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Use of antidepressants and the risk of Parkinson's disease: a prospective study

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Abstract

Background—Individuals with depression have a higher risk of Parkinson's disease (PD), but the timing of the association is unknown. We assessed whether initiation of antidepressant therapy was associated with PD risk in a large population-based database from the United Kingdom and explored the timing of this association.

Methods—We conducted a case-control study nested in the General Practice Research Database (GPRD) cohort, a large computerized database with clinical information from more than 3 million individuals in the UK. Cases of PD were identified from the computer records from 1995 to 2001 and matched with up to 10 controls by age, sex and practice. Use of antidepressants was obtained from the computer records.

Results—We included 999 PD cases and 6,261 controls. The rate ratio (RR) and 95% confidence interval (CI) of PD in initiators of antidepressant therapy compared with non-initiators was 1.85 (1.25, 2.75). The association was stronger during the first two years after initiation of medication use (RR 2.19; 95% CI 1.38, 3.46) than later (RR 1.23; 95% CI 0.57, 2.67). Results were similar for selective serotonin reuptake inhibitors and tricyclic antidepressants separately.

Conclusion—Initiation of any antidepressant therapy was associated with a higher risk of PD in the two years after initiation of treatment, which suggests that depressive symptoms could be an early manifestation of PD, preceding motor dysfunction.

Keywords

Parkinson's disease; depression; antidepressants; prospective studies

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Introduction

Parkinson's disease (PD) is a disorder of the central nervous system, characterized by gradual loss of dopaminergic neurons in the substantia nigra.[1] Growing evidence suggests that PD and depression are linked. On the one hand, patients with PD often present depressive symptoms during the course of their disease.[2] On the other hand, several prospective studies have reported a higher risk of developing PD among individuals with depressive symptoms or taking antidepressants.[3-6] Some proposed mechanisms to explain this link include a reactive drop-off in serotonin as a consequence of the dopaminergic depletion observed in PD,[7] mood alterations following basal ganglia dysfunction[8] or involvement of dopaminergic structures both in depression and PD.[9] It is therefore unclear whether 1) depression increases the risk of PD, 2) depressive symptoms are just another clinical manifestation of PD, preceding in some cases the onset of the classical motor symptoms, or 3) depression and PD are different consequences of common pathophysiologic mechanisms.

To better understand the role of depression on PD pathogenesis, we evaluated the association between initiation of antidepressant therapy, as a marker of significant depressive symptoms, and the risk of PD in a large population-based database in the United Kingdom (UK). We also assessed differences in this association by time elapsed since antidepressant therapy initiation.

Methods

Study population

The General Practice Research Database (GPRD) is a large computerized database that includes longitudinal clinical information on more than 3 million Britons attended by selected general practitioners in the UK. These physicians have been trained to record clinical information in a standardized manner and agreed to provide this information anonymously for research purposes. The information on drug prescriptions and clinical diagnoses in the GPRD has been shown to be of satisfactory quality for epidemiologic research.[10-12] For the purpose of this study, we defined a cohort of GPRD participants free of PD or not taking parkinsonism-related drugs at baseline in the period 1995-2001. A detailed description of the study population has been published elsewhere.[13,14] This study was approved by the Institutional Review Board at Harvard School of Public Health.

Case ascertainment

We identified 1,904 individuals with a computer diagnosis of PD among cohort participants. The validation of the computer-recorded PD diagnosis has been previously published.[13] Participants with a computerized diagnosis of PD and two or more PD-related prescriptions were classified as cases.

Study design

The date of PD onset (index date) was defined as the date of the first symptom of PD, first computerized diagnosis, or first prescription of a PD-related drug, whichever came earlier. Because PD usually has an insidious onset, we advanced two years the index date to avoid changes in exposures as a consequence of symptoms. Up to 10 controls, free of PD on the index date, and matched with the cases by age, sex, practice and year of enrollment in the GPRD, were randomly selected. Of the 1,258 cases with both a computerized PD diagnosis and two or more PD-related prescriptions, 1,052 had at least one eligible control (6,634 eligible controls).

Exposure assessment

In the GPRD drug prescriptions are computer generated by the physicians and automatically transcribed into the computer record. Information on prescriptions for antidepressant medication was obtained from the computer records. More than 95% of antidepressant prescriptions were for tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs). Prescriptions for the most frequent tricyclic and SSRIs antidepressants were classified in low or high dosage. We used the following cutoff points to define high dose, based on habitual clinical use: amitriptyline ≥75 mg, clomipramine ≥50 mg, fluoxetine ≥20 mg, imipramine ≥100 mg, lofepramine ≥140 mg, paroxetine ≥20 mg, trimipramine ≥150 mg. These medications accounted for more than 90% of total tricyclic antidepressants and SSRIs.

Statistical analysis

We obtained "intention-to-treat estimates" by comparing the risk of PD between individuals that did and did not start antidepressant medication between January 1993 (the earliest possible time for the index date after advancing it two years) and July 1999. We conceptualized our study as a series of case-control studies nested in a corresponding series of non-randomized trials. This methodology has been described elsewhere.[15,16] We pooled the results from each case-control study in a single conditional logistic model adjusted for matching factors, smoking status (never smoker, past smoker, current smoker and advice/treatment for quitting, current smoker without advice or treatment for quitting, missing smoking information), past history of depression, past use of medication, and calendar month. We computed the confidence interval (CI) for the RR using a robust variance estimator to account for within-person correlation.

Results

Of 1052 cases and 6634 eligible controls, 999 cases and 6,261 controls were eligible for at least one trial. Characteristics of the study sample have been reported elsewhere.[13,16]

Initiation of antidepressant medication was associated with a higher risk of developing PD (table). The RR (95% CI) of PD for initiators versus non initiators was 1.85 (1.25, 2.75), after adjusting for matching factors, smoking, past use of antidepressants, and history of depression. The RR (95% CI) was 2.19 (1.38, 3.46) during the first two years after initiation and 1.23 (0.57, 2.67) after the first two years. Both tricyclic antidepressants and SSRIs were similarly associated with the risk of PD, showing stronger associations during the first two-years after initiation (table). We obtained similar results when stratifying by smoking status (current smoker, non-smoker), gender, or age (less than 65, 65 or older) (data not shown). The association between initiation of antidepressants and risk of PD was present for low- and high-dose antidepressants (table).

We estimated the association between initiation of antidepressants and the risk of PD after further classifying individuals in the following categories: recent history of depression (less than 2 years before initiation of antidepressants), long history of depression (2 or more years before initiation of antidepressants), or uncertain history of depression. Risk of PD was higher among initiators of antidepressants compared with non-initiators across all categories of depression history (figure). The highest PD risk was observed among those with recent history of depression: the odds ratio (95% CI) of PD among initiators with recent history of depression versus non initiators with uncertain history of depression was 5.02 (0.87, 29.17) (figure).

After 1 year of follow-up, more than 75% initiators had stopped using medication and less than 5% of non initiators had started using antidepressants.

Discussion

Our study shows that the risk of PD increases during the first two years of use of antidepressants, whether they are tricyclic antidepressants or SSRIs. The increased PD risk that follows initiation of antidepressants was greater among individuals with recent history of depression than among the others. These results provide further evidence for a link between depression and PD and suggest that depressive symptoms can be a first manifestation of PD, previous to the onset of classical motor symptoms (see below).

The present results are consistent with several previous epidemiologic studies reporting an association between depression or depressive symptoms and PD risk, [3,4,17] and some reports suggesting a close temporal relationship between the two conditions. [5,18]

Different hypotheses could explain our findings. First, antidepressants could cause Parkinson's disease, but this has not been substantiated in clinical trials.[19] Also, the strong association found in our study in the presence of low adherence to antidepressant treatment (consistent with previous publications)[20] does not support a direct effect of antidepressants on PD risk. Second, some motor symptoms, such as bradykinesia or rigidity, could be mistaken for symptoms of depressive mood. Third, the dopaminergic dysfunction present in depression could increase the risk of PD, or at least the risk of parkinsonism.[9,21] Finally, depressive symptoms could be an early manifestation of PD. The higher risk of PD among individuals with a recent incidence of depression in our population offers support to this last hypothesis.

Limitations in the present study include misclassification in both the exposure (antidepressants are used for other conditions different from depression) and the outcome (patients with depression or taking antidepressants could be more likely to receive a diagnosis of PD). Reverse causation bias, that is, that patients with undiagnosed PD develop depressive symptoms, could explain in part our results. To avoid this problem in some degree, we advanced the index date two years. Nonetheless, we cannot be completely certain of the clinical onset of the disease.

Confounding is an unlikely explanation for the study results since we have adjusted the analysis for the matching factors (age, sex and practice, which could be considered a marker of socioeconomic status) and smoking, probably the strongest modifiable risk factor for PD. Though physical activity could be a common protective factor for depression and PD,[22] the strength of those associations would not be enough to explain the magnitude of our results. Finally, the existence of selection bias is unlikely, given that controls were randomly selected from the same population from which the cases emerged.

To conclude, the observed association between antidepressants and PD risk could have implications for clinical practice. Depressive patients that start developing motor symptoms should be promptly evaluated to rule out a diagnosis of PD.

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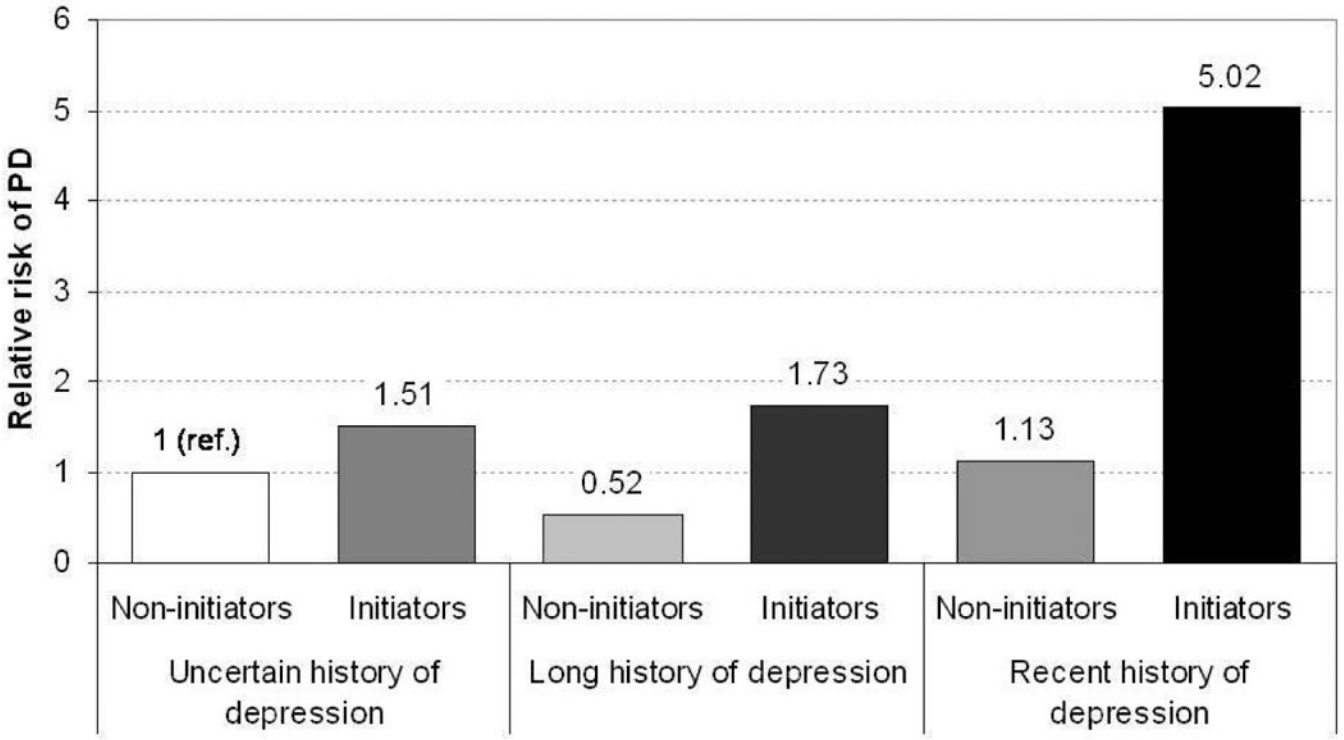

Figure.
Relative incidence of Parkinson's disease (PD) in initiators versus non-initiators of antidepressant medication according to previous history of depression. General Practice Research Database, United Kingdom

Table

Relative incidence of Parkinson's disease (PD) in initiators versus non-initiators of antidepressant medication. General Practice Research Database, United Kingdom

Use of anti-depressants	PD cases (%) [n=26,747]	Controls (%) [n=151,552]	RR (95% CI) †	RR (95% CI) ‡
All antidepressants				
Noninitiators	26,695 (99.81)	151,355 (99.87)	1 (ref.)	1 (ref.)
Initiators	52 (0.19)	197 (0.13)	1.66 (1.13, 2.43)	1.85 (1.25, 2.75)
≤24 mo follow-up	42	149	1.99 (1.30, 3.03)	2.19 (1.38, 3.46)
>24 mo follow-up	10	48	1.04 (0.45, 2.40)	1.23 (0.57, 2.67)
P for trend			0.17	0.21
Tricyclic antidepressants				
Noninitiators	26,714 (99.88)	151,423 (99.91)	1 (ref.)	1 (ref.)
Initiators	33 (0.12)	129 (0.09)	1.66 (1.02, 2.69)	1.80 (1.08, 3.01)
≤24 mo follow-up	27	97	1.98 (1.15, 3.39)	2.10 (1.17, 3.76)
>24 mo follow-up	6	32	1.04 (0.35, 3.06)	1.19 (0.42, 3.42)
P for trend			0.29	0.34
SSRIs				
Noninitiators	26,728 (99.93)	151,483 (99.95)	1 (ref.)	1 (ref.)
Initiators	19 (0.07)	69 (0.05)	1.63 (0.87, 3.03)	1.95 (1.03, 3.66)
≤24 mo follow-up	15	52	2.02 (1.01, 4.04)	2.35 (1.10, 5.01)
>24 mo follow-up	4	17	0.98 (0.27, 3.60)	1.29 (0.40, 4.23)
P for trend			0.36	0.39
Low-dose antidepressants				
Noninitiators	26,724 (99.91)	151,463 (99.94)	1 (ref.)	1 (ref.)
Initiators	23 (0.09)	89 (0.06)	1.63 (0.91, 2.89)	1.70 (0.91, 3.16)
≤24 mo follow-up	18	65	1.82 (0.94, 3.54)	1.90 (0.92, 3.94)
>24 mo follow-up	5	24	1.31 (0.43, 3.95)	1.36 (0.45, 4.13)
P for trend			0.59	0.52
High-dose antidepressants				
Noninitiators	26,724 (99.91)	151,467 (99.94)	1 (ref.)	1 (ref.)
Initiators	23 (0.09)	85 (0.06)	1.78 (1.00, 3.19)	2.09 (1.16, 3.77)
≤24 mo follow-up	19	67	2.09 (1.11, 3.93)	2.39 (1.21, 4.70)
>24 mo follow-up	4	18	1.07 (0.25, 4.57)	1.43 (0.36, 5.63)
P for trend			0.41	0.47

RR: relative rate; CI: confidence interval; SSRI: selective serotonin reuptake inhibitor

† Conditional logistic regression adjusted for matching factors (age, sex, practice, time of follow-up)

≠Conditional logistic regression adjusted for matching factors (age, sex, practice, time of follow-up), smoking, past use of antidepressants, and history of depression at baseline