Statins and memory loss: An Australian experience

Anna I Jamolowicz, Huei-Yang Chen, Peter K Panegyres

Neurodegenerative Disorders Research Pty Ltd, West Perth, WA, Australia

RESEARCH

Corresponding Author:
Prof Peter K Panegyres
Neurodegenerative Disorders Research Pty Ltd
4 Lawrence Avenue,
West Perth 6005, WA
Australia
Email: research@ndr.org.au

ABSTRACT

Background

Statins are a first-line drug treatment for hypercholesterolaemia. Recently there has been general public and media interest surrounding uses and side effects of statins, including memory loss.

Aims

We analysed an Australian experience in statin usage in an attempt to improve understanding of the relationship between statins and memory-related adverse events.

Methods

Total adverse events (TAE) and adverse events with single suspected medicines (SSM) for memory loss and other memory-related adverse events were searched for statin compounds from January 1992 to May 2013, using the Medicare Australia and Pharmaceutical Benefits Scheme (PBS) websites and Therapeutic Goods Administration (TGA) adverse events data. TAE and SSM were compared to the number of prescriptions by item number searched using the PBS. The process was repeated for non-statin cholesterol-lowering drugs.

Results

The most common adverse event was amnesia (167 events for statins and six for non-statins). There were 239 TAE (incidence rate=0.88) listed for statins and 10 for non-statins (incidence rate=0.53). There were 217 SSM events listed for the statins (incidence rate = 0.08) and eight for the alternatives (incident rate=0.04). The differences between TAE and SSM incidence rates between statins and non-statins drugs were not significant (both *p* values >0.05).

Conclusion

We found that there were no differences in memory-related adverse events between statins and other cholesterol-lowering medications using Australian PBS and TGA adverse events data.

Key Words

Statins, memory loss, dementia

What this study adds:

1. What is known about this subject?
Controversies exist regarding the impact of statins on memory loss and cognitive function.

2. What new information is offered in this study?
For TAE and SSM, rates for memory loss and memory-related adverse events were not significantly different between statins and non-statins.

3. What are the implications for research, policy, or practice?
There is no evidence of significant differences in adverse event reports involving memory-related adverse events between statins and other cholesterol-lowering agents using Australian PBS and TGA adverse events data. Statins may be used without reasonable concern of adverse effects upon memory and memory-related adverse events. Our findings do not suggest a change of practice in relation to statin usage in preventing cardiovascular events.

Background

Ischaemic heart disease is the leading single cause of death in Australia, with more than 21,500 deaths as a result in 2011.[1] Elevated concentrations of low-density lipoprotein (LDL) cholesterol, total cholesterol, and triglyceride as well as high-density lipoprotein (HDL) cholesterol levels increase coronary heart disease (CHD) risk. Statins are a first-line drug treatment for hypercholesterolaemia that does not respond to a low-fat diet and exercise regime. Statin treatment lowers cholesterol synthesis y inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase.[2]

Generally, statins are well tolerated but have some side effects, including myopathy.[3] Serious adverse side effects are rare and usually completely reversible.[4] The Understanding Statin Use in America and Gaps in Education (USAGE) study found side effects to be the primary reason for discontinuation of statin therapy, with muscle-related adverse events being the most common.[5]

Two randomised control trials using simvastatin and provastatin in large numbers of patients did not identify a relationship between statin usage and cognitive decline and dementia, using the mini-mental state examination and neuropsychiatric assessments.[6,7] The United States National Lipid Association Statin Safety Task Force Expert Panel concluded that there was no association between statin usage and memory loss and dementia and other cognitive impairment.[8] Some studies suggest that statin usage might reduce the risk of dementia and Alzheimer's disease.[9,10] However, published case reports suggest a relationship between statin usage and memory loss.[11,12] In 2012, the United States Food and Drug Administration (FDA) changed labelling for the entire class of statin drugs, advising of the potential to elevate the blood sugar with an increased risk of diabetes mellitus and irreversible dementia.[13] In Australia, the medical information program Catalyst screened a two-part series on the usefulness of statins in the treatment of cardiovascular disease, which fuelled patients' concern about memory loss and memory-related adverse events.[14] On this background we set out to determine whether a relationship exists between statin usage and memory-related adverse events in Australia.

The international controversy and media coverage has made the continued use of statins and their side effects, especially in relation to memory and cognition, an important discussion point. Recently, two-thirds of general practitioners (GPs) in the United Kingdom were reported as unwilling to prescribe statins, a figure that might be biased by small sample size. Recent UK NICE Guidelines suggest that 40 per cent of adults should take them.[15] Additionally, some sources suggest that patients consulting their doctors refuse to take statins,[16,17] and many GPs in the UK do not take them.[18]

The brain is composed of approximately 25 per cent cholesterol, where it is the main constituent of cell membranes; the brain synthesises its own cholesterol. Therefore, drugs like statins, which reduce cholesterol and affect levels of non-sterol compounds and prenylated proteins, might have adverse effects upon neuronal function and cause cognitive side effects.[19] Current evidence suggests no detrimental effect of statin use on cognitive function; however, the importance of future studies with larger sample sizes which explore their effects on memory and related cognitive functions—at large doses in randomised controlled trials and which specifically investigate cognitive endpoints—was highlighted.[20] This, coupled with limited available Australian data, led us to investigate the likelihood of statin use being associated with memory-related adverse events in Australia.

Method

This study interrogated the Therapeutic Goods Administration (TGA) online database for cognitive side effects and statin usage.

Statins reduce cholesterol synthesis by inhibiting HMG CoA and may be classified as lipophilic (atorvastatin, fluvastatin, and simvastatin) and hydrophilic (provastatin and rosuvastatin). Hydrophilic statins are generally excreted unmetabolised by the liver and lipophilic statins are metabolised by the cytochrome P450 system. The lipophilic statins are more likely to cross the blood-brain barrier and affect insulin resistance. The statins examined in this study were atorvastatin, atorvastatin with amlodipine, fluvastatin, pravastatin, rosuvastatin, and simvastatin due to their usage in Australia. A non-statin group of cholesterol lowering drugs were chosen as a control group: ezetimibe, gemfibrozil, fenofibrate, and cholestyramine.

Each medication was searched for total adverse events (TAEs) and adverse events with single suspected medicines (SSMs) using the TGA Database of Adverse Events.[21] The TGA is part of the Australian government's Department of Health and is responsible for regulating therapeutic goods and houses the Australian Adverse Drug Reactions Database, which contains reports of suspected reactions to drugs since 1 November 1972. These reports are submitted voluntarily by Australian doctors, dentists, and pharmacists.

Adverse events searched were amnesia, cognitive disorder, dementia, Alzheimer's disease type dementia, mental impairment, and memory loss/impairment from 1 January 1992 to 31 May 2013.

The number of prescriptions by item number processed for each medication was searched on the Pharmaceutical Benefits Scheme (PBS) Item Reports website.[22] The PBS is an Australian government program that provides prescription drugs to Australian residents and maintains an online database of all drugs prescribed under this scheme. These results were analysed to determine the TAE and SSM incidence rates for each statin and non-statin drug, and incidence rate ratio and confidence intervals of statin versus non-statin drugs were estimated.

Results

There were 272,801,678 prescriptions for statins recorded in the PBS dataset. Absolute numbers of patients are not provided and are not available. TAE for each medication are listed in Table 1. The most common adverse event was amnesia (167 in the statin group, six for the non-statins). Atorvastatin was associated with the most adverse events in any category; however, it was also prescribed more frequently (Table 2). Very occasionally (n=2), two or more adverse events were recorded per patient; for example, amnesia and dementia.

There were 239 TAEs reported for the statin group (incident rate=0.623) and 10 for the non-statins (incident rate=0.39) (Table 2). There were 218 SSM events reported for the statin group (incident rate=0.55) and eight for the alternatives (incident rate=0.32) (Table 2). For TAE and SSM incidence rates there were no significant differences between statins and non-statins (p=0.10 and p=0.06, respectively), implying that there were no differences between statins and non-statins in terms of reported memory-related adverse events. The incidence ratio for statin versus non-statin drugs for TAE and SSM were 1.66 (95% CI; 0.88–3.13) and 1.89 (95%CI; 0.93–3.83), respectively (Table 2).

Discussion

We are not aware of other published studies that interrogated databases of large numbers of statin prescriptions to investigate their affects on memory-related adverse events. Our findings confirm the previous findings of two large randomised studies of the investigation of statins in cerebrovascular disease, which found no relationship between their usage and cognitive side effects.[6,7] Our results also support the conclusions of the US

National Lipid Association Statin Safety Task Force Expert Panel that observed a lack of association between statin usage and memory-related adverse events. Our findings are inconsistent with case reports describing a relationship between statins and memory loss.[10] However, the dataset used in our study is subject to biases: (1) reporting is voluntary, which might underestimate the total number of cognitive reactions to statins; (2) personal identifiers were not available to assess true incidence, potentially overestimating time incidence; (3) detailed clinical information regarding the nature of the cognitive side effects, their diagnosis, duration, and resolution were not available; and (4) accurate dosage information regarding any correlation between statin use and cognitive impairment was absent in the database.

These limitations suggest that large randomised controlled trials exploring cognitive side effects and statin use, which also investigate the effects of dose, age, comorbidities, nature, and diagnosis of cognitive phenomena might be useful. A data-linkage study might also be helpful that searches out patients with multiple TAEs due to statins and the affects of concurrently prescribed medications.

Local and International media have reported on side effects and the question of over-prescription of statins.[23] The US FDA issued a warning in 2012 that statin use may increase the risk of diabetes mellitus and may cause reversible memory loss, based on pharmacological clinical trials and case reports found in the Adverse Event Reporting System.[24] This is of interest as the current UK NICE Guidelines suggest a lower threshold for prescribing statins.[25] This was classified in many media reports as dementia. In Australia, the television program Catalyst ran a two-part series, which downplayed the role of cholesterol in CHD and increased patient concerns regarding their use and side effects.[14]

From PBS and TGA adverse events data, we have found the incidence rate of cognition-related events resulting from the use of statins was no different from that of alternative cholesterol-lowering medications. Richardson et al. reviewed 27 studies (three randomised controlled trials, 16 cohort, four case-control and four cross-sectional) on statin use and cognition, finding no increased risk of Alzheimer's disease, mild cognitive impairment, or dementia amongst statin users.[20] Similarly, they found a low reporting rate for cognitive-related adverse events, which was comparable to alternative cardiovascular medications.

The US National Lipid Association Statin Safety Task Force Neurology Expert Panel evaluated evidence of a causal

relationship between impaired memory and/or cognitive dysfunction resulting from statin use.[8] They found no indication of causality based on large, randomised control trials, such as the Heart Protection Society Collaborative Group[6] and Prospective Study of Pravastatin in the Elderly at Risk study (PROSPER).[7] These reports have described individuals experiencing impairment of cognition while receiving statins, but this is rare. A review of statin-associated cognitive impairment by Rojas-Fernandez et al. similarly found rare case reports describing adverse effects on cognition and outlined that the incidence of statin-associated cognitive impairment needs more investigation and, given the numbers of patients receiving statins, uncommon side effects could affect a large population.[12]

These authors postulate that lipophillic statins (e.g., atorvastatin and simvastatin) are more likely to cross the blood-brain barrier, compared to those that are hydrophilic (e.g., pravastatin and rosuvastatin). Possible mechanisms for statin-induced cognitive difficulties include:

1. An effect on cholesterol synthesis—as the brain produces its own cholesterol, and cholesterol is a major component of myelin, reducing cholesterol with statins might impair neuronal and glial cell membrane permeability and function, resulting in impaired axonal conduction of electrical impulses and reduced myelination;[26–28]
2. Statins reduce coenzyme Q10 levels, which will impair mitochondrial function and lead to an increase in oxidative stress.[29]

Hypertension and hypercholesterolaemia in midlife can increase the risk of dementia.[30] Statin therapy before 80 years may lower the risk of Alzheimer's disease.[31] Swiger et al. conducted a meta-analysis of 16 qualitative and quantitative trials and found that in patients without cognitive dysfunction at baseline, short-term data suggests no adverse effects of statins on cognition.[32] They also found that longer-term use may be beneficial in the prevention of dementia. Arvanitakis et al. found in a sample of 929 Catholic clergy there were no differences in global Alzheimer's disease pathology and tangle density between statin users and non-users.[33] In fact, statin users were less likely to have amyloid deposition.

Conversely, other work has found no benefit of statins on cognition. The LEADe[34] and PROSPER[35] studies found no benefit on cognition from atorvastatin in Alzheimer's disease and pravastatin in vascular disease risk populations, respectively. Evans et al. suggest that while there may be a decrease in cerebral spinal fluid lipid response to statin treatment initially, this is a temporary effect and long-term protective effects cannot be assumed.[36]

A significant limitation of this investigation is that personal identifiers were not available in the data sources, suggesting the incidence rate might be overestimated, possibly through double counting. A data linkage study may overcome this limitation and identify people who have multiple TAEs due to a specific medicine. Furthermore, additional clinical information of the nature of cognitive side effects (such as their duration, methods of diagnosis, and resolution) were not available in the dataset, raising the possibility that cognitive side effects might be underreported, as voluntary reporting often has a low yield.[37]

Conclusion

Controversies surrounding memory and cognitive difficulties relating to statin usage have been triggered largely by US FDA label changes, media reporting, and interest promoted by the large-scale use of statins leading to associations in the minds of patients and their families. Studies with a greater sample size are needed where small effect sizes on vast numbers of patients might affect large numbers of people. It is our belief that unreasonable weighting has been placed on case reports. We have found that there is no apparent significant difference in memory-related adverse events between statins and other cholesterol-lowering agents using Australian PBS and TGA adverse events data.

References

1. Australian Bureau of Statistics, 3303.0. Causes of Death, Australia, 2011.
2. Fidge NH. Lipid-lowering drugs: mechanism of action. Aust Prescriber. 1990;13:73–7.
3. Fitzgerald K, Redmond E, Harbor C. Statin-induced myopathy. Glob Adv Health Med. 2012;1:32–6.
4. Armitage J. The safety of statins in clinical practice. Lancet. 2007;370:1781–90.
5. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. J Clin Lipidol. 2012;6:208–5.
6. Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc

Surg. 2007; 45:645–54.

7. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360:1623–30.

8. Brass LM, Alberts MJ, Sparks L, National Lipid Association Statin Safety Task Force Neurology Expert Panel. An Assessment of Statin Safety by Neurologists. Am J Cardiol. 2006; 97(8A):86C–88C.

9. Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. Lancet 2000;356: 1627–31.

10. Wolozin B, Kellman W, Rousseau P, Celesia GG, Siegel G. Decrease prevalence of Alzheimer's disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Arch Neurol. 2000;57:1439–43.

11. Wagstaff LR, Mitton MW, Arvik BM, Doraiswarmy PM. Statin-associated memory loss: Analysis of 60 case reports and review of the literature. Pharmacotherapy. 2003;23:871–80.

12. Rojas-Fernandez CH, Cameron JCF. Is statin-associated cognitive impairment clinically relevant? A narrative review and clinical recommendations. Ann Pharmacother. 2012; 46:549–57.

13. US Food and Drug Administration. FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs. February 28, 2012.

14. O'Leary C. Patients swamp GPs in heart pill confusion. Weekend West Australian, [cited 2013 Nov 2]. Available from: http://www.sott.net/article/268307-West-Australian-patients-swamp-GPs-in-heart-pill-confusion

15. Donnelly L, Malnick E. Doctors refusing to prescribe statins. The Telegraph, London UK, [cited 2014 Nov 1]. Available from: http://www.telegraph.co.uk/news/health/news/11201 669/GPs-refusing-to-prescribe-statins.html

16. Arca M, Pigna. Treating statin-intolerant patients. Diabetes Metab Syndr Obes. 2011;4:155–66.

17. Graedon J, Graedon T. The Peoples Pharmacy. [accessed 2014 September 24]. Available from: http://www.peoplespharmacy.com/2014

18. Health Unlocked. [accessed 2014 March 18). Available from: http://www.healthunlocked.com/

19. Stancu C, Sima A. Statins: mechanism of action and effects. J Cell Mol Med. 2001;5:378–87.

20. Richardson K, Schoen M, French B, Umscheid CA, Mitchell MD, Arnold SE, et al. Statins and cognitive function: a systematic review. Ann Intern Med. 2013; 159:688–97.

21. Australian Government Department of Therapeutic Goods Administration. Database of Adverse Event Notifications, [accessed 2013 December 2]. Available from: https://www.tga.gove.au/database-adverse-event-notifications-daen

22. Australian Government Department of Human Services. Pharmaceutical Benefits, Schedule Item Reports. [accessed 2013 Dec 1] Available from: https://www.medicareaustralia.gov.au/statistics/pbs_it em.shtml

23. Mafeed A. Statins for primary prevention of cardiovascular disease. BMJ. 2014;348:g3491.

24. Scudder L, Egan AG. Statins: The Story Behind the Label Changes. *Medscape.* 06 Mar 2012. Available from: http://www.medscape.com/viewarticle/759736

25. United Kingdom National Institute for Health Care Excellence Guidelines. TA94: Statins for the prevention of cardiovascular events. [accessed 2014 July 18]. Available from: http://www.nice.org.uk

26. Saher G, Simons M. Cholesterol and myelin biogenesis. Subcell Biochem 2010;51:489–508.

27. Miron VE, Zehntner SP, Kuhlmann T, Ludwin SK, Owens T, Kennedy TE, et al. Statin therapy inhibits remyelination in the central nervous system. Am J Pathol 2009; 17:1880–90.

28. Klopfleish S, Merkler D, Schmitz M, Klöppner S, Schedensack M, Jeserich G, et al. Negative impact of statins in oligodendrocytes and myelin formation in vitro and in vivo. J Neurosci. 2008;28:13609–14.

29. Langsjoen PH, Langsjoen AM. The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q10, A review of animal and human publications. Biofactors 2003;18:107–11.

30. Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, et al Midlife vascular risk factors and Alzhiemer's disease later in life: longitudinal, population based study. BMJ. 2001;322:1447–51.

31. Li G, Shofer JB, Rhew IC, Kukull WA, Peskind ER, McCormick W, et al. Age-varying association between Statin use and incident Alzheimer's disease. J Am Geriatr Soc. 2010;58:1311–7.

32. Swiger KJ, Manalac RJ, Blumenthal RS, Blaha MJ, Martin SS. Statins and Cognition: A Systematic Review and Meta-analysis of Short- and Long-term Cognitive Effects. Mayo Clin Proc. 2013;88:1213–21.

33. Arvanitakis Z, Schneider JA, Wilson RS, Bienias JL, Kelly JF, Evans DA, et al. Statins, incident Alzheimer disease, change in cognitive function, and neuropathology. Neurology. 2008;70:1795–1802.

34. Feldman HH, Doody RS, Kivipelto M, Sparks DL, Waters DD, Jones RW, et al. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease:

LEADe. Neurology. 2010;74:956–64.

35. Trompet S, van Vliet P, de Craen AJ, Jolles J, Buckley BM, Murphy MB, et al. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. J Neurol. 2010;257:85–90.

36. Evans BA, Evans JE, Baker SP, Kane K, Swearer J, Hinerfeld D, et al. Long-term statin therapy and CSF cholesterol levels: implications for Alzheimer's disease. Dement Geriatr Cogn Disord. 2009;27:519–24.

37. Gandhi TK, Seger DL, Bates DW. Identifying Drug Safety Issues: From Research to Practice. Intern'l J Quality in Health Care. 2000;12:69–76.

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

ETHICS COMMITTEE APPROVAL

This study had the approval of the Neurodegenerative Disorders Research Ethics Committee (NDR EC/2012/01).

Table 1: Memory-related events for statin and non-statin drugs

Medicine	Amnesia	Cognitive disorder	Dementia	Dementia Alzheimer's Type	Memory loss/impairment	Mental impairment
Statins						
Atorvastatin	117	10	5	2	39	2
Atorvastatin-amlodipine	0	0	0	0	0	0
Fluvastatin	1	0	0	0	0	0
Pravastatin	4	0	0	1	0	1
Rosuvastatin	18	3	0	0	10	0
Simvastatin	27	3	3	0	3	0
	167	16	8	3	49	3
Non-statins						
Cholestyramine	0	0	0	0	0	0
Ezetimibe	4	2	0	0	1	1
Fenofibrate	1	0	0	0	0	0
Gemfibrozil	1	0	0	0	0	0
	6	2	0	0	1	1

Table 2: Adverse event rates by medicine

Medicine	Prescriptions	TAE	TAE Incidence Rate (10^{-6})	SSM	SSM Incidence Rate (10^{-6})
Statins					
Atorvastatin	118 261 248	167	1.41	156	1.32
Atorvastatin-amlodipine	5 222 632	0	0.00	0	0
Fluvastatin	2 957 106	1	0.34	1	0.34
Pravastatin	24 801 999	6	0.24	4	0.16
Rosuvastatin	28 780 086	30	1.04	28	0.97
Simvastatin	92 778 607	35	0.38	29	0.31
TOTAL	272 801 678	239	0.88	218	0.08
Non-statins					
Cholestyramine	871 946	0	0.00	0	0
Ezetimibe	7 052 415	8	1.13	6	0.85
Fenofibrate	3 541 419	1	0.28	1	0.28
Gemfibrozil	7 498 717	1	0.13	1	0.13
TOTAL	18 964 497	10	0.53	8	0.04
Incident rate ratio		1.66 (95%CI: 0.88-3.13), p=0.11		1.89 (95%CI: 0.93-3.83), p=0.08	