Statin-Associated Adverse Cognitive Effects: Survey Results from 171 Patients

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Study Objective. To characterize the adverse cognitive effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins).

Design. Patient survey–based analysis.

Patients. One hundred seventy-one patients (age range 34–86 yrs) who self-reported memory or other cognitive problems associated with statin therapy while participating in a previous statin effects study.

Measurements and Main Results. Patients completed a survey assessing statin-associated, cognitive-specific adverse drug reaction (ADR) characteristics, relation of the ADR to specific statin and dose (or potency), and time course of symptom onset and recovery. Visual analog scales were used to assess the effect of the cognitive ADRs on seven quality-of-life domains. Demographic and clinical data were also collected. To target cognitive ADRs with a probable or definite causal relationship to statins, the Naranjo adverse drug reaction probability scale was used: 128 patients (75%) experienced cognitive ADRs determined to be probably or definitely related to statin therapy. Of 143 patients (84%) who reported stopping statin therapy, 128 (90%) reported improvement in cognitive problems, sometimes within days of statin discontinuation (median time to first-noted recovery 2.5 wks). Of interest, in some patients, a diagnosis of dementia or Alzheimer's disease reportedly was reversed. Nineteen patients whose symptoms improved or resolved after they discontinued statin therapy and who underwent rechallenge with a statin exhibited cognitive problems again (multiple times in some). Within this vulnerable group, a powerful relationship was observed between potency of the statin and fraction of trials with that agent resulting in cognitive ADRs ($p<0.00001$). Quality of life was significantly adversely affected for each of the seven assessed domains (all $p<0.00000001$).

Conclusion. Findings from the survey suggest that cognitive problems associated with statin therapy have variable onset and recovery courses, a clear relation to statin potency, and significant negative impact on quality-of-life. Administration of a patient-targeted questionnaire is a feasible approach that provides a useful complement to other ADR surveillance approaches.

Key Words: statin, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, HMG-CoA reductase inhibitor, cholesterol, memory, cognition, adverse drug reaction, ADR.

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Adverse drug reactions (ADRs) often do not manifest during clinical trial testing, frequently becoming evident only after the drug is widely used in clinical practice.[1, 2] Selection criteria used in clinical trials may result in elimination of patients with characteristics that may foster

vulnerability, such as advanced age, concurrent diseases, and use of multiple drugs[3]—variables that are often present in the target population.[4] Postmarketing surveillance provides a major source of information for drug withdrawals.[5, 6] Yet, reporting rates are low, and half the adverse effects that lead to black-box warnings on drug labels (or less often, withdrawals) are not identified for 7–25 years after the drug's release.[1] Although practicing clinicians are primarily targeted by ADR reporting entities,[7] patients have been identified as a reliable source of ADR reports[8, 9] that can enrich and indeed complement provider-targeted reporting.[10]

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), a class of cholesterol-lowering drugs, have documented benefits to cardiovascular disease. They are widely prescribed, and since revisions to the National Cholesterol Education Program guidelines advocate lower cholesterol levels as desirable,[11, 12] statin use has continued to expand. Statins are generally considered to be well tolerated, but like all drugs, there are potential adverse effects. The best recognized statin-associated ADRs affect muscle and manifest as pain, weakness, and/or fatigue,[13–15] and rarely rhabdomyolysis,[16–19] a serious condition that can result in kidney failure and death.

Less understood but also commonly reported with statin therapy are cognitive problems, often resolving after statin discontinuation. Evidence from case reports[9, 20–26] complements results of two randomized trials, which identified decreased cognitive function in patients taking statins relative to placebo.[27, 28] Little is known about statin-associated cognitive ADR characteristics, time course, quality-of-life impact, dose (or potency) dependence, and recovery. In addition, little is known about the occurrence of these effects in populations without expectation of mortality benefit from statin therapy (e.g., women and the elderly).[29] Thus, we sought to improve our understanding of statin-associated cognitive effects by using a patient-targeted survey approach.

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Methods

Patient Population and Survey Instrument

Patients in this study were selected from a subset of patients who participated in the University of California San Diego (UCSD) Statin Effects Study.[9] The subset consisted of 714 patients who reported potential statin-related problems by means of a general patient-targeted questionnaire submitted through mail or e-mail. A minority of patients reported potential ADRs from other cholesterol-modifying drugs, as well as from statins. Most patients learned about the UCSD Statin Effects Study through the media or Internet. No active recruitment or advertisement was used. No eligibility restrictions were applied beyond presence of self-reported adverse effects of lipid drugs and the ability to complete the survey in English. Of the 714 patients, 422 (59%) reported cognitive and/or memory problems, with or without other symptoms (e.g., muscle-related, neuropathic, and gastrointestinal problems). Cognitive problems were the second most reported adverse effect after muscle-related problems in this patient-targeted ADR database.

For our survey analysis, we asked the patients who had reported the statin-associated cognitive and/or memory problems to complete another survey, this one specific to their cognitive and/or memory issues. Survey questions included patient demographics, character of cognitive symptoms, time course of onset after starting statin therapy, time course and completeness of recovery after drug cessation, and symptom recurrence with rechallenge. Visual analog scales (from -10 "maximal possible worsening" to 0 "no effect" to +10 "maximal possible improvement") were used to assess the impact of cognitive ADRs on seven quality-of-life domains: emotional state or mood, family activities or function, social activities or function, occupational function, household function, recreational activities, and overall quality of life. (In addition, patients were asked if they spoke to their physician about their symptoms and their possible relation to statins; these data have been previously published[9]) Study methods and surveys were approved by the UCSD Human Subjects Protections Program, and

Table 1. Demographic and Clinical Characteristics of the Patients

Characteristic	All Patients (n=171)	Probable or Definite Causality Group (n=128)
	Mean ± SD (range)	
Age (yrs)	63 ± 11 (34–86)	63 ± 11 (39–86)
Total cholesterol level (mg/dl)[a]		
At baseline	245 ± 57 (128–427)	246 ± 57 (128–427)
During treatment	191 ± 37 (122–257)	191 ± 37 (122–257)
Decline with treatment	54 ± 47 (-5–170)	55 ± 47 (-1–170)
	Percentage of Patients	
Male	60	59
Caucasian	95	96
Married	70	68
Some college education	85	87
Cited amnesia episodes[b]	9	10
Cited concurrent statin-associated muscle-related symptoms	71	68

[a]Only 46 patients reported their total cholesterol level both at baseline and during treatment; 38 of the patients were in the probable or definite causality group. For comparison, 93 patients reported only their baseline total cholesterol level (mean ± SD 218 ± 60 mg/dl [range 110–427 mg/dl]).
[b]Defined as an episode of "lost time" or "blackout" for which the patient had no memory of events, with or without diagnosis of transient global amnesia.

patients gave written informed consent to participate.

Assessment of Causality

To target adverse cognitive effects with a probable or definite causal relationship to statin use, most analyses focused on data of patients who met the Naranjo adverse drug reaction probability scale criteria for probable or definite ADR causality.[30] It is recognized that these—or any—causality criteria have limitations and also a subjective element; however, these criteria are often used.[31] The Naranjo scale assigns positive and negative causality points based on 10 criteria, with a score of 9 or higher indicating definite ADR causality, and 5–8 probable, 1–4 possible, and 0 or lower doubtful causality.

Some criteria were not relevant as patients did not receive placebo, and objective evidence of problems was not formally elicited. (Some patients volunteered that objective evaluation was conducted with documentation of cognitive impairment with statin therapy. Consideration of this could only add positive but not negative points, thus its omission has potential only to understate ADR causality.) All patients received 1 point for the existence of previous compelling reports of cognitive ADRs to statin therapy (e.g., published case reports), 2 points for the event appearing after the drug was administered, and 2 points if no alternative cause was identified for the decline in cognition (although unknown causes may always exist). Although our point assignment provided sufficient points (a total of 5) for probable causality, we elected to err conservatively and required an additional condition for probable causality (to total 6 or 7 Naranjo points). We required that improvement was reported when the drug was discontinued (1 point) and/or the dose reduced (1 point). These criteria reflect back and strengthen the previous criteria, since other causes of cognitive symptoms would not be expected to exhibit improvement when statins were reduced or stopped. Three additional points were conferred if the patient underwent rechallenge with statins and the problem reappeared. Thus, patients who were rechallenged and experienced the same problems had a score above the threshold for classification as definite. Moreover, 1 additional point could be considered for all patients taking statins since no statin dose is free of risk for statin ADRs in some patients.

Statistical Analysis

Our analyses entailed the following: summary statistics for patient and symptom characteristics; nonparametric sign tests to appraise relative time to onset initially versus with rechallenge, and quality-of-life impact; and χ^2 tests and test-of-trend to compare fraction of trials with each statin resulting in cognitive ADRs, as a function

of that statin's usual potency. A p value of less than 0.05 was considered to indicate a statistically significant association.

Results

Of the 422 men and women who reported cognitive and/or memory problems, 181 (43%) completed our cognitive survey. Ten patients were excluded from the analysis: one whose symptoms consisted entirely of disturbing dreams (not the focus of the present analysis), six who submitted incomplete surveys, and three who cited no cognitive problems on this questionnaire. Thus 171 patients were available for analysis (Table 1). Based on the Naranjo adverse drug reaction probability scale criteria, ADRs for cognitive symptoms were classified as definite in 20 patients, probable in 108, possible in 43, and doubtful in none. Figure 1[29, 32–35] presents the breakdown of men aged 70 years or older and women (groups without expectation of a mortality benefit from statin use[29]) among the 128 patients with ADRs classified as probable or definite: 38 men and women (30%) were elderly, and 53 patients (41%) were women, with 16% overlap (i.e., 20 elderly women).

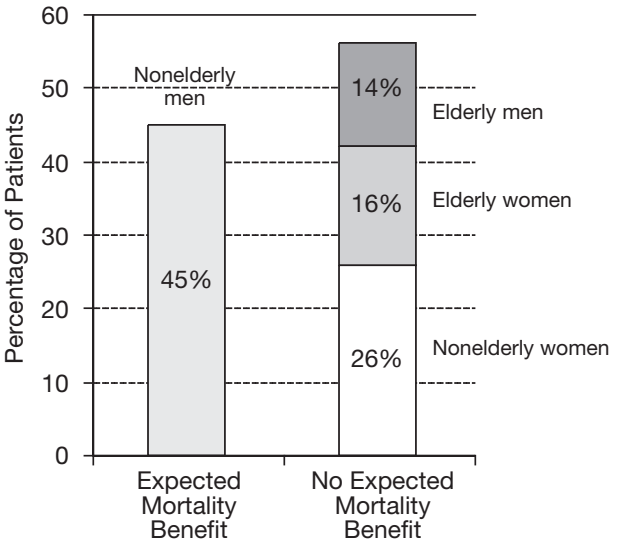

Figure 1. Percentage of patients with probable or definite statin-related cognitive adverse drug reactions (ADRs) (n=128); similar results were obtained by including patients with possible ADRs (n=43). Data are grouped by expected mortality benefit from statins. Expected mortality benefit of taking statins refers to the benefit exceeding the risk on objective indexes (all-cause mortality and all-cause serious morbidity—indexed by serious adverse events—in randomized trials). These end points show no trend to the benefit of lower cholesterol levels in women[32, 33] or individuals aged 70 years or older[34] even if at high cardiac risk. The bar graph on the left overstates the benefit of lowering cholesterol levels in nonelderly men, as not all these men had or were at high risk for heart disease, and one study of predominantly middle-aged men not at high cardiac risk showed no trend to benefit to mortality or all-cause morbidity.[29, 35]

Fifteen patients (9%) reported episodes of amnesia apparently associated with statin therapy, some with formal diagnoses of transient global amnesia (TGA). These episodes lasted 6–48 hours and were often characterized by the patient as episodes of "lost time" or "blackouts." (In TGA, there is anterograde memory loss during the episode—that is, failure to lay down new memories—which contributes to the subsequent retrograde memory loss for the period of the episode.[36, 37]) In 11 patients, amnesia episodes accompanied other cognitive or memory symptoms, whereas in three others (one of whom experienced five episodes of TGA while taking statins) the amnesia incidents were the sole statin-related symptom. One additional patient with amnesia had no other cognitive symptoms but experienced an unexplained 40-lb weight gain (a reported statin adverse effect[14]); both conditions resolved with statin discontinuation. No patient had a history of previous amnesia episodes or head trauma before starting statin therapy. Two of the 15 patients with amnesia had not discontinued statin therapy at the time they completed the survey. One of them experienced a diagnosed 8-hour episode of TGA shortly after his simvastatin dose was doubled from 20 to 40 mg; he had a reported 3-year history of progressively declining memory while taking statins. He completed the survey 6 days later with no additional amnesia episodes in this brief time. The second patient experienced an isolated, diagnosed 10-hour episode of TGA. The other 13 patients discontinued statin therapy and did not experience amnesia episodes while not taking therapy. Because of the severity of the effect, few of these patients elected to be rechallenged. Two patients who did attempt to resume statin therapy experienced amnesia episodes again with the statin.

The distribution of statin use among these patients correlates with the rank order of overall statin prescriptions,[38–41] both in the percentage of patients who tried each drug and the number of trials involving each drug (Table 2). The spectrum of cholesterol-lowering drugs (including nonstatins) that resulted in the onset of cognitive symptoms is shown in Table 3. However, not all usages of each drug led to cognitive complaints.

Table 2. Distribution of Statin Use Relative to Prescribing Pattern

Drug	No. (%) of Patients Who Tried the Drug (n=168)[a]	No. (%) of Trials with the Drug (n=308)[b]	Rank Order Tried	Rank Order of Overall Prescribing[c]
Atorvastatin	118 (70)	134 (44)	1	1
Simvastatin	69 (41)	76 (25)	2	2
Pravastatin	42 (25)	45 (15)	3	3
Lovastatin	20 (12)	20 (7)	4	4
Fluvastatin	10 (6)	14 (5)	5	5
Rosuvastatin	10 (6)	10 (3)	6	—
Cerivastatin	9 (5)	9 (3)	7	—

[a]Excludes three patients who tried only nonstatin drugs. Percentages total greater than 100% because several patients tried more than one drug.
[b]A different "trial" is defined as a transition to a different statin or dose, with or without a period of statin withdrawal.
[c]Prescribing order excludes cerivastatin (withdrawn from the U.S. market) and rosuvastatin (recently introduced to the U.S. market) and was determined from data spanning 2001–2007.[38–41]

Table 3. Distribution of Lipid-Lowering Drug Use, Potency, and Cognitive Symptoms

Drug	No. of Trials with This Drug	No. (%) of Trials That Resulted in Cognitive Symptoms[a]	Rank Order, Potency
Current statins[b]			
Atorvastatin	134	97 (72)	1, 2[c]
Rosuvastatin	10	7 (70)	1, 2[c]
Simvastatin	76	43 (57)	3
Pravastatin	45	19 (42)	4
Lovastatin	20	6 (30)	4
Fluvastatin	14	7 (50)	5
Other lipid-lowering agents			
Cerivastatin[d]	9	3 (33)	—-
Simvastatin-ezetimibe	8	3 (38)	—-
Niacin	9	1 (11)	—-
Red yeast rice	2	1 (50)	—-
Fenofibrate	1	1 (100)	—-

If a patient switched to a new drug without time off between drugs, the drug used during the onset of cognitive symptoms was reported here; subsequent drugs used that did not result in new symptoms were not counted as additional trials. $p<0.00001$, χ^2 test of trend for fraction of statin usages resulting in statin adverse drug reactions as a function of expected potency. (However, p value also applies with direct analysis of the groups as shown.)
[a]Percentages are derived from patients reporting cognitive symptoms from at least one statin and should not be taken to represent expected rates of cognitive problems in statin users more generally.
[b]Current statins were grouped according to high (atorvastatin and rosuvastatin), intermediate (simvastatin), and low (pravastatin, lovastatin, fluvastatin) potency to provide ample size for each potency group.
[c]Rosuvastatin is more potent than atorvastatin by milligram; however, atorvastatin 80 mg is widely advocated, but use of rosuvastatin 40 mg is discouraged by the U.S. Food and Drug Administration.
[d]Cerivastatin was withdrawn from the U.S. market.

The fraction of trials on each drug that resulted in cognitive ADRs was strongly related to relative potency of that statin ($p<0.00001$, χ^2 test of trend) in these patients with vulnerability to cognitive ADRs.

Time reported to cognitive symptom onset after beginning statin therapy was variable, ranging from 1 day to nearly 10 years (median time to onset 5 mo; Table 4). Discontinuation of statin therapy was reported by 143 patients (84%), of whom 128 (90%) cited cognitive symptom improvement after stopping the statin therapy, 55 of whom reported complete recovery. Eighty-nine patients (52%) provided information on recovery time (for patients who recovered multiple times, time to recovery after the

Table 4. Time of Cognitive Symptom Onset and Recovery

Parameter	No. of Patients Responding	Time (weeks)		
		Median	Mean ± SD	Range
Time to cognitive symptom onset				
First occurrence after starting statin	106	20	53 ± 89	1 day–480 wks
First occurrence in those with rechallenge data[a, b]	16	6	41 ± 85	1 day–336 wks
With rechallenge[a, b, c]	16	1	5 ± 7	1 day–28 wks
Time to recovery after statin discontinuation				
First-noted recovery	89	2.5	10 ± 19	1 day–144 wks[d]
Maximal recovery	78	8	21 ± 29	1 day–144 wks[d]

[a]Two-sided p=0.039 (sign test) for difference in time to first onset vs time to onset with rechallenge, limited to patients who reported this information for both.
[b]For patients who underwent rechallenge more than 1 time (three patients), the first rechallenge data are reported.
[c]Only two patients reported longer time to onset of cognitive symptoms on rechallenge compared with first onset. Both underwent rechallenge with less potent lipid agents (atorvastatin 20 mg followed by atorvastatin 10 mg; atorvastatin 10 mg followed by niacin 500 mg).
[d]The 144-wk values for first-noted recovery and maximal recovery were reported by different patients.

cessation of the first statin was used for analysis). Time course of recovery varied, ranging from 1 day to several years (Table 4). Appendix 1 describes briefly the recovery of a few patients with cognitive decline associated with statin therapy. The median time to first-noted improvement in cognitive symptoms was 2.5 weeks. Fifteen (10%) of the 143 patients who stopped statins perceived no subjective recovery after stopping therapy at the time the survey was submitted, but cognitive symptom progression had usually arrested or slowed. For some patients, however, insufficient time for recovery may have elapsed between drug discontinuation and survey completion (elapsed time was as little as 1 day).

Of 29 patients whose cognitive symptoms resolved after discontinuation of statin therapy and who underwent rechallenge (although not always at an equivalent lipid-lowering dose), 19 (66%) reported recurrence of cognitive symptoms as a result. Time from statin initiation to cognitive symptom onset was significantly shorter with statin rechallenge (median 1 wk) than for first cognitive symptom occurrence while taking statins (median 6 wks) for patients who reported time to symptom onset for both (p=0.039; Table 4).

Among 24 patients who underwent rechallenge with statin therapy and who reported the dose used for each trial of statin therapy, rechallenge with a higher expected potency statin (10 trials) yielded 80% recurrence of cognitive symptoms, rechallenge with similar expected potency (four trials) yielded 75% recurrence, and rechallenge with lower expected potency (10 trials) yielded 50% recurrence. Thus, a trend was noted toward greater cognitive symptom recurrence in those undergoing rechallenge with a higher or similar potency statin than with a lower potency statin; however, with the modest sample size, the difference was not significant (one-sided p=0.07, χ^2). Power was limited for this assessment: four patients who were rechallenged did not provide dose information, and other patients underwent rechallenge with nonstatin lipid-lowering drugs that act primarily through modification of non–low-density lipoprotein lipid elements, rendering dose "equivalencies" less meaningful (five trials, two of which resulted in recurrence of cognitive symptoms). "Effective dose" was calculated according to expected potency (cholesterol reduction) based on approximate statin dose equivalencies reported in the literature.[42–45]

Of the four patients who underwent rechallenge with putatively similar doses (potencies), the only patient in the group who underwent rechallenge with the same agent and dose experienced the same problem. In two others, symptoms recurred (rechallenge with pravastatin 40 mg after atorvastatin 10 mg, and cerivastatin 0.4 mg after atorvastatin 10 mg); however, in the fourth patient, symptoms did not recur (rechallenge with atorvastatin 10 mg after simvastatin 20 mg).

One hundred forty-three patients rated the impact of their cognitive symptoms on their quality of life, across seven domains, by means of visual analog scales. The average effect of cognitive problems on each domain was highly significantly negative (p<0.00000001, sign test for each) in patients meeting probable or definite ADR criteria (110 patients; Figure 2), with

similar results and significance in the total sample. Ratings of the occupation, emotional state, and recreation domains showed the largest reported reductions; recreation (mean -4.7 on a scale from -10 to +10) and occupation (mean -4.0) were the domains most affected in younger patients (age ≤ 55 yrs). For each domain, some patients noted a severely negative impact, with a score of -10 "maximal possible worsening."

Discussion

This study sought to capitalize on an enhanced patient-targeted ADR surveillance approach with a survey design to address issues related to cognitive adverse effects of statins that have not been captured through existing study approaches. Most cases met criteria for probable or definite ADR causality, with cognitive problems improving after statin therapy was discontinued, and in some, with statin rechallenge occurring and leading to recurrence. Time to recurrence with statin rechallenge was significantly shorter than initial time to onset of cognitive problems. A strongly significant relationship was seen between potency of the statin tried and likelihood of occurrence of cognitive problems, within this group selected for having cognitive problems while taking statins, providing internal support for validity of a statin relationship. Recovery varied from rapid to prolonged, and complete to incomplete (as has been reported for muscle problems with statins[16, 46]). The quality-of-life impact was strongly negative and extended across all assessed quality-of-life domains.

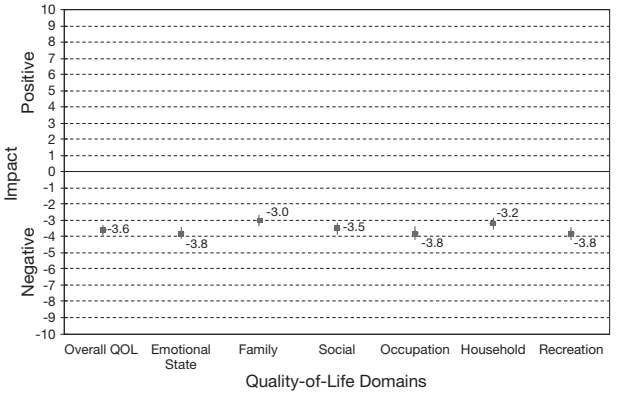

Figure 2. Mean impact of statin-associated cognitive symptoms on quality of life was negative across all seven quality-of-life (QOL) domains. Data are from the 110 patients from the probable or definite causality group who rated these domains using visual analog scales. Similar results were obtained when patients whose symptoms were possibly related to a statin were included. Error bars indicate standard error. Some positive values for quality of life appeared to reflect misinterpretations by two patients (e.g., all quality-of-life domains were rated neutral or positive on this scale in the context of narrative comments citing unfavorable quality-of-life effects); however, significance was high despite inclusion of these patients (two-sided $p<0.00000001$, sign test).

Although the statin potency analysis was strongly significant, the analysis by dose did not reach significance. This analysis included fewer patients (since not all recorded their dose for each statin). In addition, the dose equivalencies used are subject to error. Similar potency doses of different drugs that were deemed "equivalent" for our analyses are not truly equivalent based on average values in groups (e.g., simvastatin 20 mg, although listed as "equivalent" to pravastatin 40 mg,[42] in fact produces greater lipid level reduction than pravastatin 40 mg.[47]) Moreover, individuals differ in the relative effects of different statin drugs, due to genetic variations in metabolism or drug-drug or drug-food interactions (which may also lead to differences in effective potency of the same statin at different times).[48, 49] Thus, there is expected bias toward the null. Nonetheless, the primary concern is that the analysis was underpowered; given significance of the statin-potency association, a larger sample might be expected to affirm a dose association.

Of the cognitive ADRs deemed probably or definitely related to statin therapy, fewer than half of reports (45%) were from nonelderly men (age < 70 yrs), a group in whom there are prospects for survival benefit with statins, based on randomized trial data[29] (although these benefits are absent, even in this group, in those without high cardiovascular risk[50]). The remainder were female (42%) and/or elderly (age ≥ 70 yrs, 30%), groups in whom clinical trials (women[32, 51] and elderly[34]) show no trend to survival benefit with statins, even among those at high cardiovascular risk. Where mortality is neutral and data on all-cause serious morbidity are available, all-cause serious morbidity in patients taking statins tracks all-cause mortality,[34, 50, 52] with these indexes reflecting the sole available outcomes that equitably (and for mortality, objectively) balance risks and benefits of therapy to the patient. This suggests that many instances of cognitive problems potentially related to statins may arise in individuals in whom there is no clear evidence that benefits of treatment would exceed risks.

There is biologic plausibility for potential

cognitive effects of statins—negative as well as positive. (Indeed, we do not presume from the existence of cognitive adverse effects that cognition is necessarily adversely affected by statins on average.) Cholesterol is an important biologic molecule present in all cells and cell membranes, as well as in the blood, with a suite of pivotally important functions, including the following (among many others): myelin sheath formation; neurotransmitter receptor expression; neuron synapse development; production of steroid hormones (e.g., testosterone, estrogen, cortisol, and vitamin D) involved in brain and peripheral signaling, as well as in healthy cell function; and transport of antioxidants such as vitamin E, carotenoids, and coenzyme Q_{10} (important for energy production, cell function, and free radical defense throughout the body).[48, 53, 54] Although many mechanisms could play a role, we consider statins' potential impact on oxidative stress and mitochondrial function to be particularly germane, as we have described elsewhere.[48] The literature links mitochondrial mechanisms to the muscle-related adverse effects of statins[48]; however, mitochondrial dysfunction classically targets brain as well as muscle, manifesting symptoms in either or both.[55–57] This provides a foundation both for the primacy of these symptoms among statin-associated ADR reports as well as for their high coincidence (~70% of these patients with statin-associated cognitive ADRs also cited statin-associated muscle-related ADRs). This potential common mechanism also reinforces prospects for a range of vulnerability factors that may influence susceptibility to cognitive ADRs, including factors already shown to influence muscle-related ADR risk, such as genetic and biologic factors that modify drug metabolism, oxidation or antioxidation, and mitochondrial function.[48, 49] Whether other factors, such as apolipoprotein E genotype, may serve as effect modifiers for statin effects specifically on cognition remains to be established. (This could occur most obviously by statin antiinflammatory effects boosting the benefit side of the statin-cognition risk-benefit equation in those who have apolipoprotein E genotypes that confer vulnerability to Alzheimer's disease, an inflammatory condition; some preliminary evidence supports this possibility at least with established disease.[58])

The adverse cognitive experience while taking statins reported by patients is buttressed by previous case reports,[9, 20–26] as well as two randomized trials in which statins led to significant worsening of cognitive indexes relative to placebo.[27, 28] The existence of adverse cognitive effects while taking statins has no implications for average effects of statins on cognition, and it is possible that benefits or neutral effects on cognition may predominate in some settings.

Statins can benefit endothelial function or flow and blood pressure,[47] and protect against stroke in clinical trials[59] (although no stroke protection was seen in those aged > 70 yrs[34]), and benefits to ischemic cerebrovascular disease might improve cognition. This, and perhaps other effects (e.g., antiinflammatory), might help explain other clinical trials that found neutral average effects of statins on cognition. Statins did not affect cognition on average in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial,[34] which targeted elderly patients with high cardiovascular risk. Nor were effects on cognition seen, on average, in the Heart Protection Study.[60] However, the latter study used limited cognitive assessment and an active drug (statin) compliance run-in, with the combined run-ins leading to one third of patients being excluded. Since poor compliance with statins is associated with adverse effects of statins,[61] and with poor cognition,[62] patients exhibiting cognitive loss while taking statins would be expected to be disproportionately excluded, which could bias the comparison. One randomized trial comparing simvastatin and pravastatin with placebo, in patients of younger and older age, showed intermediate findings of statins on cognition, with trends to harm overall, and significance identified in subgroups specified prior to analysis, including a subgroup defined by presumptive mitochondrial vulnerability.[63]

Two randomized clinical trials in patients with Alzheimer's disease suggest possible trends to cognitive benefit, although these appeared to dissipate at 1 year.[64, 65] Other studies correlating statin use with lower rates of Alzheimer's disease have been observational.[66–69] Note that these findings could arise spuriously from selection bias (as those who use preventive drugs have higher socioeconomic status and education, which predict significantly lower Alzheimer rates) or from indication bias.[70, 71] (Analogously, observational data had previously suggested that users of hormone replacement therapy [HRT] had dramatically lower rates of dementia; however, when HRT users were compared with otherwise similar persons through placebo-controlled randomized trials, HRT was found to significantly increase dementia.[72–74] Debate

remains about whether HRT of some kinds may confer protection in some groups, but as of this writing there were no randomized controlled trials that support this.)

A key limitation of passive surveillance approaches is that the base population is not defined and there is no control group, precluding calculation of rates and risk ratios. However, we did not seek to define rates, which require knowledge of the base population, or risk ratios, which require a control group. We sought rather to characterize the natural history or time course, potency relationship, and potential quality-of-life impact of statin-associated cognitive effects, and the only patients relevant to this characterization were those who actually experienced adverse effects.

A second concern is generalizability. Data are limited by self-selection of patients for participation. (It merits emphasis that this limitation is common to all studies in which patients must volunteer.) Severity of an adverse effect, particularly a cognitive one, may influence how willing and/or able patients are to participate. Those least affected may not be motivated to participate, whereas those most affected (or with least recovery on discontinuation) may be unable to do so. In addition, since many patients learned of the study through the media or the Internet, patients who are not exposed to these sources may be relatively underrepresented. This is a problem primarily if there is a relationship between exposure to these sources and the characteristics or severity of symptoms.

However, this study also has advantages for generalizability. There were no exclusions based on age, statin drug or dose, or other factors, providing potential to better draw from the range of real-world statin-using experiences. For instance, in contrast to clinical trial settings, patients were not excluded on grounds of medical comorbidities, polypharmacy, or older age—conditions that may be widespread in the population, may predispose to statin adverse effects, but may be unrepresented in settings such as clinical trials, which on this basis have been recognized to underreflect adverse effects.[3, 4] Some of our patients continued to take the drug after the onset of putative adverse effects (a situation that might not arise in a clinical trial); it is only such patients that can inform the range of severity that may develop if symptoms progress. Patients who develop adverse effects may stop drug therapy, resume, and then stop again—conditions that trial designs are unequipped to detect. Also, patients with such reversals serve as their own controls. (In randomized trials, randomization is used in an effort to achieve average comparability, which is generally affirmed on a subset of markers. Here, where patients are compared with themselves, comparability is high, extending beyond measured markers.)

Some of the cognitive symptoms reported could be coincidental rather than causal with statin use. This concern was addressed by rating patients using the Naranjo scale[30]: most patients met criteria for definite or probable ADRs, and analyses focused on this group.

Some patients did not report cognitive improvement after statin discontinuation and were grouped as having possible ADR causality. Although this precludes them from meeting our criteria for causality, it is recognized both that some patients had insufficient time to allow improvement (e.g., 1 day) and that drugs including statins can cause persistent problems, as in the case of statin-induced polyneuropathy[75–77] and persistent muscle symptoms after statin-induced myopathy or rhabdomyolysis.[16, 46] Moreover, the mechanisms by which statins may, we hypothesize, cause cognitive ADRs might be expected to produce persistent symptoms in some instances.[48] Confinement to patients whose symptoms resolve after statin discontinuation may exclude consideration of what may be the most profound and disabling adverse effects.

The use of a patient-targeted survey inherently introduces potential for reporting or recall bias. This issue arises in all survey-based study designs, including those with physician reporting. Moreover, since physicians may dismiss patients' reports of ADRs,[9] or fail to report those ADRs they do recognize,[78] and since patients' emphasis in ADR reports may differ from those of physicians,[10] targeting patients provides an alternative mechanism of adverse effect reporting that may complement existing approaches quantitatively and qualitatively.

Patients with past or current memory problems might be presumed to be poor judges of the presence of these problems. Although this may be true for advanced dementia, few such patients participated, and they did so with aid of a proxy (and/or after recovery). For milder cognitive loss, evidence suggests that patients' self-ratings of memory problems sensitively index objective brain volume loss (including key memory areas),[79, 80] and strongly predict incident dementia even when neuropsychologic tests are normal,[81–83]

suggesting that subjective reporting has convergent and predictive validity, as well as higher sensitivity than commonly employed "objective" tests.

Approximately 60% of UCSD Statin Effects Study patients reporting statin-associated ADRs included problems with cognition or memory among their ADRs, second only to muscle-related adverse effect reports. Thus, these problems may not be rare. Moreover, in some instances effects were severe and apparently reversible. For these reasons, awareness of the possibility that statins may be linked to cognitive adverse effects is important, as it enables consideration of a trial of discontinuation and may increase likelihood that function and quality of life may be restored.

Conclusion

The possibility of debilitating and variably reversible cognitive effects of statins should be considered by physicians when prescribing these drugs. Future studies, such as double-blind N-of-1 trials, or randomized trials or crossover studies, should focus on samples selected for history of putative cognitive ADRs. Our findings extend existing literature on cognitive adverse effects of statins by providing new information on the characteristics, timing, relation to statin potency, reversibility, and quality-of-life impact of these symptoms. This study also confirms the feasibility of patient-targeted postmarketing adverse drug effect surveillance, which may supplement existing data sources.

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Appendix 1. Cases of Cognitive Adverse Drug Reactions Illustrating a Range of Recovery Time

Rapid recovery (within days)

- The family of a patient was seeking assisted-living arrangements for her because of presumed Alzheimer's disease. However, within days of discontinuing atorvastatin, the patients's cognitive dysfunction resolved, apparently fully. She was restored to full functionality and a productive life that included active volunteer work. Significant cognitive compromise recurred on each of several subsequent statin rechallenges.
- In a patient with presumed dementia who was living in a nursing home, atorvastatin use was discontinued by the patient's physician, who had recently read of the possible connection between statins and cognitive loss. Within a week the patient was independent and driving.
- A young physician lost his medical license due to severe unexplained cognitive loss. A colleague familiar with our study asked whether he was taking a statin. He discontinued atorvastatin and his cognitive loss reportedly resolved rapidly, apparently within days.

Prolonged recovery (within years)

Full recovery

- A retired academician developed rapidly progressive and ultimately severe cognitive loss. He could no longer read a page of text, recall what he had just said, or recognize associates he had known closely for decades. He received a diagnosis of rapidly progressive Alzheimer's disease from two academic medical centers. His family discontinued his simvastatin, and on his next evaluation—for participation in an Alzheimer's drug trial—he was informed he no longer met criteria for Alzheimer's disease, nor indeed dementia. However, subjective "full" recovery took approximately 2 years, at which time he had resumed daily reading of three top national newspapers.

Partial recovery

- A top-level executive developed progressive and ultimately severe cognitive loss during which he became unable to balance a checkbook or track accounts, and ultimately lost his companies' and his family's accumulated wealth. He tested at the fifth percentile for age on neuropsychologic testing. Although cognitive loss arrested with statin discontinuation, it was several years before clear evidence of improvement on neuropsychologic testing began to emerge. His recovery has progressed, but it remains incomplete.
- A high-functioning individual with a postgraduate degree who held the top position in an organization developed rhabdomyolysis with severe cognitive loss while taking statins. He became unemployable due to severe cognitive compromise and was dependent on his wife for income. Recovery of both muscle function and cognitive function remain limited several years later.

These cases are from the University of California San Diego Statin Effects Study.[9] Not all of these patients completed (or were able to complete) the secondary cognitive survey for our analysis.