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REVIEW ARTICLE

A Potential Role for Statins in the Long-term Reduction in the Risk of Neurodegenerative Disease

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Abstract

Statins reduce the progression of cerebrovascular atherosclerosis and so may reduce the risk of vascular dementia. Statins may also reduce the formation of beta-amyloid and increase the clearance of amyloid precursor protein and so reduce the risk of Alzheimer's disease (AD). A meta-analysis of 46 longitudinal observational studies of statin therapy found that in all primary and almost all secondary analyses, statin use was associated with a lower risk of incident AD and all-cause dementia. A cohort study found that statin use was associated with a lower risk of development of Parkinson's disease (PD); the benefit appeared to be mediated by a lower risk of atherosclerosis. Whereas observational studies cannot establish a causal protective role for statins against dementia and PD, given that statins are primarily indicated for the prevention of ischemic cardiovascular and cerebrovascular events, whether or not they prevent dementia and PD is not relevant to their prescription; but if they do prevent these, it's a bonus. It should be kept in mind that even if statins do play a significant preventative role in neurodegenerative disease, as with the benefits in the prevention of cardiovascular disease, the benefits will only be observed after many years or decades of treatment, and the numbers needed to treat will be large. Expressed otherwise, the effect size is likely to be small.

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Introduction

A large proportion of the population above age 60 years receives a statin, and the prescription of statins is continued for decades. Thus, statins are among the most widely prescribed drugs in the pharmacopeia in terms of ubiquity and duration of use. The primary role of a statin is to reduce low-density lipoprotein cholesterol and hence the risk of hypertension as well as major and minor cardiovascular and cerebrovascular events and mortality associated therewith. However, the use of statins has also been associated with neuropsychiatric benefits. This article discusses the mechanisms of benefit and examines recent evidence that supports hypotheses for statin-associated benefit in neurodegenerative disease.

Mechanisms of Statin Benefits in Neuropsychiatry

Statin use has been associated with a reduced risk of Alzheimer's disease (AD) and all-cause dementia. What may be the mechanisms? An obvious first

mechanism is that if statins reduce the progression of atherosclerosis, they will reduce cerebrovascular atherosclerosis, as well. This means that blood supply to brain tissue will be less compromised and that vascular insufficiency will contribute less to neurodegeneration. An obvious second mechanism is that statins protect against ischemic stroke, thus reducing the risk of dementia associated with stroke. These two mechanisms together reduce the risk of vascular dementia, which is responsible for about a quarter of the burden of dementia worldwide.[1]

The third mechanism is more specific to alzheimer disease (AD). Beta- and gamma-secretase are enzymes that cleave amyloid precursor protein (APP), leading to the formation of beta-amyloid, the main constituent of amyloid plaque that is the hallmark of AD. A small proportion of APP follows this pathway; the rest is cleaved by alpha-secretase to form other, non-harmful products. Statins inhibit beta-secretase and so reduce the formation of beta-amyloid, and statins activate alpha-secretase, and so increase the clearance of APP. So, statins potentially reduce plaque formation in AD.[2]

Meta-analysis: Statins may Protect against Dementia

Many but not all observational studies suggest that statin use is associated with a lower risk of development of AD and all-cause dementia. Olmastroni *et al*.[3] described a systematic review and meta-analysis of the studies on the subject. These authors searched electronic databases and reference lists and identified 46 longitudinal observational studies that examined the relationship between statin use and incident dementia. There were 38 cohort studies and eight case-control studies. Sample sizes in these studies ranged from a low of 123 to a high of 2,004,692 subjects.

The authors[3] found that statin use was associated with a reduced risk of all-cause dementia (36 studies; N = 5,738,737; or, 0.80; 95% CI, 0.75-0.86); however, examination of the funnel plot suggested publication bias. Statin use was also associated with a reduced risk of AD (21 studies; N=1,188,377; or, 0.68; 95% CI, 0.56-0.81); examination of the funnel plot did not suggest publication bias.

The findings held true for both AD and all-cause dementia in subgroup analyses conducted by age (75 years and above) and study design (cohort, case-control). The findings held true for both men and women in the all-cause dementia analysis but not in the AD analysis; the latter may have been because too few studies were available, and so the confidence intervals were very wide. The findings also held true for lipophilic and hydrophilic statins, and for low potency and high potency statins.

In summary, this meta-analysis[3] of 46 longitudinal observational studies of statin therapy found that in all primary and almost all secondary analyses, statin use was associated with a lower risk of incident AD and all-cause dementia.

Readers must keep in mind the limitations of this meta-analysis. For example, the median duration of follow up was not specified for the observational studies in this meta-analysis, and so we don't know the average duration of statin use that establishes potential preventive benefits against AD and all-cause dementia. More importantly, the meta-analysis examined observational studies. Observational studies are not randomized controlled trials (RCTs) and so cannot establish cause-effect relationships.

Cohort Study: Statins may Protect against Parkinson's Disease

Might statins reduce the risk of Parkinson's disease (PD), in addition to reducing the risk of AD? Whereas the mechanisms of benefit in PD are less clear than those in the case of AD and other dementias, the possibility was examined in an observational cohort study by Oveisgharan *et al*.[4] The sample comprised 2841 elderly subjects. The mean age of the subjects was 76 years. The sample was 75% female. At baseline, 32.9% of subjects were using statins. These subjects were followed for a mean duration of 5.6 years.

PD was diagnosed if 2 or more PD signs were identified at annual clinical examinations. By the end of follow up, 50.4% the sample had been diagnosed with PD. Postmortem data, at a mean age of 89 years, was available for 36.7% of the sample. Analyses were controlled for important confounders, including demographic variables, vascular risk factors, and comorbidities.

The authors[4] found that statin use at baseline was

associated with a lower risk of development of PD (HR, 0.84; 95% CI, 0.74–0.96). In the postmortem sample (n=1044), statin use before death was associated with a lower risk of atherosclerosis (OR, 0.63; 95% CI, 0.50–0.79). In mediation analysis, statins were linked through severe atherosclerosis to PD by both a direct (OR, 0.73; 95% CI, 0.54-0.93) and indirect (OR, 0.92; 95% CI, 0.88-0.97) pathway; atherosclerosis mediated 17% of the association between statins and PD.

In summary, in older adults followed for a mean of 5.6 years, statin use was associated with a lower risk of development of PD; the benefit appeared to be mediated by a lower risk of atherosclerosis. As already observed in the context of statins and AD, this was not an RCT, and so cause and effect relationships are speculative, not confirmatory.

General Notes

In earlier sections of this article, it was observed that the benefits of statins in AD and PD were recorded in observational studies, and that observational studies cannot establish cause-effect relationships. In other words, despite apparent evidence of benefit, we cannot conclude that statins were responsible for the benefit. Why is this? The answer is that confounding may play a role. For example, patients who can afford statins, or patients who take statins, may be patients who are more concerned about health. These patients may eat a healthier diet, exercise more, adhere better to medical prescriptions, and generally lead a healthier lifestyle, all of which may reduce their risk of neurodegenerative disease. So, statin use may merely be a marker and not the cause of the observed benefits.

An additional caveat is that even if statins do play a significant preventative role in neurodegenerative disease, as with the benefits in the prevention of cardiovascular disease, the benefits will only be observed after many years or decades of treatment, and the numbers needed to treat will be large. Expressed otherwise, the effect size is likely to be small.

Parting Notes

Statins have also been trialed for the treatment of AD. A meta-analysis of these RCTs found that statins did not improve cognition but did improve neuropsychiatric symptoms and activities of daily living.[5] The magnitude of improvement, however, was so small as to probably be clinically undetectable. RCT data on the use of statins for the prevention of dementia are inconclusive because the number of studies is small and the trial duration too brief for a sufficient number of cases to be diagnosed and compared between groups.[6]

On a final note, statins are primarily indicated for the prevention of ischemic cardiovascular and cerebrovascular events; whether or not they prevent dementia and PD is not relevant to their prescription. If they do prevent these, it's a bonus.

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