function and cholesterol reduction by means of low-fat diets.[15] These trials are described in Table 1.

The Heart Protection Study[9] involved 20,536 patients who were randomized to simvastatin 40 mg/day or placebo and were followed for 5 years. Patients in the study met the following criteria: aged 40–80 years, nonfasting serum total cholesterol level of 135 mg/dl, and at a considerable risk of death in 5 years from coronary heart disease based on medical history. Primary outcomes measured were mortality and fatal or nonfatal vascular events. In addition, the investigators used the validated modified

Telephone Interview for Cognitive Status questionnaire[16] during the final phase of the trial to monitor cognitive decline. No significant differences were noted in cognition between patients who received statin therapy and those who received placebo, either overall or in subgroups defined with respect to age at study entry or to previous stroke history.[9]

In the Prospective Study of Pravastatin in the Elderly at Risk of Vascular Disease (PROSPER),[10] 5804 patients aged 70–82 years, with a history of or risk factors for vascular disease, randomized to either pravastatin 40 mg/day or placebo, were followed for an average of 3.2 years. Pravastatin lowered low-density lipoprotein cholesterol (LDL) by 34% (hazard ratio [HR] 0.85, 95% CI 0.74–0.97, p=0.014) and reduced coronary mortality by about 24% (HR 0.76, 95% CI 0.58–0.99, p=0.043). Stroke risk was unaffected although the hazard ratio for transient ischemic attack was lower. Pravastatin had no significant effects on disability or on cognition (measured by the Mini-Mental State Examination [MMSE], word recall tests, or performance time).[10]

A double-blind, placebo-controlled trial[11] assessed cognitive function and psychological well-being in 194 healthy adults. Subjects were aged 24–60 years and had an LDL level of 160 mg/dl or higher. Each was randomly assigned to receive lovastatin 20 mg/day or placebo for 6 months. Serum lipid levels were measured throughout the study. At baseline and at completion of treatment, comprehensive neuropsychological tests were conducted for attention (digit vigilance, letter rotation, digit span, recurring words), psychomotor speed (grooved pegboard, maze, digit symbol), mental flexibility (Stroop interference, trail making, digit vigilance, letter rotation), working memory (associative learning, digit span), and memory retrieval (controlled oral word association, digit symbol recall, verbal recall, complex figure).

Psychological well-being was assessed by daily diaries and subject interviews. At 6-month follow-up, the placebo group had improved significantly in all five domains of cognitive function ($p<0.04$). The lovastatin group improved only on memory recall tests (p=0.03). Improvement in the placebo group was significant compared with the lovastatin group in tests of attention (p=0.03) and psychomotor speed (p=0.004). Cognitive function decreased in subjects whose mean LDL level was 109 ± 11 mg/dl (p=0.007).[11]

A crossover study[12] investigated the effects of simvastatin and pravastatin on cognitive function in 36 patients (aged 40–60 years) who had hypercholesterolemia. Patients were randomized to receive simvastatin 20 mg/day or pravastatin 40 mg/day in a double-blind, placebo-controlled fashion for two 4-week periods separated by a 1-week washout period. Both simvastatin and pravastatin produced a statistically significant reduction in total cholesterol and LDL levels compared with placebo. Neither drug produced any significant differences compared with placebo in central nervous function.

A randomized, double-blind, placebo-controlled crossover trial[13] measured the effects of simvastatin and pravastatin on central nervous system activity in 25 healthy subjects. Two 4-week periods were separated by a washout period of 4–6 weeks. No significant differences in electroencephalographic evoked potentials, mood, sleep, or cognitive performance (assessed by the digit symbol substitution test) were observed with either drug compared with placebo.[13]

A randomized, double-blind study[14] investigated whether statins would alter cholesterol metabolites and reduce amyloid-β levels in the cerebrospinal (CSF) fluid of 44 patients with Alzheimer's disease. Overall, simvastatin did not significantly alter CSF levels of either Aβ40 or Aβ42.

A randomized study of 155 healthy adults[15] examined low-fat diets as a way to lower cholesterol and assess whether a low-cholesterol diet would adversely affect mood and/or cognitive function. After 12 weeks, subjects consuming a low-cholesterol diet had significantly lower total serum cholesterol levels ($p<0.001$); all three groups (low-fat diet, low-cholesterol diet, and control) showed some improvement on three of four psychological tests. Subjects consuming a low-cholesterol diet had significantly worse ($p<0.001$) results than the control group on a fourth psychological measure, which required the greatest amount of processing. The change in performance on the sustained-attention cognitive test was correlated with the change in total serum cholesterol level (r=0.21, p=0.01).

Observational Studies of Statin Therapy and Risk of Dementia

We identified five published observational studies[2–6] (Table 2) examining the effects of statin use on cognitive function or risk of dementia.

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Table 2. Observational Studies of Effects of Statins on Cognition

Design	Statins Prescribed	Treatment Group, No. of Patients	Age (yrs)	Results
Epidemiologic, retrospective nested case-control study[2]	Atorvastatin, cerivastatin, fluvastatin, pravastatin, simvastatin	Group 1: Dementia, 284, Statins, 13 Group 2: Controls, 1080 Statins, 104	≥ 50	Relative risk of dementia was reduced 0.29 in patients taking statins (95% CI 0.13–0.63, p=0.002).
Retrospective, multicenter, epidemiologic, cross-sectional analysis[3]	Lovastatin, pravastatin, simvastatin	Lovastatin, 4180 Pravastatin, 2326 Simvastatin, 3580	≥ 60	Prevalence of AD was 60–73% lower in patients receiving lovastatin or pravastatin than in the entire cohort (p<0.001).
Retrospective cohort case-control study[4]	Not specified	Statins, 57 Controls, 2248	≥ 65	Statins were associated with a lower risk of dementia in patients aged < 80 years (OR 0.26, 95% CI 0.08–0.88).
Multicenter secondary analysis[5]	Simvastatin, atorvastatin, pravastatin, lovastatin, fluvastatin	Statins, 583 Controls, 454	< 80	Modified MMSE scores were higher in the statin group (93.7) vs the control group (92.7) (p=0.02).
Retrospective study of postmenopausal women[6]	Not specified	Statins, 113 Controls, 542	52–98	Prevalence of dementia-AD was decreased (p<0.05) and MMSE scores were higher in the statin vs the control group (p=0.025).

CI = confidence interval; AD = Alzheimer's disease; MMSE = Mini-Mental State Examination.

database from 368 general practitioners in the United Kingdom, 284 patients with dementia were each matched with up to four controls (1080 controls).[2] Patients who started receiving lipid-lowering or statin therapy 180 days before the index date were considered users. The risk of dementia for patients aged 50 years or older who received statins (adjusted relative risk 0.29, 95% CI 0.13–0.63, p=0.002) was significantly lower than for those with untreated hyperlipidemia or those prescribed nonstatin lipid-lowering agents. This study did not distinguish between the risk of Alzheimer's disease and the risk of other forms of dementia. Also, it did not examine whether the effects were related to lipid levels or verify the charts to confirm the accuracy of dementia diagnoses.

A retrospective, cross-sectional analysis of rates of diagnosis of probable Alzheimer's disease, reviewed all medical records over a 2-year period from three different hospitals.[3] Patients receiving statins were compared with those receiving drugs to treat hypertension or cardiovascular disease. The overall frequency of dementia diagnosis was 1.28%. The frequency of diagnosed Alzheimer's disease in patients taking lovastatin or pravastatin was 60–73% lower than in the total population or those taking other drugs (p<0.001). Simvastatin was not associated with this effect. Two of the study authors have submitted a patent application for administration of statins in treating Alzheimer's disease.

A retrospective case-control study analyzed data from a subset of 2305 patients, aged 65 years or older, for whom health information, drug use, and cognitive status were known.[4] Use of lipid-lowering agents was significantly more common in younger (65–79 yrs) than older (≥ 80 yrs) patients (p<0.001). Statins as well as other lipid-lowering agents reduced the risk of Alzheimer's disease in patients younger than 80 years (odds ratio [OR] 0.26, 95% CI 0.08–0.88), but not in those aged 80 years or older.[4]

A multicenter observational study examined the cognitive correlates of use of statins and changes in serum lipoprotein levels.[5] This was a secondary analysis of data from 1037 postmenopausal women with coronary disease who were enrolled in an estrogen-progestin replacement research study; 583 (56%) were taking statins. Patients receiving statins had a minimally higher mean modified MMSE score than those not receiving statins, (93.7 vs 92.7, respectively, p=0.02). This translated into a 1%

difference on this test. Women in the highest quartile for LDL levels had lower mean MMSE scores by about 2% (93.7 vs 91.9) and an increased likelihood of cognitive impairment (OR 1.76, 95% CI 1.04–2.97).

A retrospective, case-control cohort study investigated the association between statin use and prevalence of dementia.[6] The study involved a convenience sample (655 patients, mean age 78.7 yrs) derived from the population, based on easy availability and/or accessibility, in a general practice. Cognitive tests such as the MMSE, clock-drawing test, and geriatric depression scale were performed at baseline and follow-up. Among the patients selected, 233 (36%) were positive for dementia. At the initial visit, 113 (17%) patients were receiving statin therapy; the other 542 patients served as controls. At baseline, the mean MMSE score for the statin group was 26.5 vs 21.4 for the control group ($p<0.0001$). The number of dementia diagnoses at baseline was also higher in the control group. Compared with baseline cognitive test results, at follow-up the statin group showed improvement in MMSE scores by 0.7 versus a 0.5-point decline in the control group ($p=0.025$).[6]

Discussion

The cardiovascular benefits of statins are well established, and they reduce the risk of death by 14–28% in specific populations.[17] However, the effects of these agents on the human brain are not as well established. The more lipid-soluble the statin, the greater propensity it has to cross the blood-brain barrier and affect the central nervous system.[18] According to some reports,[1, 8] simvastatin is the most lipophilic drug in its class; pravastatin is the least lipophilic. Some reports state that atorvastatin does not cross the blood-brain barrier, whereas others state that the drug has intermediate lipophilicity.[1, 8] If the effects of statins on memory and dementia are mediated directly at the neural level, then one would predict that lipophilicity would be correlated with both the protective and the adverse neural effects associated with statins.

As reported above, there is great interest in developing statins as a treatment for dementia and as an agent for prevention of dementia in healthy elderly individuals. Our study was initiated because of this interest, along with reports in the lay press and consumer forums regarding statin-associated memory loss. Because an initial literature search yielded few such published cases, we searched MedWatch to study the clinical characteristics of reported statin-associated memory loss. As such, this is the first scientific endeavor to systematically analyze a relatively large series of cases (60) of documented memory loss associated with statins. In our series, more than half the reports were from consumers. The main symptom appeared to be short-term memory loss that occurred a few months after the start of statin therapy or after a dosage increase.

Global or partial amnesia was also reported. All but one of the reports identified using our search criteria involved atorvastatin or simvastatin. In some cases, memory loss resolved completely after discontinuation of the statin; in others it did not. In four cases, rechallenge appeared to reproduce memory loss. Most reports contained only subjective information. No dose-effect relationship could be demonstrated because of insufficient data. Similarly, no relationship between any laboratory parameters (e.g., lipid levels) and memory could be demonstrated because of the lack of such data in the reports. Confounding concomitant variables (e.g., transient ischemic attacks or other drugs that may cause memory loss) were present in some but not all reports. Information on medical history, or concomitant diseases or drugs, was absent or incomplete in most reports. Because many of the reports were from consumers, there is some reason to be cautious about the accuracy of reported medical information. However, lay persons can accurately notice short-term cognitive impairments caused by drugs such as alcohol or benzodiazepines.

The information in the 60 reports of spontaneous adverse events we analyzed do not permit conclusive judgments about causality. The high background rate of memory loss in this population due to aging and vascular risk factors could lead to detection bias. Likewise, the absence of objective memory tests or lipid data made it difficult to confirm the memory change and establish a dose-severity relationship or links with cholesterol levels. Cognitively high-functioning individuals may often experience subtle memory loss that they can accurately report but is often not detectable even with neuropsychological testing.

A review of the randomized clinical trial data does not shed additional light on this issue. Many large published cardiovascular trials of statins did not use a formal neuropsychological

test battery to assess for memory outcomes, but used quality-of-life measures, which are not as sensitive or specific for memory. There may be a number of other statin studies that collected such memory data but are not published.

In one published placebo-controlled trial of lovastatin, the placebo appeared to have greater consistent cognitive benefits than lovastatin on some measures over a 6-month period.[11] It has been suggested that a very low cholesterol level in neuronal membranes may decrease cognitive function, whereas others have disagreed with this hypothesis.[19] More important, one large prospective study (PROSPER) found no significant benefit for pravastatin regarding stroke risk, cognition, or disability.[10] As cognitive measures, this study used a global measure of cognition as well as measures of memory and speed of performance. Although cognition was a secondary outcome, it can be reasonably concluded from this study that pravastatin over a 3-year period does not provide any cognitive benefits.[10]

A review of observational studies in the literature[2–6] yielded several large case-control studies that suggest a substantial protective effect of statins on lowering the risk of dementia. These studies used statistical adjustments or case-control matching to account for potential biases (e.g., concomitant illnesses or other baseline differences). The fact that these findings were present in diverse population samples across five studies in the United States and the United Kingdom is a strength. Because any protective effect against dementia must be associated with a slower rate of memory loss, these data argue against an adverse effect of statins on memory.

The observational studies[2–6] may have been limited by their retrospective design, inaccurate diagnoses of dementia, and indication biases. These studies did not distinguish type of statin, dosage, or duration of therapy. In the absence of dosage or duration effects and retrospective data analyses, their findings are at best preliminary. Patients with dementia, lower economic status, or less education may be less likely to be prescribed statins than those without dementia; hence, there could be a cohort bias as well.[20]

Our report does not estimate frequency or prevalence of statin-associated memory loss since MedWatch case reports are likely to underestimate the true rates of adverse events. Approximately 2% of all reports or statin-associated adverse events in MedWatch appear to have a cognitive or amnestic identifier. Likewise, the prescribing information for pravastatin lists memory loss as an adverse event in less than 1% of patients,[21] whereas that for simvastatin reports memory loss as a class effect.[22] The prescribing information for atorvastatin lists amnesia as an adverse event in less than 2% of patients[23] (Table 3). Hence, these are likely to be rare.

Table 3. Comparison of Prescribing Information

Statin	Recommended Dosage (mg/day)	Frequency of Cognitive-Related Adverse Events
Atorvastatin[23]	10–80	< 2% (amnesia)
Pravastatin[21]	10–80	< 1% (memory impairment)
Simvastatin[22]	5–80	Not specified

According to a written communication from the manufacturer of atorvastatin (O. J. Lopena, Pharm.D., Pfizer Inc., written communication, 2002), amnesia during clinical trials occurred in 7 (0.3%) of 2502 patients receiving atorvastatin and in 2 (0.3%) of 742 subjects during comparative trials with other statins (lovastatin, pravastatin, simvastatin). Abnormal thinking was reported in 4 (0.2%) of 2502 patients receiving atorvastatin therapy and in none of 742 patients receiving other statins (lovastatin, pravastatin, simvastatin).[24] None of these data may provide a true estimate of the frequency or prevalence since memory loss was not specifically studied in many of these trials. Incidence studies of other adverse events (e.g., sexual dysfunction with antidepressants) have shown that spontaneous reporting may underestimate prevalence, in some cases by 5–20-fold.

Our review of MedWatch reports and the literature provided no definite evidence that a particular statin is more likely than others to be associated with cognitive adverse effects or benefits. Because of limited resources, we examined only three statins. There appear to be fewer cases of memory loss associated with pravastatin in the 60 case reports we selected, although this may simply reflect our selection criteria or less frequent use of the drug.

There are many possible mechanisms by which statins may benefit or impair cognition. Statins may increase endothelial nitric oxide synthase and reduce endothelin-1, thereby increasing cerebral blood flow.[25] The antioxidant, antiinflammatory, and platelet effects of statins may also play a role in neuroprotection (Table 4).[25–27]

Table 4. Potential Mechanisms by Which Statins May Affect Brain Function

Effect	Mechanism
Platelet activity	↓ platelet aggregation and ↓ deposition onto damaged vessel walls
Thrombin generation	↓ thrombus generation ↓ generation of thrombin cleavage peptides
Nitric oxide formation	↑ cerebral blood flow ↓ toxic production of nitric oxide
Antiinflammatory effects	↓ β-amyloid peptides Aβ42 and Aβ40 ↓ formation of proinflammatory isoprenoids ↓ expression of adhesion molecules ↓ elaboration of potentially damaging cytokines from macrophages during cerebral ischemia
Antioxidant effects	↓ free radical injury and lipoprotein oxidation
Inhibition of cholesterol synthesis	Can be good or bad. May interfere with neuronal function if statin is lipophilic; cholesterol essential for membrane integrity.

Data from references 1, 25–27.

In vitro and in vivo experimental animal studies indicate that statins reduce amyloidogenesis,[1, 26] although a human study found no effects of simvastatin on amyloid.[14] Cholesterol is critically involved in cell membrane integrity and function; thus, one could speculate that cognitive function may worsen if excess inhibition of cholesterol synthesis reduces neuronal membrane levels. Optimal harnessing of the cardiac and neural benefits of statins remains a desirable goal.

Conclusion

The cardiovascular benefits of statins are established; we reviewed the emerging links between statins and human memory. Research using MedWatch data has many limitations, such as incomplete data, lack of controls, and various biases, such as detection or attribution bias. Nevertheless, MedWatch reports can provide a signal for infrequent adverse events. In particular, the reports of statin-associated memory loss suggest that some patients may experience subjective memory loss after statin therapy is begun. In some patients the memory loss appeared to resolve after discontinuation of the statin. The relationship between statin dosage, lipid levels, and memory loss could not be determined in our series because of lack of information. More reports of memory loss were associated with lipophilic statins (e.g., atorvastatin and simvastatin), although it is not clear whether atorvastatin actually crosses the blood-brain barrier. Until causality is assessed in more rigorous studies, awareness of this issue may help clinicians better counsel patients and improve monitoring of adverse events.

Neither observational studies nor case reports can prove causality. There is no prospective evidence of any neurocognitive benefits or risks associated with statins. Overall, statins clearly offer substantial cardiovascular benefits, and a small number of case reports of memory loss should not discourage appropriate statin administration. Because cholesterol synthesis is essential for neuronal function, greater attention to cognitive outcomes in patients receiving statins is warranted, especially in populations already at risk for memory loss. Although the evidence does not yet support routine administration of serial bedside memory tests in otherwise healthy patients receiving statins, clinicians must be able to detect memory changes among their patients and routinely inquire about mental status. Given the high background rate of memory loss in the population receiving statins, prospective controlled studies comparing the short- and long-term effects of various statins on cognitive function are warranted.

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