STATIN-ASSOCIATED MEMORY LOSS – One Mechanism Identified

by
Sharon Hope, October 9, 2007

ABSTRACT: HMG CoA reductase inhibitors, the cholesterol-lowering class of statin drugs, are associated with memory loss. A recent publication provided evidence of long term potentiation (LTP) [1], demonstrating the physical process for formation of memory and verifying the necessary environment, which must include actin and cofilin. The researchers used (+/-)-3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), a product of nitric oxide synthase (NOS), to prevent new memory formation and erase existing memory. A survey of the literature indicates that statins inhibit Rho, essential for actin and cofilin, and that statins upregulate NOS, and thereby CPP. This suggests that one mechanism responsible for statin memory loss is the modification of the hippocamal synaptic environment by these statin actions. Thus, statin memory loss is a pharmacologically predictable outcome of statin treatment. Prescribing physicians should monitor statin patients for cognitive decline and intervene prior to significant impact to quality of life.

PURPOSE: Identify the mechanism by which HMG CoA reductase inhibitors, the cholesterol-lowering class of statin drugs, induce memory loss.

BACKGROUND: Cognitive adverse drug reactions (ADRs), including, amnesia, transient global amnesia, aphasia and impairment of short term memory, have been documented in association with statins. The damage is measurable and persistent, affects both the patient and family caregiver, and is underreported.

The Australian Adverse Drug Reactions Bulletin listed Simvastatin under "Drugs that make you forget," referring to reports of memory impairment or amnesia, including transient global amnesia, associated with drug therapy in 1998 [2]. In 2004, Australia's National Prescribing Service Limited released a fact sheet entitled "Statins and Memory Loss," based on reports of statins and amnesia or memory loss in Australia, specific to Atorvastatin, Fluvastatin, Pravastatin, and Simvastatin [3]. In 2005, the Canadian Adverse Reaction Newsletter identified adverse reaction reports of amnesia, to include forgetfulness, memory disturbance, memory impairment and memory loss, submitted to Health Canada in association with Atorvastatin, Cerivastatin, Lovastatin, Pravastatin, Rosuvastatin, and Simvastatin [4].

Journal publications reviewing ADRs include "Statin-associated memory loss: analysis of 60 case reports and review of the literature" by Wagstaff, et al [5], examining ADR reports to the United State's Federal Drug Administration (FDA), and "Psychiatric adverse reactions with statins, fibrates and ezetimibe: implications for the use of lipid lowering agents," by Tatley and Savage [6], reviewing the increase in ADR reports to the New Zealand Centre for Adverse Reactions Monitoring (CARM). Published case reports have detailed individual or multiple patients experiencing statin-associated impairment of short term memory or amnesia [7,8,9,10, 11,12].

Anecdotal and other information on statin-associated amnesia and memory loss, less constrained to clinical and statistical data and more oriented to impact on patient daily living and quality of life, has been published in books [13, 14, 15], magazines [16], and newspapers [17, 18]. The journal article, "Implications of statin adverse effects in the elderly," by Golomb, emphasizes that the elderly are more vulnerable to and less likely to recover from statin ADRs [19]. Muldoon, et al [20,21], repeatedly succeeded in identifying and measuring cognitive changes in statin patients in placebo-controlled trials, and identified the specific neuropsychological tests most sensitive to statin cognitive damage. Golomb reported that patients that experienced statin-associated memory loss were subsequently unable to recover more than 85% of their pre-statin cognitive abilities after halting the statin, and upon rechallenge, they were unable to recover more than 85% of the previously recovered cognitive ability [22].

Memory loss not only affects the patient but the family, regardless of cause. It is commonly acknowledged that upon the death of an elderly spouse, the risk that the surviving spouse will die within one year increases. However, Christakakis and Allison [23] found that hospitalization for a diagnosis of psychiatric disease or dementia resulted in an even greater increase in risk of mortality for the care giving spouse, and that risk was also higher than if the diagnosis had been cancer or stroke. Damjanovic, et al, [24] found that caregivers of Alzheimer's patients experienced a decline in immune cells due to chronic stress, as evidenced by accelerated telomere erosion.
The incidence of statin patients developing memory loss or amnesia is underreported. Golomb, et al, found that physicians were more likely to deny than endorse the association between statins and cognitive ADRs when the symptoms were reported by the patient [25].

METHODS: Retrospective review using Pub Med, a service of the National Library of Medicine and the National Institutes of Health, and other sources.

RESULTS: Memory is formed by Long Term Potentiation (LTP) in the Hippocampus, whereby a change in the shape of a synapse ensures that subsequent signaling will follow the same pathway between neurons [26]. Researchers at University of California at Irvine, in a recent publication of physical evidence of LTP [1,27], demonstrated the physical process for formation of memory and verified the necessary environment for this change in shape. The researchers demonstrated that phosphorylated cofilin (pCofilin) caused actin polymerization, affecting actin filaments (f-Actin) to achieve a larger synapse. They used NMDA receptor agonist (+/-)-3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), a product of nitric oxide synthase (NOS), to disrupt memory formation. A retrospective review of the literature indicates that CPP prevents new memory formation and erases existing memory.

Thus, both pCofilin and f-Actin are essential to forming memory, but they are products of Rho, which is produced in the mevalonate pathway. Statins interfere with the mevalonate pathway, by inhibiting HMG CoA reductase, and thereby inhibit other downstream products, including production of Coenzyme Q 10, dolichols, and Rho, and thus inhibit f-Actin and pCofilin. Statins affect the actin cytoskeleton, inhibit RhoA activation, andCofilin phosphorylation [28,29,30,31,32].

Statins upregulate Nitric Oxide, which produces CPP [33,34,35], thereby increasing the substance that erases existing memory and prevents formation of new memory. Researchers report that cholesterol and Coenzyme Q10 are needed for memory function [36,37,38,39,40]. Cholesterol and Coenzyme Q10 production are also inhibited by statins, and likely contribute to statin cognitive ADRs, as may other mechanisms, above and beyond the suppression of LTP.

CONCLUSIONS: Statins are the most prescribed class of drugs in the world, and in the history of the world, and there is a bias against reporting of adverse effects. Even so, memory impairment has been established as an adverse effect of statin drugs, and various mechanisms may be involved. However, the fact that statins inhibit Rho and upregulate NOS, and thereby interfere with LTP, is sufficient to indicate that statin memory loss is a pharmacologically predictable statin outcome.

Prescribing physicians should monitor for statin memory loss, and consider establishing a pre-statin cognitive baseline using the statin sensitive neuropsychiatric tests. When memory loss is identified, the physician should proactively intervene, treat the patient and family through recovery, and file an ADR report. Emergency and other physicians should consider statin-associated memory loss in evaluation of patients presenting with Transient Global Amnesia, amnesia, memory loss, or aphasia.

Researchers should build on the understanding of LTP, recognize statin interference with LTP is repeatable, which is consistent with Muldoon's and with Golomb's findings [20,21,22], and begin to identify treatment toward recovery for statin memory loss patients based on this new understanding.

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