

Statins Protect Against, and Accelerate, Cognitive Impairment and Dementia



By Chuck Dinerstein, MD, MBA — February 10, 2020

At least 10% of the U.S. population is currently taking a statin to help lower cholesterol. But can statins help prevent dementia? More importantly, can these same statins accelerate dementia? And how can we explain how statins are responsible for such dramatically different responses? Let's take a look.



Image courtesy of Gerd Altmann on Pixabay [1]

Statin use is ubiquitous, and a careful read of the literature will demonstrate some small percentage of each clinical trial having increased or decreased risk of dementia and Alzheimer's Disease (AD). It is not a new issue; in 2012, the FDA felt it necessary to warn physicians about a small but real incidence of reversible cognitive impairment associated with their use. Of course, the real-world evidence is a bit more ambiguous than that FDA pronouncement would suggest.

Cognitive impairment

- Phase I statin studies demonstrated short-term reversible cognitive loss at increasing doses.
- A double-blind RCT in 308 participants "showed detrimental effects on cognitive performance" and learning
- A patient survey indicated that high statin dosages were associated with reversible changes

when statins were discontinued. Patients re-challenged with statins found their symptoms returned.

- A review of the FDA's Adverse Event Reporting System (AERS), suggested those patients at higher doses and using the lipophilic, "fat-loving" forms of statins (atorvastatin and simvastatin), were at highest risk, about 1% of patients. Another review of the AERS reports suggested that the incidence of cognitive change was similar to that seen with other medications.
- Systematic review and meta-analysis of randomized controlled trials (RCT) found rare reports with no evidence of impairment with the use of statins. But cognitive impairments were not primary measured outcomes, and many of the RCT trials excluded patients most at risk.
- The American Heart Association and American College of Cardiology guidelines "recommended avoiding consideration of cognitive impairment ... when prescribing statins."

Alzheimer's Disease (AD) and dementia

- Two epidemiologic studies demonstrated a lower risk of dementia in statin users.
- Statin's beneficial effects accrue to specific sub-groups, such as patients under age 80, and women. Similarly, the use of statins in mid-life seemed to reduce AD and dementia in later life.
- The effect of statins, if present, were not directly related to subsequent cholesterol levels.
- Several large clinical trials failed to demonstrate a benefit, but again, dementia was not a measured primary outcome.
- The Cochrane Systematic Review did not identify any protective effect.

As you can see, at least in this instance, you are entitled not only to your own opinion as to statin's beneficial or harmful effects, but you are entitled to your own facts. Pick the study that supports your position best. This lack of clarity typifies what happens when the laboratory comes to the real world.

Bioplausibility

Despite the drumbeat of the media, cholesterol is not solely a health villain, inflicting injury to your vascular bed. Cholesterol is vital in the formation of myelin sheaths and neurotransmitter expression, both affecting the speed and timing of neural signals; in the function of our cellular powerhouses, the mitochondria, even the transport of anti-oxidants. Two theories are advanced to explain statins paradoxical effect on cognition.

The protective aspect of statins may be due to their effect on the vasculature. Specifically, in stabilizing plaque preventing small bits from breaking free and obstructing the downstream microvasculature, a finding consistent with the statins' reduction in stroke and dementia from microvascular disease. Some have suggested that statins directly affect the formation of beta-amyloid, a marker for AD, but not it's cause.

The deleterious effects are felt to be due to statins lowering of cholesterol levels within the brain - interfering with all neurologic and cellular functions. High statin dosages, combined with their physical preference for fat over watery environments (the expression fathead contains a great deal

of physiologic truth), increases their transportation across the blood-brain barrier. For those looking for a genetic component, an individual's ability to metabolize statins, slowly or quickly, involves genes associated with enzymes and transporters; slower metabolism means higher dosages for more extended periods. Muscle pain, a typical "side-effect" of statins, is due to their interaction with muscle mitochondria, and some scientists feel that a similar, more muted process occurs within the mitochondria of the brain, impairing their energy production and therefore impacting cellular health.

Despite the confident tones of articles, physicians and media's talking heads, we know little about how statins protect or harm us. We have real-world evidence that for the majority of individuals, they may increase our good days, although not necessarily our total days, and we may have to content ourselves with that for the moment.

Source: The role of statins in both cognitive impairment and protection against dementia: a tale of two mechanisms. Translational Neurodegeneration DOI: 10.1185/s40035-018-01 10-3

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