Anti-inflammatory drugs and risk of Parkinson disease: a meta-analysis

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CRD summary
This review concluded that non-aspirin non-steroidal anti-inflammatory drugs may provide a protective effect against Parkinson disease. Overall, this was a well-conducted systematic review and the authors' conclusion is likely to be reliable.

Authors' objectives
To assess whether anti-inflammatory drugs reduce the incidence of Parkinson's disease.

Searching
MEDLINE and EMBASE were searched from inception to April 2009; search terms were available as an appendix on the journal's website. Searching was undertaken without language restrictions. Reference lists of included studies were searched for additional relevant studies.

Study selection
Observational studies of anti-inflammatory drug use (non-aspirin non-steroidal anti-inflammatory drugs, aspirin or acetaminophen) that assessed the incidence of Parkinson's disease as an outcome (based on clearly stated diagnostic criteria or identified through diagnostic codes with additional confirmation) were eligible for inclusion. Studies had to ascertain exposure status at least one year before Parkinson's disease diagnosis and describe adjustment for potential confounding. Studies also had to report effect estimates with confidence intervals, standard errors, or provide sufficient information for their calculation.

The included studies assessed non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), aspirin and acetaminophen. Assessment of exposure to anti-inflammatory drugs was made by self-report questionnaire, automated pharmacy database, automated prescription data or medical chart review. Parkinson's disease diagnosis was confirmed by treating physician, chart review, computerised diagnosis with at least two prescriptions used to treat Parkinson's disease, or clinical evaluation with defined diagnostic criteria.

The authors did not state how the papers were selected for the review.

Assessment of study quality
Studies had to meet at least five criteria on the eight-item Newcastle-Ottawa quality assessment scale to be included in the review.

Two reviewers assessed the quality of the studies; disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted data on effect estimates (relative risks or odds ratios) along with confidence intervals (CIs) or standard errors, or the information required to calculate these; disagreements were resolved by consensus. Results were extracted on the longest follow-up period reported. When multiple effect estimates were reported, maximally adjusted estimates were extracted.

Methods of synthesis
Summary relative risks (RRs) were estimated, using random-effects models, separately for each of the three anti-inflammatory drugs (non-aspirin NSAIDs, aspirin, and acetaminophen). For studies that only reported stratified results (e.g. by sex), a Mantel-Haenszel fixed-effect model was used to summarise the stratified estimates into a single parameter for each study. The analysis assumed that odds ratios (ORs) were accurate approximations of relative risks.

Where possible, subgroup analyses were conducted to examine differences by sex, duration and intensity of use.
Sensitivity analyses were performed based on whether exposure status was defined, on the basis of prescription data alone, or whether it also captured possible over-the-counter use. Sensitivity analyses were also performed by repeating the original analyses and omitting one study at a time to assess the effect of single studies on the results, and by including four of the studies that did not meet inclusion criteria for the review.

Heterogeneity was assessed using the Cochrane Q test and the $I^2$ test.

Publication bias was assessed via visual inspection of the Begg funnel plot.

**Results of the review**

Five case-control studies (n=11,570 participants) and two cohort studies (n=289,850 participants) were included in the review, with an additional four studies included in sensitivity analyses (two were excluded from the review because they did not report separate results for different anti-inflammatory drugs, and two were excluded as the anti-inflammatory drug use was within one year of Parkinson's disease diagnosis).

The incidence of Parkinson's disease was reduced in people who used non-aspirin NSAIDs (RR 0.85, 95% CI 0.77 to 0.94; $I^2$=0%; seven studies). Subgroup analyses assessing the effects of duration and intensity of use indicated a dose-response relationship. Subgroup analysis based on sex indicated similar results amongst men and women. Subgroup analysis indicated that ibuprofen had a stronger effect (RR 0.75, 95% CI 0.64 to 0.89; three studies) than for all non-aspirin NSAIDs. Sensitivity analysis based on exposure status indicated a larger effect in studies that assessed prescription and over-the-counter use, rather than just prescription use. Sensitivity analyses omitting one study at a time did not significantly alter the results.

There was no significant difference in the incidence of Parkinson disease between people who used aspirin and those who did not (six studies); there was evidence of significant heterogeneity for this result. There was an increase in the incidence of Parkinson disease amongst men who used aspirin (RR 1.22, 95% CI 1.03 to 1.44), but not women. Sensitivity analyses omitting one study at a time did not significantly alter the results.

There was no significant difference in the incidence of Parkinson disease between people who used acetaminophen and those who did not (two studies).

Results of the sensitivity analyses, including the studies excluded from the review based on exposure ascertainment, were similar but there was greater heterogeneity.

The funnel plot did not indicate the presence of publication bias.

**Authors' conclusions**

Non-aspirin NSAIDs may provide a protective effect against Parkinson disease, consistent with a possible neuroinflammatory pathway in Parkinson disease pathogenesis.

**CRD commentary**

The review addressed a clear question, with well defined inclusion criteria. Two databases were searched for relevant studies, with no language restrictions, reducing the potential for language bias. No sources of unpublished data were searched, but the authors assessed the potential for publication bias, although they acknowledged that the assessment was limited by the small number of included studies. Two reviewers undertook data extraction and validity assessment, which reduced the potential for reviewer bias and error.

The quality of the studies was assessed using validated criteria and low quality studies were excluded from the review, but the results of the quality assessment were not reported. Appropriate methods were used to pool the studies and investigate statistical heterogeneity; multiple subgroup and sensitivity analyses were performed.

Overall, this was a well-conducted systematic review and the authors’ conclusion, that non-aspirin NSAIDs may provide a protective effect against Parkinson disease, is likely to be reliable.
Implications of the review for practice and research

Practice: The authors stated that the prudent long-term public health strategy would focus on preventing exposure to the causes of Parkinson disease, rather than relying on mitigating the consequences of such exposures through long-term NSAID administration.

Research: The authors stated that further research is needed to determine whether the observed increase in Parkinson disease amongst men using aspirin is real or due to confounding or selection bias. They also recommended additional well-designed and well-conducted epidemiological studies investigating the relative effects of specific agents, doses, timing and durations of use to increase understanding of the relationship between anti-inflammatory use and Parkinson disease. Studies investigating the biological mechanism of neuro-inflammation in Parkinson disease, along with the mediators of this process, may aid in identifying causes of Parkinson disease.

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