

# Statins and their effect on cognition: Let's clear up the confusion

Jérémie M. Gauthier, BScPharm; Anne Massicotte, BPharm, MSc

We received a question in the drug information centre about statins possibly inducing confusion in a patient. This clinical request prompted us to review the evidence on this topic. We retrieved articles discussing the impact of statins on cognition but also found research investigating statins to prevent or treat cognitive impairment.

*Une question a été soumise au Centre d'information sur les médicaments concernant la possibilité que les statines entraînent un état de confusion chez un patient. La demande de données cliniques nous a incités à examiner les données probantes à ce sujet. Nous avons trouvé des articles qui investiguaient un lien entre les statines et les troubles cognitifs ainsi que des projets de recherche portant sur l'utilisation des statines pour prévenir ou traiter les troubles cognitifs.*

## Introduction

Lipid-lowering drugs, such as statins, rank in the top 5 most frequently used prescription drugs in Canada. In fact, between 2007 and 2011, more than 2.9 million Canadians were taking a lipid-lowering drug.<sup>1</sup> With a plethora of robust evidence for secondary prevention of cardiovascular disease, coupled with a well-tolerated adverse effect profile, it is no wonder that statins are prescribed quite often. In the past decade, however, some case reports have suggested a possible increase in the risk of cognitive adverse events, such as memory loss, forgetfulness or feeling “fuzzy,” associated with their use.<sup>2</sup>

In 2005, Health Canada released a statement in the *Canadian Adverse Reaction Newsletter* suggesting a possible association between statins and memory loss.<sup>3</sup> The onset of these adverse events described in the case reports varied, but most occurred within 1 year of statin initiation. Most of the cases (11/19) reported an improvement in cognitive symptoms once the statin was stopped or the dose reduced. In 2012, the Food and Drug Administration (FDA) issued a safety announcement to health care professionals, warning them about the potential risk of cognitive impairment (memory loss, forgetfulness, amnesia, memory impairment, confusion) with the use of statins for a period of 1 day to years.<sup>2</sup> Review of these cases did not reveal an association between cognitive impairment and a specific statin, dose or age of patient. These cases were generally reversible, with symptoms disappearing approximately 3 weeks after statin discontinuation. The FDA also enforced a change in the monograph of statin products to warn health care professionals about this rare, but possible, adverse event. This change in monograph has not been mandated in Canada. On the opposite end of the

spectrum, some research evaluated the potential use of statins in the prevention and treatment of Alzheimer disease (AD).<sup>4</sup> This article focuses on the effects of statins on cognition and the use of statins for the prevention and treatment of AD.

## Search strategy and findings

For this review, searches of the following databases were initially carried out on July 4, 2014, and then subsequently on January 30, 2015: MEDLINE, PubMed and the Cochrane Library. Search terms in MEDLINE included *hydroxymethylglutaryl-CoA reductase inhibitors, cognition, dementia, cognition disorders, mild cognitive impairment, Alzheimer disease, memory and memory disorders*. In PubMed and Cochrane Library, search terms included *atorvastatin, rosuvastatin, fluvastatin, pravastatin, simvastatin, lovastatin, statin\*, cogniti\*, dement\*, and memory*. Searches were limited to systematic reviews and meta-analyses only and restricted to English language and humans. A total of 71 potentially relevant articles were identified. After removal of duplicates and irrelevant and older systematic reviews, which contained trials that were analyzed in more recent systematic reviews, a total of 5 articles were considered the best available evidence. Based on the Evidence Updates from *BMJ News Alerts*, another recently published meta-analysis, which was not identified with our search strategy due to its recent publication, was also examined.

## Statins and their effect on cognition

Broadly speaking, cognition may be subdivided under 4 domains: executive function, memory, language and visuospatial ability. Cognitive impairment can therefore be defined as a decline from baseline in any of the 4 domains, sometimes

overlapping one another.<sup>4</sup> For an overview of some validated tests used to examine cognition, refer to Table 1.<sup>5-8</sup>

In 2013, Richardson et al.<sup>9</sup> conducted a systematic review of observational and randomized trials looking at the effects of statins on cognition. Except for 2, all trials in this systematic review were designed to look at cognitive function. A meta-analysis of 4 cohort trials ( $n > 4019$ ) demonstrated a lower risk for mild cognitive impairment associated with statin use in patients with intact cognition at baseline (relative risk [RR], 0.66; 95% confidence interval [CI], 0.51-0.86). On the other hand, one large randomized controlled trial (RCT) ( $n = 20,536$ ) from the systematic review revealed no difference in incidence of cognitive impairment between statin and placebo use (RR, 0.98; 95% CI, 0.93 to 1.03). The authors also looked at Mini-Mental State Examination (MMSE, Table 1) scores in their systematic review. When analyzing these scores in patients with intact cognition at baseline, the trials demonstrated no difference in MMSE scores between placebo and statin use on global cognitive performance. With regards to declarative memory (learning, representation, recalling facts and events) ( $n = 6434$ ), processing speed (time required to process set amount of information) ( $n = 6975$ ), and visuoperception (perception and interpretation of visual signs) ( $n = 556$ ), several RCTs demonstrated no difference between statins and placebo. The authors assessed most of the larger trials to be at low risk of bias, based on the Cochrane Risk of Bias Assessment Tool and the Newcastle-Ottawa Scales, which suggests a greater validity and applicability of the results.<sup>10,11</sup> One limitation of this systematic review is that results from different trials could not be pooled together for analysis due to nonstandardized methods of assessment for the various cognitive components.

Swiger et al.<sup>12</sup> examined the effects of statins on short-term cognition, defined as “impairment in mental faculty of knowing, including perceiving, recognizing, conceiving, judging, reasoning and imagining within 1 year of drug initiation,” by conducting a systematic review of trials that examined validated tests of cognitive impairment. They conducted a meta-analysis of 3 RCTs ( $n = 296$ ), which used the Digit Symbol Substitution Test (DSST, Table 1) scores, as this was the most prominent cognitive assessment in the trials. The meta-analysis found a nonsignificant

## KNOWLEDGE INTO PRACTICE



- Despite some case reports of statin-induced memory loss and confusion, statins do not appear to be associated with an increased risk of cognitive impairment.
- If cognitive impairment is suspected in a patient taking a statin, look for other medications that may be contributing.
- It is important to highlight the cardiovascular benefits of statins in patients concerned about cognitive impairment effects.
- With the current level of evidence, especially from the analyses of randomized controlled trials, statins cannot be recommended for the prevention or treatment of dementia.

trend towards improvement in DSST scores in patients taking statins vs those taking placebo (mean difference, 1.65; 95% CI, -0.03 to 3.32). This increase of 1.65 in score means that participants exposed to statins were able to match almost 2 pairs more within the time limit compared to patients not exposed to statins. The clinical significance of this increase in score has not been determined. Despite a small sample size used to perform the meta-analysis, there was little heterogeneity ( $I^2 = 2\%$ ), and all studies had low risk of bias based on the Cochrane Risk of Bias Assessment Tool.<sup>10</sup>

In 2014, Macedo and colleagues<sup>13</sup> conducted a meta-analysis of observational trials looking at the unintended effects of statins, including cognitive impairment, in the general population. They identified 2 trials looking at specific cognitive scores, a modified MMSE (3MS, Table 1) and the Community Screening Interview for Dementia (CSI-D), which together demonstrated an effect size of 0.18 (95% CI, 0.09-0.27). This means that 57% of individuals in the control group had lower scores than the average individual in the statin group, suggesting a greater incidence of cognitive impairment in the control group.<sup>14</sup> These 2 trials had almost 5000 patients when combined, but they were observational in nature, and therefore results must be interpreted carefully. No heterogeneity was reported, but 2 different cognitive tests were used in each individual trial, which suggests high heterogeneity and thus limits the applicability of the pooled result.

The most recent meta-analysis published in 2015 by Ott et al.<sup>15</sup> evaluated the risk of cognitive impairment from statins vs placebo, analyzing exclusively RCTs. Three RCTs ( $n = 38,360$ )

TABLE 1 Cognition tests<sup>5-8</sup>

	MMSE	3MS Test	ADAS-Cog	DSST
Goal	To evaluate orientation (time, place), registration, attention and calculation, recall, language, ability to follow commands			To evaluate attention, short-term memory, processing speed
Description	11 questions (10-min test)	24 questions (15-min test) As the MMSE but more comprehensive with different levels of difficulties	11 blocks of different tasks to do (30- to 45-min test). More in-depth test	Consists of 9 digits and symbols to pair. Under each digit, the subject writes down the corresponding symbol, pairing as many as possible in 90 s.
Score range	0-30	0-100	0-70	0-76* (number of correct pairs of symbols/digits)
Threshold for diagnosis	≥26: no or questionable impairment 21-25: mild 11-20: moderate 0-10: severe	<79 suggests cognitive impairment <48 suggests severe impairment	Score ≥18 suggests greater cognitive impairment. A 4-point change in 6 months is a clinically significant difference.	A low score indicates cognitive impairment but no specific threshold defined.

ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognition; DSST, Digital Symbol Substitution Test; MMSE, Mini Mental State Examination; 3MS Test, Modified Mini-Mental State Test.

\*In theory, the maximum score is 90; in practice, the maximum is set at 76.

in patients with normal cognition at baseline reported the incidence of dementia, confusion and other cognitive adverse events. This analysis did not find a significant difference between the statins and placebo groups for the development of these events. When looking at cognitive test outcomes (measuring attention, executive function, memory, processing speed), data from 16 RCTs ( $n = 27,693$ ) did not find a difference across all cognitive domains between the 2 groups. Heterogeneity was low between the studies, and most RCTs in this meta-analysis were at low risk of bias. With a large sample size, including patients from a wide range of ages (20-86 years), and good-quality evidence, this meta-analysis demonstrates that the risk of cognitive impairment with statins is not substantiated in cognitively normal patients.

Bottom Line: Observational data and RCTs do not support a decrease in cognition with statin use.

### Managing cognitive impairment as a side effect

Despite most of the data showing no impairment in cognition associated with statins, the

Statin Cognitive Safety Task Force (SCSTF) recommends a series of steps, based on expert opinion, to perform should a patient report cognitive impairment after initiation of therapy.<sup>4</sup> It recommends cognitive testing, looking at other potential contributors such as anticholinergic medications (e.g., diphenhydramine, tricyclic antidepressants, some antipsychotics) and performing a risk assessment of stopping or decreasing the dose vs continuing the statin. Statins have robust evidence supporting their use in secondary prevention of cardiovascular events. It is therefore of utmost importance to discuss with the patient the risks of stopping (increased risk of cardiovascular events) or continuing (cognitive impairment) the statin. If it is suspected that the statin is contributing to the symptoms, a drug-free period of 1 to 2 months is recommended prior to a rechallenge. Expert opinion suggests a switch to a less lipophilic statin, such as rosuvastatin or pravastatin, to limit drug entry into the central nervous system and diminish the effects on cognition.

### Statins and dementia

In 2012, 747,000 Canadians were living with AD and other dementias. This number is expected

to increase to over 1.4 million by 2031.<sup>16</sup> It is therefore not unexpected that a lot of effort and resources are going into dementia prevention and treatment research. Pathological hallmarks of AD include senile neuritic plaques and neurofibrillary tangles, which are potentially related to high levels of brain cholesterol and some degree of inflammation.<sup>17</sup> Due to the beneficial effects of statins on lipids, as well as their pleiotropic effects, this class of medication has been the subject of much research for the prevention as well as the treatment of dementia. Some recent meta-analyses have examined the use of statins in this off-label setting.

### *Prevention of dementia*

A meta-analysis of observational studies conducted by Macedo et al.<sup>13</sup> looked at the association between development of all-type dementia and exposure to statins. A pooled analysis of 13 trials ( $n = 2,762,899$ ) demonstrated an odds ratio of 0.70 (95% CI, 0.59-0.83) for the development of all-type dementia and cognitive impairment without dementia in patients exposed to statins, suggesting a protective effect from their use. A similar odds ratio of 0.74 (95% CI, 0.62-0.87) was calculated when low-quality studies were excluded from the analysis. Looking at participants who developed AD specifically, exposure to statins was associated with an odds ratio of 0.61 (95% CI, 0.50-0.75). These results signify a 39% reduction in odds of developing AD in patients taking statins compared with control patients. Although this meta-analysis comprised a large amount of participants, all these trials were observational, and the pooled analysis had significant heterogeneity.

In 2013, Swiger and colleagues<sup>12</sup> published a meta-analysis examining the use of statins for the prevention of dementia. Following exclusion of trials with a high risk of bias, the pooled results of the remaining 8 trials ( $n = 23,443$ ), in which patients had a mean statin exposure time of 3 to 24.9 years, demonstrated a favourable hazard ratio (0.71; 95% CI, 0.61-0.82) for statin users in the prevention of all-type dementia. Five trials in this meta-analysis provided sufficient information and follow-up time for the authors to calculate an absolute risk reduction of 2%. This means that for every 50 patients treated with a statin for 6.2 years, 1 case of dementia will be prevented compared with patients who were not treated with a statin. Strokes are one of the most common

## MISE EN PRATIQUE DES CONNAISSANCES



- Malgré le fait que certains rapports recensent des cas de pertes de mémoire et de confusion imputables à la prise de statines, ces dernières ne semblent pas être associées à un risque accru de trouble cognitif.
- En cas d'apparition de troubles cognitifs chez un patient qui prend une statine, déterminez si d'autres médicaments peuvent contribuer aux symptômes.
- Il importe d'insister sur les avantages des statines sur la santé cardiovasculaire auprès des patients préoccupés par les effets associés aux troubles cognitifs.
- Compte tenu des données probantes disponibles à ce jour, particulièrement celles issues d'essais contrôlés randomisés, les statines ne peuvent faire l'objet d'une recommandation pour prévenir ou traiter la démence.

causes of vascular dementia, and since this type of dementia was included in the definition of all-type dementia, statins may overestimate this benefit on dementia prevention.<sup>18</sup> Heterogeneity was not significant for this analysis.

Richardson et al.<sup>9</sup> also looked at prevention of dementia in statin users. The meta-analysis of cohort trials ( $n = 4,360,137$ ) found that statin use was associated with a relative risk reduction of 13% (RR, 0.87; 95% CI, 0.82-0.92) and 21% (RR, 0.79; 95% CI, 0.63-0.99) for all-type dementia and AD, respectively. Pooling the results of case-control trials demonstrated similar results, but these trials had a much smaller sample size. Once again, these results, although interesting, come from observational trials and therefore are of low quality of evidence.

A Cochrane review conducted in 2009 examined the potential use of statins for the prevention of dementia by retrieving RCTs addressing this topic.<sup>19</sup> The review identified only 2 RCTs, for a total of 26,340 patients. The first and also the largest RCT is the Heart Protection Study (HPS) ( $n = 20,536$ )—the only RCT in this systematic review to include dementia as an outcome. However, as dementia was not a primary outcome, no baseline cognitive test was performed. Despite this potential source of bias, 31 participants in each group developed dementia by the end of the trial, suggesting no role for statins in the prevention of dementia. The second RCT included 5804 patients at a reasonable risk of developing dementia over the 3.2 years of follow-up. Cognitive decline was similar in the statin group and

the placebo group. This Cochrane review thus reinforces that statins have no effect on the prevention of dementia.

#### *Treatment of dementia*

On top of examining dementia prevention, Richardson et al.<sup>9</sup> also conducted a meta-analysis looking at the potential benefits of statins on cognitive scores in patients already living with AD. Four RCTs were identified, comprising a total of 1127 patients, all with probable to possible AD of mild to moderate severity. Of the 4 RCTs, 3 of the trials were pooled ( $n = 1064$ ) using the ADAS-Cog score (Table 1) and revealed no significant difference in score between statin and placebo users (difference in score, 0.11; 95% CI, -1.76 to 1.97). The MMSE scores were also examined but, due to high heterogeneity, could not be pooled together. Each of the 3 largest trials ( $n = 1083$ ) showed no significant difference in MMSE score, while the smallest one ( $n = 44$ ) found a significant difference favouring the statins. The authors determined that the 2 largest trials in this meta-analysis had a low risk of bias. With these results, it appears that statins do not improve cognition in patients with dementia, but on the other hand, they are not associated with a worsening of cognition.

Another Cochrane review published in 2014 included 4 RCTs ( $n = 1154$ ) examining the role of statins in the treatment of dementia.<sup>20</sup> All trials compared statins with placebo, had a low risk of bias and assessed a change in ADAS-Cog and MMSE from baseline, although these were secondary endpoints in 1 and 3 of the trials, respectively. Duration of trials varied from 6 to 18 months. After combining the results, there was no difference between the placebo and statin groups

when examining the ADAS-Cog score changes (mean difference, -0.26; 95% CI, -1.05 to 0.52;  $p = 0.50$ ) or the MMSE score changes (mean difference, -0.32; 95% CI, -0.71 to 0.06;  $p = 0.10$ ). Both analyses of ADAS-Cog and MMSE scores had an  $I^2$  score of 62% and 81%, respectively, suggesting high heterogeneity between trials. This meta-analysis does not support the use of statins in the treatment of dementia.

**Bottom Line:** Although meta-analyses of observational trials are suggestive of some benefit from statins in the prevention of AD, the review of RCTs found no effect of statins in the prevention of dementia. When looking at statins for the treatment of dementia, 2 meta-analyses of RCTs at low risk of bias concluded that statins have neither positive nor negative effects on cognition in this population of patients.

#### **Conclusion**

Despite case reports suggesting a risk of impairment in cognitive function with the use of statins, several large meta-analyses seem to suggest no increase in risk. If cognitive impairment is suspected in a patient taking a statin, it would be important to look at other causes, such as those suggested by the SCSTF, before attributing it to the statin. The well-established cardiovascular benefits of statins, including stroke reduction, should always be highlighted to the patient.

With the current level of evidence, especially from the analyses of RCTs, statins cannot be recommended for the prevention or treatment of dementia. ■

---

*From the Pharmacy Department of The Ottawa Hospital, General campus (Gauthier) and Civic campus (Massicotte), Ottawa, Ontario. Contact jergauthier@toh.on.ca.*

**Acknowledgments:** *The authors thank Dina MacLeod, Drug Information Pharmacist at The Ottawa Valley Regional Drug Information Service, for her valuable comments during the preparation of the manuscript.*

**Author Contributions:** *J. Gauthier initiated the project, searched the literature, wrote the initial drafts and made revisions to the final manuscript prior to submission. A. Massicotte initiated the project; reviewed the search literature, initial drafts and references used; and revised the final manuscript prior to submission.*

**Declaration of Conflicting Interests:** *The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.*



**Funding:** The authors received no financial support for the research, authorship and/or publication of this article.

## References

1. Statistics Canada. Prescription medication use by Canadians aged 6 to 79. June 2014. Available: [www.statcan.gc.ca/pub/82-003-x/2014006/article/14032-eng.pdf](http://www.statcan.gc.ca/pub/82-003-x/2014006/article/14032-eng.pdf) (accessed July 7, 2014).
2. Food and Drug Administration. Important safety label changes to cholesterol-lowering statin drugs. 2012. Available: [www.fda.gov/Drugs/DrugSafety/ucm293101.htm](http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm) (accessed July 7, 2014).
3. Health Canada. Statins and memory loss. *Canadian Adverse Reaction Newsletter*; 2005. Available: [http://hc-sc.gc.ca/dhp-mps/alt\\_formats/hpfb-dgpsa/pdf/medeff/carn-bcei\\_v15n4-eng.pdf](http://hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n4-eng.pdf) (accessed July 8, 2014).
4. Rojas-Fernandez CH, Goldstein LB, Levey AI, et al. An assessment by the Statin Cognitive Safety Task Force: 2014 update. *J Clin Lipidol* 2014;8:S5-16.
5. Mungas D. In-office mental status testing: a practical guide. *Geriatrics* 1991;46:54-66.
6. Dementia Collaborative Research Centres. Cognition assessment measures. Available: [www.dementia-assessment.com.au/cognitive/index.html](http://www.dementia-assessment.com.au/cognitive/index.html) (accessed Feb. 2, 2015).
7. Rockwood K, Fay S, Gorman M, et al. The clinical meaningfulness of ADAS-Cog changes in Alzheimer's disease patients treated with donepezil in an open-label trial. *BMC Neurol* 2007;7:26.
8. Proust-Lima C, Amieva H, Dartigues JF, et al. Sensitivity of four psychometric tests to measure cognitive changes in brain aging-population-based studies. *Am J Epidemiol* 2007;165:344-50.
9. Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. *Ann Intern Med* 2013;159:688-97.
10. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
11. Ottawa Hospital Research Institute. The Newcastle-Ottawa Scale for assessing the quality of nonrandomised studies in meta-analyses. Available: [www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) (accessed July 13, 2014).
12. Swiger KJ, Manalac RJ, Blumenthal RS, et al. Statins and cognition: a systematic review and meta-analysis of short- and long-term cognitive effects. *Mayo Clinic Proc* 2013;88:1213-21.
13. Macedo AF, Taylor FC, Cassas JP, et al. Unintended effects of statins from observational studies in the general population: systematic review and meta-analysis. *BMC Med* 2014;12:51.
14. McGough JJ, Faraone SV. Estimating the size of treatment effects: moving beyond *p* values. *Psychiatry (Edgmont)* 2009;6:21-9.
15. Ott BR, Daiello LA, Dahabreh IJ, et al. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. *J Gen Intern Med* 2015;30:348-358.
16. Alzheimer Society Canada. A new way of looking at the impact of dementia in Canada. 2012. Available: [www.alzheimer.ca/~media/Files/national/Media-releases/asc\\_factsheet\\_new\\_data\\_09272012\\_en.pdf](http://www.alzheimer.ca/~media/Files/national/Media-releases/asc_factsheet_new_data_09272012_en.pdf) (accessed July 13, 2014).
17. Kandiah N, Feldman HH. Therapeutic potential of statins in Alzheimer's disease. *J Neurol Sci* 2009;283:230-4.
18. National Stroke Association. Vascular dementia. 2012. Available: [www.stroke.org/we-can-help/survivors/stroke-recovery/post-stroke-conditions/cognition/vascular-dementia](http://www.stroke.org/we-can-help/survivors/stroke-recovery/post-stroke-conditions/cognition/vascular-dementia) (accessed December 5, 2014).
19. McGuinness B, Craig D, Bullock P, et al. The Cochrane collaboration: statins for the prevention of dementia (review). *Cochrane Library* 2009;2:1-31.
20. McGuinness B, Craig D, Bullock R, et al. The Cochrane collaboration: statins for the treatment of dementia (review). *Cochrane Library* 2014;7:1-77.