Nonsteroidal anti-inflammatory drugs and the incidence of Parkinson disease

Abstract—Animal and epidemiologic studies suggest that nonsteroidal anti-inflammatory drugs (NSAIDs) decrease the incidence of Parkinson disease (PD). The authors studied 1,258 PD cases and 6,638 controls from the General Practice Research Database. The odds ratios (95% CI) for ever vs never use were 0.93 (0.80 to 1.08) for nonaspirin NSAIDs, 1.29 (1.05 to 1.58) for aspirin, and 1.16 (1.00 to 1.35) for acetaminophen. Nonaspirin NSAID use was associated with a higher risk in women and a lower risk in men.

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Animal^{1,2} and epidemiologic³ studies suggest that nonsteroidal anti-inflammatory drugs (NSAIDs) decrease the incidence of idiopathic Parkinson disease (PD). We investigated this association in a prospectively followed population.

Methods. *Study population.* The General Practice Research Database (GPRD) includes over three million Britons whose physicians have been trained to record their patients' information and have agreed to supply it anonymously for research purposes. GPRD information is considered to be of satisfactory quality for epidemiologic research.⁴

We conducted a case-control study nested within a GPRD cohort of subjects with no history of PD or parkinsonism-related drug use at baseline. Each individual's follow-up started on January 1, 1995, or after 3 years of continuously recorded medical history, whichever came later, and ended at the first computerized PD symptom (tremor, rigidity, bradykinesia, abnormal gait), PD diagnosis, use of drugs that may cause parkinsonism, last data collection, death, or December 31, 2001, whichever came first. The cohort included 2,005,552 individuals and 8,431,277 person-years (4,098,918 from subjects aged 40 and older). Compared with our previous study,⁵ we extended the follow-up and included data recorded using both the VM and the Vision software.

PD ascertainment. The cohort included 1,904 individuals with a computerized diagnosis of PD. Of these, 1,258 received two or more prescriptions to treat PD symptoms during the follow-up. To evaluate the accuracy of the diagnosis of PD, we requested photocopies of all PD-related paper records from a random 7% of patients. The diagnostic procedure is described in detail elsewhere⁵ and outlined below.

First, we diagnosed parkinsonism as the presence of two cardinal signs: lateralized isolated resting tremor or a cardinal sign in the presence of an antiparkinsonian treatment. We classified parkinsonism as drug-induced, vascular, other secondary parkinsonism, Parkinson-plus syndrome, parkinsonism dementia, unspecified parkinsonism, and PD (parkinsonism that did not fit in the above categories and that did not show any important signs of involvement of other CNS regions in the first year). Second, we classified the diagnosis of PD as definite, probable, or possible. We excluded atypical parkinsonian disorders. The criteria we used for this classification have been found to be accurate in the diagnosis of PD from medical records.⁶

Our medical records review confirmed the computerized PD diagnosis in 90% of those with two or more antiparkinsonian prescriptions. As an indirect measure of the validity of the PD

diagnosis, our study found age- and sex-specific PD incidences and an association between smoking and lower PD risk, similar to those estimated from other prospective studies.⁵

Case-control design. The index date of the 1,258 cases was the minimum of the date of first diagnosis of PD, date of first prescription of a PD-related drug, and date of first report of PD symptoms. We randomly selected up to 10 controls per case, matched by age, sex, start date, and practice. Controls had the same index date as their matched case.

Drug use. Drug prescriptions are computer generated by the physicians and automatically transcribed into the computer record. We identified all prescriptions of nonaspirin NSAIDs, aspirin, and acetaminophen. To reduce the possibility that drug use was a consequence of unrecognized first symptoms of PD, we advanced the index date 2 years in our primary analysis (i.e., prescriptions recorded in the 2-year period before the original index date were ignored). Cases and controls were classified as never (no recorded drug use) or ever (some recorded use before the index date) users. Ever users were classified as past users if their last prescription was issued at least 1 year before the revised index date, and as current users otherwise. For current users, we determined duration of use by adding the periods of "consecutive" prescriptions (interval of <3 months between prescriptions). Daily dose of nonaspirin NSAIDs was categorized as low-medium, or high for each individual drug, and daily dose of aspirin was classified as ≤ 75 , > 75 to < 300 , and ≥ 300 mg. We used conditional logistic regression to compute odds ratios (ORs) and their 95% CIs conditional on the matching factors and adjusted for smoking status, history of myocardial infarction, and arthritis.

Results. Our analysis included 1,258 cases (39.2% women, mean age 70.7 years) and 6,638 controls (40.9% women, mean age 68.7 years). Compared with never use of nonaspirin NSAIDs, past users and long-term current users had a lower PD risk, but the estimates did not reach the traditional significance level (table 1). The ORs (95% CI) for past vs never use were 0.77 (0.61 to 0.98) for ibuprofen, 0.97 (0.72 to 1.29) for diclofenac, 0.93 (0.63 to 1.37) for naproxen, and 0.96 (0.72 to 1.28) for other NSAIDs. Aspirin or acetaminophen use was associated with a higher PD risk (table 1), but current aspirin use of ≥ 300 mg/day for > 3 years was associated with a lower PD risk (OR 0.62; 95% CI: 0.26 to 1.49) compared with never use.

Exclusion of individuals with a history of stroke or dementia (134 cases, 434 controls) had little effect on the estimates: The OR (95% CI) for ever vs never use was 0.94 (0.80 to 1.10) for nonaspirin NSAIDs, 1.16 (0.88 to 1.54) for aspirin, and 1.20 (1.02 to 1.40) for acetaminophen. The corresponding estimates based on the original index date (without advancing it 2 years) and all subjects were 0.95 (0.81 to 1.10), 1.34 (1.12 to 1.60), and 1.21 (1.04 to 1.41). The estimates were similar in analyses stratified by age (> 60 , ≤ 60 years) and smoking (never, ever). The OR (95% CI) for current vs never aspirin use was > 1 for all indications: 1.10 (0.82 to 2.33) for cardiovascular prevention,

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Table 1 Association between drug use and the incidence of PD

	PD cases (%)	Controls (%)	Odds ratio	95% CI
Nonaspirin NSAIDs				
Never use	652 (51.8)	3264 (49.2)	1	—
Ever use	606 (48.2)	3374 (50.8)	0.93	0.80–1.08
Past use	305 (24.2)	1802 (27.2)	0.85	0.71–1.02
Current use	301 (23.9)	1572 (23.7)	1.04	0.86–1.25
≤3 y	267 (21.2)	1338 (20.2)	1.06	0.88–1.28
>3 y	34 (2.7)	234 (3.5)	0.88	0.58–1.34
Aspirin				
Never use	1047 (83.2)	5805 (87.4)	1	—
Ever use	211 (16.8)	833 (12.6)	1.29	1.05–1.58
Past use	32 (2.5)	155 (2.3)	1.04	0.67–1.61
Current use	179 (14.2)	678 (10.2)	1.35	1.09–1.68
≤3 y	137 (10.2)	490 (7.4)	1.42	1.12–1.81
>3 y	42 (3.3)	188 (2.8)	1.16	0.78–1.73
Acetaminophen				
Never use	666 (52.9)	3685 (55.5)	1	—
Ever use	592 (47.1)	2953 (44.5)	1.16	1.00–1.35
Past use	247 (19.6)	1277 (19.2)	1.15	0.96–1.38
Current use	345 (27.4)	1676 (23.3)	1.17	0.98–1.40
≤3 y	297 (23.6)	1417 (21.4)	1.20	1.00–1.44
>3 y	48 (3.8)	259 (3.9)	1.00	0.67–1.48

PD = Parkinson disease; NSAIDs = nonsteroidal anti-inflammatory drugs.

1.66 (1.18 to 2.33) for cerebrovascular prevention, 1.23 (0.59 to 2.58) for peripheral vascular disease, and 2.00 (1.07 to 3.74) for others. The OR (95% CI) for long-term current use vs never use of nonaspirin NSAID use were 0.89 (0.53 to 1.49) for osteoarthritis, 0.39 (0.12 to 1.30) for rheumatoid arthritis, and 1.39 (0.65 to 2.95) for others (85% analgesia).

The estimates for nonaspirin NSAIDs, but not for aspirin or acetaminophen, differed by sex (table 2). Nonaspirin NSAID use was associated with a higher risk in women and a lower risk in men. The lower risk in men was especially marked for high doses and long duration of use. The risk in women was elevated for all indications.

Discussion. Use of nonaspirin NSAIDs was associated with a 20% reduction in the incidence of PD among men and a 20% increase in the incidence of PD among women. These findings cannot be explained by recall bias because drug use was prospectively recorded before PD patients were diagnosed or a biased control selection because controls were randomly selected from the population from which the cases arose. A small degree of nondifferential misclassification of PD diagnosis is expected according to our validation study, but its likely consequence would be an attenuated association. Aspirin and acetaminophen use was not associated with a lower PD risk.

Table 2 Association between drug use and the incidence of Parkinson disease by sex

	Odds ratio (95% CI)		<i>p</i> Value for interaction
	Women	Men	
Nonaspirin NSAIDs			
Never use	1	1	
Ever use	1.21 (0.95–1.54)	0.79 (0.65–0.96)	0.007
Past use	0.99 (0.75–1.33)	0.78 (0.62–0.98)	0.25
Current use	1.50 (1.13–2.00)	0.80 (0.63–1.02)	0.001
Duration			
≤3 y	1.50 (1.12–2.04)	0.84 (0.65–1.07)	0.005
>3 y	1.54 (0.84–2.80)	0.59 (0.33–1.07)	0.04
Dose			
Low-medium	1.45 (1.03–2.03)	0.94 (0.70–1.26)	0.08
High	1.57 (1.10–2.24)	0.67 (0.49–0.93)	0.001
Aspirin			
Never use	1	1	
Ever use	1.13 (0.79–1.62)	1.37 (1.07–1.76)	0.52
Past use	1.10 (0.55–2.23)	0.98 (0.56–1.72)	0.69
Current use	1.13 (0.76–1.69)	1.46 (1.12–1.89)	0.42
Acetaminophen			
Never use	1	1	
Ever use	1.19 (0.94–1.52)	1.13 (0.94–1.37)	0.67
Past use	1.16 (0.92–1.62)	1.14 (0.90–1.43)	0.61
Current use	1.22 (0.87–1.56)	1.13 (0.89–1.43)	0.88

Most regular NSAID use is by prescription and thus recorded in the GPRD because the British health care system covers a substantial part of the cost. In fact, a comparison between the frequency of NSAID use in GPRD studies^{7,8} and in another population-based study that ascertained NSAID use by interview⁹ shows no major underrecording of NSAID use in the GPRD. Ibuprofen was the only NSAID that could be purchased over the counter. Because the misclassification of nonaspirin NSAID exposure before the index date is expected to be similar for cases and controls, our estimates can be viewed as conservative.

Our study suggests that nonaspirin NSAID use reduces PD risk in men but not in women. Although sex differences in PD risk have been previously reported for caffeine consumption¹⁰ and alcoholism⁵ (but, noticeably, not for cigarette smoking), ours was an unexpected finding that warrants further research.

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NeuroImages

Figure. Diffusion-weighted and fluid-attenuated inversion recovery MRI showed hyperintense signal changes around the precentral gyrus in the vicinity of the somatotopic representation of the truncal muscles (A, C, arrows). Three months later, a follow-up MRI revealed that the cortical abnormalities had disappeared (B, D), thus supporting the diagnosis of idiopathic epilepsy partialis continua.

VIDEO

Epilepsia partialis continua of the abdominal muscles with transient MRI abnormalities

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Stefanie Becker, MD; and Gereon R. Fink, MD, Aachen, Germany

A 62-year-old man presented with a 36-hour history of painless clonic twitching of his left abdominal muscles (video, part 1).

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the April 11 issue to find the title link for this article.

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After IV administration of 2 mg of clonazepam, the twitching stopped (video, part 2). We diagnosed an idiopathic epilepsy partialis continua (EPC) of the abdominal muscles. In adults, the most common etiologies of EPC include inflammatory diseases of the brain, acute strokes, metastasis, and metabolic encephalopathies, especially hyperosmolar nonketotic hyperglycemia. However, we could not confirm any of these, although a watershed ischemia could not be excluded entirely. The observed transient MRI abnormalities are probably related to an uncoupling of cerebral metabolism and blood flow (figure).¹ It has been shown that such changes can be detected by diffusion-weighted and perfusion-weighted MRI in the peri-ictal phase of status epilepticus.²

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