ORIGINAL RESEARCH ARTICLE

Drug Safety 2008; 31 (5): 399-407
0114-5916/08/0005-0399/$48.00/0

Use of Statins and the Risk of Parkinson's Disease

A Retrospective Case-Control Study in the UK

Claudia Becker,[1] *Susan S. Jick*[2] and *Christoph R. Meier*[1,2]

1 Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacology and Toxicology, University Hospital Basel, Basel, Switzerland
2 Boston Collaborative Drug Surveillance Program, Boston University Medical Center, Lexington, Massachusetts, USA

Abstract

Background: Case reports have related the use of HMG-CoA reductase inhibitors ('statins') to Parkinson's disease (PD). Paradoxically, however, statins may have potentially beneficial effects on neurodegenerative diseases due to their anti-inflammatory properties.

Objective: To explore the risk of the development of PD in association with untreated hyperlipidaemia and with hyperlipidaemia treated with lipid-lowering drugs in the UK primary care setting.

Methods: We conducted a case-control analysis using the UK-based General Practice Research Database (GPRD). Cases were incident PD cases ≥40 years of age between 1994 and 2005. One control was matched to each PD case based on age, sex, general practice and index date. Lipid-lowering drug use was assessed by exposure timing (current vs past use) and by exposure duration (1–9, 10–29 or ≥30 prescriptions) prior to the index date for both cases and controls. Odds ratios (OR) were calculated using conditional logistic regression, adjusted for body mass index, smoking and various cardiovascular, metabolic and psychiatric co-morbidities.

Results: We identified 3637 cases with an incident idiopathic PD diagnosis, and the same number of controls. Compared with patients without hyperlipidaemia, those with untreated hyperlipidaemia did not have an altered relative PD risk (adjusted OR 0.98, 95% CI 0.74, 1.30). The adjusted ORs for current use of ≥30 prescriptions for statins or fibrates compared with non-use of statins or fibrates were 1.06 (95% CI 0.75, 1.51) and 1.25 (95% CI 0.51, 3.06), respectively.

Conclusions: In this observational study, the long-term use of statins or fibrates was not associated with a substantially altered relative risk of developing PD.

Background

Parkinson's disease (PD) is a neurological disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta.[1] The aetiology is still largely unknown, with suggested involvement of oxidative stress,[2] neuroinflammation[3] and mitochondrial dysfunction.[4]

HMG-CoA reductase inhibitors ('statins') have been shown to increase striatal dopamine concentration in animal models of PD.[5] Additionally, they have anti-inflammatory properties and decrease oxidative stress,[6] which may be beneficial in reducing

neuroinflammatory processes in PD. Observational studies have also found associations with statin use and a reduced risk of other neurodegenerative diseases,[7,8] although discussion of this effect has been controversial[9] and the association may be influenced by reverse protopathic bias, which can occur if cases are more likely than controls to stop a treatment prior to the index date due to early symptoms of the disease under study.[10] On the other hand, case reports have related the use of statins to PD.[11,12] In two recent observational studies, low levels of cholesterol and low-density lipoprotein (LDL) have been associated with PD,[13,14] raising the question whether pharmacological lowering of cholesterol may trigger PD. Data on a possible effect of fibrates on PD are scarce.

It was the aim of the current study to explore, in a large patient sample within the UK primary care setting, the association between diagnosed hyperlipidaemia, with or without the use of lipid-lowering agents, and the risk of being diagnosed with PD.

Methods

Data Source

We performed a retrospective case-control analysis using data from the General Practice Research Database (GPRD), which provides healthcare information on some 5 million people in the UK and has been previously described in detail.[15-17] Specially trained general practitioners (GPs) record information on demographics, diagnoses and drug prescriptions as well as patient referrals and hospital admissions in the GPRD. Drug prescriptions are generated directly from the computer and recorded in each patient's computerized profile. Hospital discharge as well as referral letters are available on request to review and validate recorded diagnoses. The recorded information on drug exposure and on diagnoses has been validated repeatedly and proven to be of high quality;[18,19] GPRD data have been used recently in studies examining PD.[20,21] The patients enrolled in the GPRD are representative of the UK with regard to age, sex and geographic distribution.[17] The database is managed by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK, and the protocol for this study was reviewed and approved by the Independent Scientific Advisory Committee for MHRA database research (ISAC). The investigators only had access to anonymous information.

Study Base, Case Identification and Validation

The study base included all patients in the GPRD who were ≥40 years old, covering the period 1 January 1994–31 December 2005. Cases were all individuals in the study base with a code for idiopathic PD recorded for the first time during the study period. The codes qualifying for case status were OXMIS (Oxford Medical Information System) codes 342 ('Paralysis agitans') and 342D ('idiopathic parkinsonism') as well as READ-codes F12..00 ('Parkinson's disease'), F12z.00 ('Parkinson's disease NOS [not otherwise specified]') and F120.00 ('Paralysis agitans'). All cases were required to have a minimum of 3 years of medical history in the GPRD computer record prior to the first recorded diagnosis of PD. The date of the first code for PD will subsequently be referred to as the 'index date'.

A validation of the PD diagnosis in the GPRD was conducted in a recent study by Hernan et al.[20] in which GP-recorded PD diagnoses were confirmed for 90% of PD cases receiving at least two prescriptions for the treatment of PD during follow-up.

Because 28% of our cases had received one or more prescriptions for an anti-PD medication prior to the first recorded PD diagnosis, we manually reviewed a random sample of 100 case profiles to find out more about the reasons for PD medication use prior to the index date. This profile review revealed that a substantial proportion of PD patients received treatment due to early symptoms of PD, before the GP recorded the PD diagnosis at some later point in time. This led us to set up an algorithm for inclusion of cases into the analysis; in order to be eligible as a case with a first-time diagnosis of idiopathic PD, patients had to meet the following three criteria: (i) they had to have less than two prescriptions for any drug used to treat PD (levodopa, dopamine agonists, selegiline, amantadine, apomorphine, anticholinergic drugs or catechol-*O*-methyltransferase [COMT] inhibitors) prior to the index date; (ii) they had to have received two or

more prescriptions for levodopa, selegiline, dopamine agonists or a COMT inhibitor after the index date; and (iii) they must not have had any prescriptions recorded for drugs known to cause parkinsonism (typical antipsychotics, metoclopramide or cinnarizine) within 180 days prior to the index date.

Controls

We identified at random from the base population one control per PD case, matched to the case for year of birth, sex, general practice, index date and number of years in the GPRD prior to the index date. Thus, controls also had to have a recorded history ≥3 years prior to the index date.

Statistical Analysis

We conducted conditional logistic regression analyses to explore the association between the risk of PD and previous use of various lipid-lowering drugs using the statistical software SAS (release 9.1, SAS Institute, Cary, NC, USA). Relative risk estimates (odds ratios [ORs]) are presented with 95% confidence intervals.

Patients with no exposure to any lipid-lowering drugs formed the reference group. For the main analysis we created a model in which we compared users of lipid-lowering drugs versus non-users, whereby use of more than one lipid-lowering drug prior to the index date was possible. We adjusted for such sequential or concurrent use of various lipid-lowering drugs in the multivariate model. In addition, we also ran a model in which subjects were categorized into mutually exclusive groups of users of statins only, fibrates only, other lipid-lowering drugs (anion-exchange resins, derivates of niacin and omega-3-fatty acids) only, or any combination of these lipid-lowering drugs (patients 'switching' drugs or those using the drugs in combination), and compared them with non-users of any lipid-lowering drugs.

We grouped users of lipid-lowering drugs, according to the date of their last prescription issued prior to the index date, into 'current' (last prescription <90 days) or 'past' (last prescription ≥90 days) users, and according to the number of recorded prescriptions (1–9, 10–29 and ≥30) for the study drugs prior to the index date. In order to identify potential confounding, we also assessed the prevalence of various diagnosed and recorded chronic diseases prior to the index date such as hyperlipidaemia, diabetes mellitus, hypertension, ischaemic heart disease, congestive heart failure, stroke or transient ischaemic attack (TIA), arrhythmias, asthma, chronic obstructive pulmonary disease (COPD), epilepsy, affective disorders, schizophrenia, or neurotic and somatoform disorders. Other covariates such as smoking (never smoked, ex-smoker, current or smoking status unknown) and body mass index (BMI) [<25, 25–29.9, ≥30 kg/m^2] were also assessed and included in the analyses.

Results

After application of the exclusion criteria described in the methods section we identified 3637 cases and the same number of matched controls (figure 1). Approximately 90% of the cases had their first PD diagnosis recorded after the age of 60 years, there were more males than females (60% vs 40%), and being a current smoker was associated with a reduced risk of developing PD (OR 0.51; 95% CI 0.43, 0.60). Table I displays the age and sex distribution, smoking status, BMI and the prevalence of comorbidities in cases and controls. Among the PD cases, 378 (10.4%) had ever used a lipid-lowering drug prior to the index date: 340 (9.4%) had used or were currently using statins, 61 (1.7%) fibrates, and 24 (0.7%) another lipid-lowering agent (the individual percentages do not total 10.4% because combined use was possible).

The adjusted relative risk (OR) of a PD diagnosis among those with an untreated but recorded diagnosis of hyperlipidaemia compared with those with no such diagnosis was 0.98 (95% CI 0.74, 1.30). Among subjects treated for hyperlipidaemia, the ORs of developing a first-time PD diagnosis, adjusted for the covariates listed in table I, were 0.92 (95% CI 0.73, 1.16) for current statin use, 1.29 (95% CI 0.65, 2.56) for current fibrate use, and 0.24 (95% CI 0.06, 0.91) for current use of other lipid-lowering drugs, compared with non-use of these drugs. Since only a few patients were exposed to 'other lipid-lowering' drugs, we did not analyse this group further.

The results of the analysis in which we combined timing and duration of use are displayed in detail in

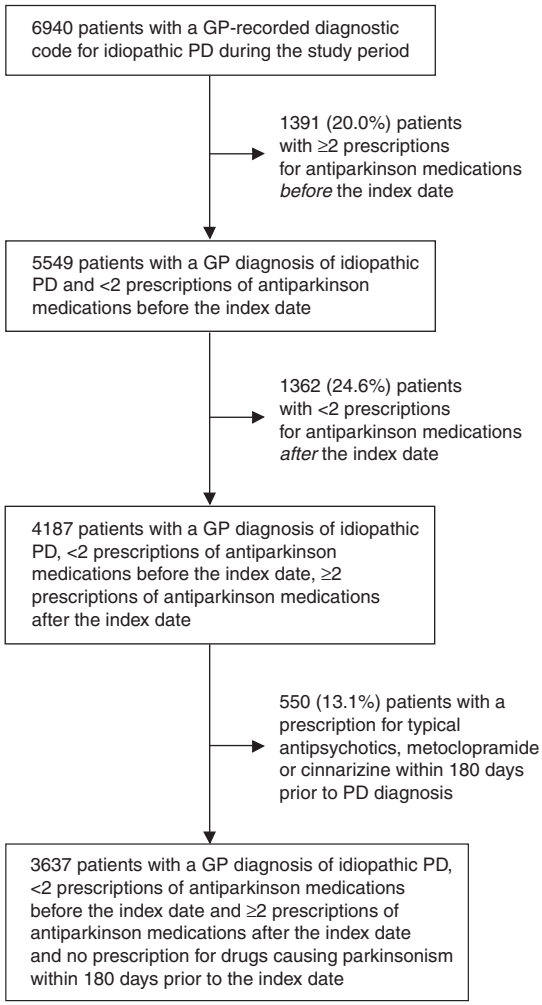

Fig. 1. Procedure for exclusion of uncertain Parkinson's disease (PD) cases. **GP** = general practitioner.

table II. Compared with non-use, the adjusted ORs for current use of ≥30 prescriptions for statins or fibrates were 1.06 (95% CI 0.75, 1.51) and 1.25 (95% CI 0.51, 3.06), respectively (one prescription for a statin or a fibrate covers, on average, approximately 60 days, so that 30 prescriptions reflect a treatment duration of approximately 5 years). We further stratified the analysis on statin use by age and sex and found no evidence of effect modification (data not shown). In the analysis of mutually exclusive exposure groups, the adjusted OR for current use of ≥30 prescriptions was 1.14 (95% CI 0.79, 1.64) for statins only and 1.44 (95% CI 0.50, 4.15) for fibrates only, compared with non-use of any lipid-lowering drugs.

The adjusted OR for past use of ≥30 statin prescriptions was 5.02 (95% CI 0.53, 47.38), based on only seven exposed cases and one exposed control subject. It is possible that early PD symptoms could have led to the cessation of the statin therapy shortly prior to the index date (i.e. 'reverse protopathic bias'). This bias may have led to an underrepresentation of current statin users and thereby to a dilution of the real PD risk associated with statin use. We therefore ran sensitivity analyses in which we used various exposure timing categories for current versus past use. The adjusted ORs for past use of ≥10 statin prescriptions, compared with non-use, were 1.53 (95% CI 0.66, 3.54), 1.31 (95% CI 0.50, 3.46) and 1.02 (95% CI 0.33, 2.09), respectively, when we defined 'past use' as having received the last statin prescription >90, >180 or >365 days prior to the index date.

We separately analysed the risk of developing a PD diagnosis associated with use of individual statins, stratifying the subgroup of subjects with current use of ≥30 statin prescriptions (104 cases and 98 controls) by the last statin prescribed prior to the index date. The results are presented in table III. While there was no evidence for an altered PD risk associated with the more lipophilic statins simvastatin and atorvastatin, there was a suggestion of an increased risk associated with current long-term use of the more hydrophilic pravastatin (OR 2.41; 95% CI 1.01, 5.72); we therefore stratified current long-term pravastatin users into users of a low to medium dose (10 or 20 mg) or of a high dose (40 mg), yielding adjusted ORs of 4.51 (95% CI 1.40, 14.58) for low- to medium-dose users and 0.86 (95% CI 0.22, 3.36) for high-dose users.

Discussion

The results of this large observational case-control study suggest that neither current nor past exposure to a statin or any other lipid-lowering drug substantially alters the risk of developing a PD diagnosis. In addition, there was no association between duration of use of these study drugs and the risk of PD. To our knowledge, so far only one study has been published in the literature analysing statin use

Table I. Characteristics of cases and controls and the multivariate effects on the risk of Parkinson's disease

Variable	No. of cases (%) [n = 3637]	No. of controls (%) [n = 3637]	Adjusted OR[a] (95% CI)	p-Value
Age (y)				
<60	320 (8.8)	321 (8.3)		
60–69	752 (20.7)	751 (20.7)		
70–79	1522 (41.9)	1520 (41.8)		
≥80	1043 (28.7)	1045 (28.7)		
Sex				
Male	2167 (59.6)	2167 (59.6)		
Female	1470 (40.4)	1470 (40.4)		
Smoking status				
Non-smoking	2186 (60.1)	1866 (51.3)	1.00 (reference)	
Current smoker	326 (9.0)	521 (14.3)	0.51 (0.43, 0.60)	<0.0001
Ex-smoker	581 (16.0)	697 (19.2)	0.67 (0.58, 0.77)	<0.0001
BMI (kg/m^2)				
15–24.9	1239 (34.1)	1192 (32.8)	1.00 (reference)	
25–29.9	1121 (30.8)	1104 (30.4)	1.01 (0.89, 1.14)	0.93
≥30	364 (10.0)	399 (11.0)	0.89 (0.75, 1.06)	0.19
Co-morbidities				
Diabetes mellitus	291 (8.0)	308 (8.5)	0.94 (0.79, 1.13)	0.51
Asthma/COPD	431 (11.9)	536 (14.7)	0.78 (0.67, 0.90)	0.001
Hypertension	1197 (32.9)	1286 (35.4)	0.83 (0.75, 0.93)	0.001
IHD	815 (22.4)	755 (20.8)	1.05 (0.93, 1.19)	0.45
CHF	291 (8.0)	282 (7.8)	0.94 (0.78, 1.14)	0.53
Stroke/TIA	541 (14.9)	349 (9.6)	1.68 (1.44, 1.97)	<0.0001
Arrhythmia	385 (10.6)	370 (10.2)	1.01 (0.86, 1.19)	0.92
Hyperlipidaemia	338 (9.3)	314 (8.6)	1.07 (0.90, 1.29)	0.44
Epilepsy	91 (2.5)	62 (1.7)	1.34 (0.95, 1.89)	0.10
Affective disorders	786 (21.6)	527 (14.5)	1.49 (1.30, 1.71)	<0.0001
Schizophrenia	30 (0.8)	24 (0.7)	1.01 (0.57, 1.79)	0.98
Neurotic and somatoform disorders	692 (19.0)	442 (12.2)	1.58 (1.36, 1.82)	<0.0001

a Adjusted for the other variables in this table.

BMI = body mass index; **CHF** = congestive heart failure; **COPD** = chronic obstructive pulmonary disease; **IHD** = ischaemic heart disease; **TIA** = transient ischaemic attack.

in prevalent PD patients.[22] The authors of this interview-based study concluded that statins did not seem to worsen PD in 173 patients with PD who used statins.

In theory, statins may be able to protect glial cells from inflammation and subsequent neuronal cell death. Various pharmacological effects beyond inhibiting the synthesis of cholesterol have been demonstrated for this drug class, such as neuroprotective and anti-inflammatory effects.[23] Furthermore, positive effects of statins on dopamine metabolism have been shown in rodents, such as prevention of striatal dopamine depletion,[5] reversal of down-regulation of dopamine D_1 and D_2 receptors in the prefrontal cortex,[24] or the enhancement of striatal dopamine concentrations.[25] However, these studies were carried out with doses clearly exceeding human therapeutic doses, and therefore these effects may not be reproducible with therapeutic doses in humans.

On the other hand, case reports have related statin use to the onset of PD.[11,12] Two patients receiving lovastatin therapy and one patient receiving fluvastatin therapy developed PD symptoms emerging 3 months to 2 years after starting the statin therapy. In all cases, the symptoms disappeared or at least improved after statin discontinuation. In addition, several case reports have linked statins with other diseases of the CNS, such as depression[26,27] or sleep

Table II. Antihyperlipidaemic drug use vs non-use prior to the index date in Parkinson's disease patients and controls and associated relative-risk estimates

Exposure	No. of cases (%) [n = 3637]	No. of controls (%) [n = 3637]	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	p-Value
Statins					
None	3297 (90.7)	3327 (91.5)	1.00 (reference)	1.00 (reference)	
Current use	285 (7.8)	275 (7.6)	1.06 (0.88, 1.28)	0.92 (0.73, 1.16)	0.48
no. of prescriptions					
1–9	82 (2.3)	78 (2.1)	1.07 (0.77, 1.47)	0.86 (0.60, 1.24)	0.43
10–29	99 (2.7)	99 (2.7)	1.02 (0.76, 1.37)	0.85 (0.61, 1.20)	0.36
≥30	104 (2.9)	98 (2.7)	1.09 (0.81, 1.45)	1.06 (0.75, 1.51)	0.75
Past use	55 (1.5)	35 (1.0)	1.60 (1.04, 2.46)	1.34 (0.83, 2.16)	0.23
no. of prescriptions					
1–9	34 (0.9)	26 (0.7)	1.33 (0.79, 2.24)	1.38 (0.77, 2.47)	0.28
10–29	14 (0.4)	8 (0.2)	1.75 (0.74, 4.18)	1.10 (0.43, 2.80)	0.84
≥30	7 (0.2)	1 (0.1)	7.07 (0.87, 57.4)	5.02 (0.53, 47.38)	0.16
Fibrates					
None	3576 (98.3)	3589 (98.7)	1.00 (reference)	1.00 (reference)	
Current use	23 (0.6)	17 (0.5)	1.36 (0.73, 2.55)	1.29 (0.65, 2.56)	0.46
no. of prescriptions					
1–9	4 (0.1)	4 (0.1)	1.00 (0.25, 4.00)	0.57 (0.13, 2.42)	0.44
10–29	7 (0.2)	3 (0.1)	2.33 (0.60, 9.02)	2.43 (0.52, 11.35)	0.26
≥30	12 (0.3)	10 (0.3)	1.22 (0.53, 2.83)	1.25 (0.51, 3.06)	0.63
Past use	38 (1.0)	31 (0.9)	1.23 (0.77, 1.98)	1.02 (0.60, 1.73)	0.93
no. of prescriptions					
1–9	17 (0.5)	14 (0.4)	1.21 (0.60, 2.46)	1.13 (0.51, 2.47)	0.77
10–29	8 (0.2)	8 (0.2)	1.00 (0.38, 2.66)	0.67 (0.22, 2.02)	0.47
≥30	13 (0.4)	9 (0.3)	1.46 (0.62, 3.41)	1.11 (0.43, 2.85)	0.83

a Adjusted for each other, body mass index, smoking status, use of antihypertensive drugs and the following co-morbidities: diabetes mellitus; asthma/chronic obstructive pulmonary disease; hypertension; ischaemic heart disease; congestive heart failure; stroke/transient ischaemic attack; arrhythmia; hyperlipidaemia; epilepsy; affective disorders; schizophrenia and neurotic/somatoform disorders.

OR = odds ratio.

Table III. Current long-term use of individual statins

Exposure	No. of cases (%) [n = 104]	No. of controls (%) [n = 98]	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	p-Value
None	3297 (90.7)	3327 (91.5)	1.00 (reference)	1.00 (reference)	
Current use of ≥30 prescriptions					
simvastatin	53 (1.5)	51 (1.4)	1.06 (0.72, 1.57)	1.01 (0.65, 1.57)	0.98
atorvastatin	31 (0.9)	35 (1.0)	0.91 (0.55, 1.50)	0.88 (0.50, 1.54)	0.65
pravastatin	19 (0.5)	9 (0.3)	2.13 (0.96, 4.72)	2.41 (1.01, 5.72)	<0.05
fluvastatin	1 (0.03)	2 (0.05)			
rosuvastatin	0	1 (0.03)			

a Adjusted for each other, body mass index, smoking status, use of antihypertensive drugs and the following co-morbidities: diabetes mellitus; asthma/chronic obstructive pulmonary disease; hypertension; ischaemic heart disease; congestive heart failure; stroke/transient ischaemic attack; arrhythmia; hyperlipidaemia; epilepsy; affective disorders; schizophrenia and neurotic/somatoform disorders.

OR = odds ratio.

disturbances[28,29] – symptoms that are also highly prevalent in PD. Another argument supporting a possible association between statins and PD onset or progression is that statins inhibit the endogenous production of coenzyme Q_{10} (CoQ_{10}, ubidecarenone). This enzyme is important for the function of the mitochondrial electron transport chain,[30,31] and mitochondrial dysfunction is also discussed as one of the possible mechanisms of idiopathic PD.[32] CoQ_{10} is generated by the same pathway as cholesterol.[30] Thus, inhibiting the synthesis of cholesterol may also decrease the amount of available CoQ_{10} and thereby inhibit certain physiological functions. Human plasma levels of CoQ_{10} have been shown to be inversely associated with statin use,[33-37] and beneficial effects of orally administered CoQ_{10} on PD have been shown in trials in humans,[38,39] whereby high doses of CoQ_{10} seemed to delay progression of early PD.[38]

Recent publications suggest a possible association between low cholesterol levels and an increased risk of PD.[13,14] We did not analyse cholesterol levels in the current analysis, but future studies may address this possible association.

The findings of our study suggest that statins as a class do not substantially alter the risk of a first-time diagnosis of PD. There is a suggestion, however, that the use of pravastatin may be associated with an increased risk of a PD diagnosis. However, this finding was based on small numbers, and the increased risk was driven by users of a low daily dose (10–20 mg), but not seen in high-dose users, making a causal association rather unlikely.

Little is known about the effect of fibrates or other lipid-lowering agents in relation to the risk of PD. In a mouse model, fenofibrate exerted a neuroprotective effect, while bezafibrate did not.[40] In our study population the exposure to fibrates and other lipid-lowering agents was too low to allow meaningful conclusions.

Some limitations of our study need to be addressed. We did not control for certain demographic factors in our study population such as level of education or socio-economic status, which have been associated with PD.[41] However, we matched for general practice and therefore controlled at least to some degree for socioeconomic status, since cases and controls came from the same area and therefore saw the same GP at the time of the study. In addition, we may not have detected all statin use, since low-dose simvastatin (10 mg) became available as an over-the-counter drug in the UK in August 2004.[42] However, most PD diagnoses in our study population occurred before 2004, and it is likely that we captured a high proportion of all statin use in the study population.

It is a strength of the study that it encompassed a large population sample, and that the GPRD is a validated database of high quality. The GPRD has already been used for two observational studies on PD.[20,21] Their case validation resulted in a high proportion (90%) of confirmed computerized PD diagnoses for those who received two or more prescriptions for specific medication to treat PD after the index date. Furthermore, our finding of a substantially reduced PD risk for current smoking is

consistent with previous studies[43-45] and lends further credibility to the validity of our study results.

It is difficult to define the index date for chronic diseases such as PD that do not have an acute and well defined onset. We tried to address this problem by restricting the analysis to a well defined group of patients with a GP-recorded diagnosis of PD who were most likely idiopathic PD cases and who had little or no drug use suggestive of previous PD symptoms. In addition, to address the uncertainty around the index date we explored current as well as past use of study drugs, and we also assessed duration of use; we found no evidence for an increased risk in any exposure group. We also conducted various sensitivity analyses in which we analysed statin use in a group of cases with a broader case definition that includes PD patients with more than one recorded prescription for an antiparkinson medication prior to the index date (the results remained unchanged, data not shown), as well as analyses in which we used different definitions for current versus past exposure, with similar findings.

We matched cases and controls for age, sex, general practice and calendar time (by using the same index date), and therefore controlled for important potential confounders. In addition, we adjusted the analyses for a range of co-morbidities to further reduce the risk of observing a spurious association between lipid-lowering drug use and the risk of developing PD. The findings could not be influenced by recall bias because the drug use of interest was recorded prior to the PD diagnosis.

Conclusion

This large observational study based on UK primary care data provides evidence that the use of statins (as well as use of fibrates or other lipid-lowering drugs, although based on a limited number of exposed patients) is not associated with a substantially altered risk of a first-time diagnosis of idiopathic PD.

Additional observational studies in other populations are needed to confirm this finding, whereby analyses involving cholesterol levels and their association with the risk of developing Parkinson's disease would be of particular interest.

Acknowledgements

No sources of funding were used to conduct this study. None of the authors have any conflicts of interest directly relevant to the content of this study.

References

1. Lang AE, Lozano AM. Parkinson's disease: first of two parts. N Engl J Med 1998; 339: 1044-53
2. Jenner P. Oxidative stress in Parkinson's disease. Ann Neurol 2003; 53 Suppl. 3: S26-36; discussion S36-8
3. Hirsch EC, Hunot S, Hartmann A. Neuroinflammatory processes in Parkinson's disease. Parkinsonism Relat Disord 2005; 11 Suppl. 1: S9-15
4. Schapira AH, Gu M, Taanman JW, et al. Mitochondria in the etiology and pathogenesis of Parkinson's disease. Ann Neurol 1998; 44: S89-98
5. Selley ML. Simvastatin prevents 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced striatal dopamine depletion and protein tyrosine nitration in mice. Brain Res 2005; 1037: 1-6
6. Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol 2005; 45: 89-118
7. Jick H, Zornberg GL, Jick SS, et al. Statins and the risk of dementia [erratum appears in Lancet 2001 Feb 17; 357 (9255): 562]. Lancet 2000; 356: 1627-31
8. Stepien K, Tomaszewski M, Czuczwar SJ. Neuroprotective properties of statins. Pharmacol Rep 2005; 57: 561-9
9. Rea TD, Breitner JC, Psaty BM, et al. Statin use and the risk of incident dementia: the Cardiovascular Health Study. Arch Neurol 2005; 62: 1047-51
10. Levesque LE, Delaney JA, Etminan M, et al. Pharmacologic interventions for the prevention of Alzheimer's disease: an example of reverse protopathic bias [abstract no. 65]. 22nd International conference on pharmacoepidemiology and therapeutic risk management; 2006 Aug 24-27; Lisbon. Pharmacoepidemiol Drug Saf 2006; 15: S31
11. Muller T, Kuhn W, Pohlau D, et al. Parkinsonism unmasked by lovastatin. Ann Neurol 1995; 37: 685-6
12. Muller T. Statininduziertes Parkinson-Syndrom. Leserbrief zum Beitrag von J. Finsterer in "Der Nervenarzt" (2003) 74: 115-122. Nervenarzt 2003; 74: 726-7
13. Huang X, Chen H, Miller WC, et al. Lower low-density lipoprotein cholesterol levels are associated with Parkinson's disease. Mov Disord 2007; 22: 377-81
14. de Lau LM, Koudstaal PJ, Hofman A, et al. Serum cholesterol levels and the risk of Parkinson's disease. Am J Epidemiol 2006; 164: 998-1002
15. Jick H. A database worth saving. Lancet 1997; 350: 1045-6
16. Lawson DH, Sherman V, Hollowell J. The General Practice Research Database: scientific and ethical advisory group. QJM 1998; 91: 445-52
17. Wood L, Martinez C. The general practice research database: role in pharmacovigilance. Drug Saf 2004; 27: 871-81
18. Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. Pharmacotherapy 2003; 23: 686-9
19. Walley T, Mantgani A. The UK General Practice Research Database. Lancet 1997; 350: 1097-9
20. Hernan MA, Logroscino G, Rodriguez LA. A prospective study of alcoholism and the risk of Parkinson's disease. J Neurol 2004; 251 Suppl. 7: vII14-7
21. Hernan MA, Logroscino G, Garcia Rodriguez LA. Nonsteroidal anti-inflammatory drugs and the incidence of Parkinson disease. Neurology 2006; 66: 1097-9

22. Lieberman A, Lyons K, Levine J, et al. Statins, cholesterol, coenzyme Q_{10}, and Parkinson's disease. Parkinsonism Relat Disord 2005; 11: 81-4

23. Rajanikant GK, Zemke D, Kassab M, et al. The therapeutic potential of statins in neurological disorders. Curr Med Chem 2007; 14: 103-12

24. Wang Q, Wang PH, McLachlan C, et al. Simvastatin reverses the downregulation of dopamine D_1 and D_2 receptor expression in the prefrontal cortex of 6-hydroxydopamine-induced Parkinsonian rats. Brain Res 2005; 1045: 229-33

25. Wang Q, Tang XN, Wang L, et al. Effects of high dose of simvastatin on levels of dopamine and its reuptake in prefrontal cortex and striatum among SD rats. Neurosci Lett 2006; 408: 189-93

26. Duits N, Bos FM. Depressive symptoms and cholesterol-lowering drugs. Lancet 1993; 341: 114

27. Tatley M, Savage R. Psychiatric adverse reactions with statins, fibrates and ezetimibe: implications for the use of lipid-lowering agents. Drug Saf 2007; 30: 195-201

28. Gregoor PJ. Atorvastatin may cause nightmares [letter]. BMJ 2006; 332: 950

29. Sinzinger H, Mayr F, Schmid P, et al. Sleep disturbance and appetite loss after lovastatin [letter]. Lancet 1994; 343: 973

30. Ernster L, Dallner G. Biochemical, physiological and medical aspects of ubiquinone function. Biochim Biophys Acta 1995; 1271: 195-204

31. Shults CW, Haas RH, Passov D, et al. Coenzyme Q_{10} levels correlate with the activities of complexes I and II/III in mitochondria from parkinsonian and nonparkinsonian subjects. Ann Neurol 1997; 42: 261-4

32. Schapira AH, Mann VM, Cooper JM, et al. Mitochondrial function in Parkinson's disease. The Royal Kings and Queens Parkinson's Disease Research Group. Ann Neurol 1992; 32 Suppl.: S116-24

33. Kaikkonen J, Nyyssonen K, Tuomainen TP, et al. Determinants of plasma coenzyme Q_{10} in humans. FEBS Lett 1999; 443: 163-6

34. Folkers K, Langsjoen P, Willis R, et al. Lovastatin decreases coenzyme Q levels in humans. Proc Natl Acad Sci USA 1990; 87: 8931-4

35. Ghirlanda G, Oradei A, Manto A, et al. Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. J Clin Pharmacol 1993; 33: 226-9

36. Laaksonen R, Ojala JP, Tikkanen MJ, et al. Serum ubiquinone concentrations after short- and long-term treatment with HMG-CoA reductase inhibitors. Eur J Clin Pharmacol 1994; 46: 313-7

37. Mortensen SA, Leth A, Agner E, et al. Dose-related decrease of serum coenzyme Q10 during treatment with HMG-CoA reductase inhibitors. Mol Aspects Med 1997; 18 Suppl.: S137-44

38. Shults CW, Oakes D, Kieburtz K, et al. Effects of coenzyme Q_{10} in early Parkinson disease: evidence of slowing of the functional decline. Arch Neurol 2002; 59: 1541-50

39. Muller T, Buttner T, Gholipour AF, et al. Coenzyme Q_{10} supplementation provides mild symptomatic benefit in patients with Parkinson's disease. Neurosci Lett 2003; 341: 201-4

40. Kreisler A, Gele P, Wiart JF, et al. Lipid-lowering drugs in the MPTP mouse model of Parkinson's disease: fenofibrate has a neuroprotective effect, whereas bezafibrate and HMG-CoA reductase inhibitors do not. Brain Res 2007; 1135: 77-84

41. Frigerio R, Elbaz A, Sanft KR, et al. Education and occupations preceding Parkinson disease: a population-based case-control study. Neurology 2005; 65: 1575-83

42. OTC statins: a bad decision for public health. Lancet 2004; 363: 1659

43. Nefzger MD, Quadfasel FA, Karl VC. A retrospective study of smoking in Parkinson's disease. Am J Epidemiol 1968; 88: 149-58

44. Quik M. Smoking, nicotine and Parkinson's disease. Trends Neurosci 2004; 27: 561-8

45. Hancock DB, Martin ER, Stajich JM, et al. Smoking, caffeine, and nonsteroidal anti-inflammatory drugs in families with Parkinson disease. Arch Neurol 2007; 64: 576-80

Correspondence: Dr *Christoph R. Meier*, Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacology and Toxicology, University Hospital Basel, Hebelstrasse 2, Basel, CH-4031, Switzerland.
E-mail: Meierch@uhbs.ch