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Published in:
Movement Disorders

DOI:
10.1002/mds.27721

Publication date:
2019

EDITORIAL

Statins and Parkinson's: A Complex Interaction

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The relationship between statin use and the risk of developing Parkinson's disease (PD) is complex and remains the subject of debate. Previous epidemiological studies provide conflicting data, discussed by Jeong and colleagues in this issue,[1] likely attributed, in part, to variation in study design, but also reflecting the complexity of the interactions between vascular risk factors, incident Parkinson's, and Parkinson's progression. The reason to continue to search for clarity is to identify both modifiable risk factors and potential neuroprotective agents for use in prodromal and established disease.

There are strong preclinical data supporting a neuroprotective effect of statins with regard to disease mechanisms of relevance to PD,[2] supporting the rationale for simvastatin currently being the subject of a phase 2 neuroprotective trial.[3] The potential protective effects of statins are also the subject of investigation in other disease areas, including multiple sclerosis, with a successful phase 2 study[4] leading to a current phase 3 trial,[5] and previous investigation in Alzheimer's disease (AD), with a suggestion of both reduced risk of dementia development and a slowing of cognitive decline.[6]

However, for an agent to have efficacy in both PD prevention and progression assumes similarity of disease process in both stages of disease—that the "triggers" and "facilitators" are the same as the "aggravators."[7] We already have a good illustration in Parkinson's why this may be a false assumption: Smoking is protective of incident PD,[8] but once Parkinson's is diagnosed, smoking appears to increase the rate of progression.[9]

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Relevant conflicts of interest/financial disclosures: Dr. Carroll is chief investigator of PD STAT (a clinical trial of simvastatin as a neuroprotective agent in Parkinson's disease); Dr. Wyse is Research Director of the Cure Parkinson's Trust, major funder of the PD STAT trial.
Full financial disclosures and author roles may be found in the online version of this article.

Received: 25 April 2019; **Accepted:** 29 April 2019

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27721

The situation is complicated further with regard to statins because the indication for their initiation (generally cardiovascular disease) is itself a risk factor for PD development, as are associated factors (such as physical inactivity and diabetes). In addition, the therapeutic effect of statins (lowering of cholesterol) also influences PD risk, with low cholesterol being associated with a higher risk of incident PD, a finding which was previously reported[10] and is replicated in Jeong's study.[1] The postulated mechanisms for this include alteration of lysosomal membrane stability (which is cholesterol dependent) or reducing levels of coenzyme Q10. Additionally, higher cholesterol may be associated with a lower risk of incident PD. These findings are counterintuitive within the context of cardiovascular health and risk factors, and tend to conflict with our current understanding of the role these play in the development of neurodegenerative diseases, including PD and AD, as well as our understanding of their role in disease progression.[11]

Epidemiological studies are fraught with difficulties and the potential for methodological confounders and biases. Data ascertainment is typically dependent on insurance databases which are reliant on accurate clinical diagnosis and declaration, which in practice may be an under- or over-representation. Patients may present late, or there may be diagnostic delay or inaccuracies reflecting health care provision in different localities. There may be ethnic differences in the effects of, or response to, statins, with varying impact of ethnicity on disease progression and heterogeneity. In addition, prescribing practice relating to statins has changed significantly over the last 15 years (the time period covered by most studies) as population screening and primary prevention have increased.

In this issue of *Movement* Disorders, Jeong and colleagues address several of the important biases using a data source which covers 97% of the Korean population.[1] The researchers adjust for a range of risk factors known to be associated with statin use, including smoking status, diabetes, hypertension, total cholesterol, age, and physical activity and demonstrate that some of these associations with statin use are themselves risk factors or associations with PD incidence (physical activity, smoking, hypertension, coronary

artery disease, and diabetes). They excluded individuals with premorbid parkinsonian conditions (another potential confounder) by incorporating a 4-year run-in period. The intriguing finding is of short-term (<1 year) statin use being associated with increased PD risk, whereas longer-term use is not.

Given the time frame of the association, it is likely that patients had prodromal PD at the time of statin initiation. Did the statin "unmask" PD, somehow acting as an aggravator to speed the progression to clinical manifestation?

Another possibility is that the process of seeking health care intervention was triggered by prodromal PD, and that the outcome of the interaction was a statin prescription. We know that health care contacts increase in the years preceding a Parkinson's diagnosis, likely reflecting the accumulation of nonspecific, nonmotor problems.[12,13] What has not been explored is the nature of the interactions and consultations that lead to statin prescription in patients who have a constellation of symptoms and no clear unifying diagnosis. Might the decision to treat with a statin be driven by factors other than cardiovascular risk? What do we know of factors that influence prescribing practice? What are the relative contributions of clinical protocols, national guidelines, clinician belief, or a shared understanding of cardiovascular risk? In the study by Jeong and colleagues, compared to nonusers, statin users were physically more active, had lower alcohol consumption, were less likely to smoke and had higher household income, had higher cholesterol and higher blood pressure, and were twice as likely (43.2% vs. 21.4%) to have a diagnosis of diabetes, which is associated with a worse prognosis in established PD. What are the health care expectations of those with prodromal Parkinson's who seek medical advice? It would have been interesting to know whether those patients who were prescribed statins were more likely to have symptoms compatible with prodromal Parkinson's. Jeong's well-designed study addresses some of the important questions relating to statins and incident Parkinson's risk, at least in the Korean population. However, the potential interactions are indeed complex, possibly too complex for traditional epidemiological methods of evaluation, and many questions remain. ■

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