Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use

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Authors' objectives
To estimate the incidence of death from gastroduodenal complications with chronic use of non-steroidal anti-inflammatory drugs (NSAIDs).

Searching
MEDLINE and EMBASE (up to December 1996) were searched for articles published in any language, using the following free text terms either alone or in combination: 'non-steroidal anti-inflammatory drug', 'aspirin', 'ulcer', 'bleeding', 'haemorrhage', 'perforation' and 'death'. Additional studies were identified by handsearching reference lists from retrieved reports, review articles on NSAIDs, relevant meta-analyses, and gastroenterology textbooks. Abstracts from scientific meetings were not considered and pharmaceutical companies and authors were not contacted.

Study selection

Study designs of evaluations included in the review
Any type of report presenting data on eligible outcomes was eligible. These included randomised controlled trials (RCTs), cohort studies, case-control studies, uncontrolled series and case reports.

Specific interventions included in the review
Oral NSAIDs, including aspirin, were compared with placebo or no treatment. NSAIDs plus placebo were compared with NSAIDs plus protective agents such as misoprostol, ranitidine, famotidine, omeprazole or nizatidine. All drugs were given orally in the included studies. Only interventions of at least 2 months in duration were eligible. The definitions of exposure to NSAID included redemption of a NSAID prescription in the previous 3 to 12 months.

Participants included in the review
The included patients were those with osteo or rheumatoid arthritis, with and without gastric or duodenal lesions; those with myocardial infarction; or those admitted to hospital with nonvariceal gastrointestinal bleeding, melaena or perforated ulcer, or for surgery to ulcer.

Outcomes assessed in the review
The three levels of harm were assessed: gastric or duodenal ulcer; ulcer haemorrhage or perforation; and death attributable to such events. Ulcers were detected by endoscopic screening or were clinically diagnosed (symptomatic). Definitions of gastric and duodenal ulcer, haemorrhage and perforation of a gastroduodenal ulcer were as defined in the original reports. The following outcomes were excluded: other signs of mucosal damage; other causes of bleeding such as oesophageal varices and other causes of perforation; and NSAID-induced complications other than upper gastrointestinal complications.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
No systematic assessment of validity was undertaken.

Data extraction
Data were extracted on: type of report; patient characteristics; dose of NSAID and exposure time; and definitions of,
and dichotomous data from different levels of harm. The ratios ‘ulcer: bleed/perforation’ and ‘bleed/perforation: death’ were estimated for each study. The authors do not state how many of the reviewers performed the data extraction. Only efficacy data were analysed because of the inconsistent reporting of intention to treat data.

**Methods of synthesis**

**How were the studies combined?**

Dichotomous data from comparative trials (RCTs and cohort studies) were combined qualitatively in a scatter diagram, as described by L’Abbé et al. (see Other Publications of Related Interest), by plotting rates of events on NSAIDs against the respective events with controls. The pooled ratios of ‘ulcer: bleed/perforation’ and ‘bleed/perforation: death’ were estimated, with weighting by sample size.

The number of patients who needed to be treated chronically with NSAIDs for one to die due to gastrointestinal complications, who would not have died had they not received NSAIDs, was estimated by considering data from RCTs and cohort studies only. A second estimate of the number-needed-to-treat (NNT) was performed, which took into account ratios between different levels of harm from all reports, independent of study design.

**How were differences between studies investigated?**

Pooled outcomes were estimated according to study design and some potential causes of differences were discussed.

**Results of the review**

The following were included:

- 15 RCTs involving 19,364 patients taking NSAIDs and 21,053 control receiving a placebo or NSAID plus a protective agent;
- 3 cohort studies with 1,131,174 patients, of whom 215,076 were exposed to NSAIDs;
- 6 case-control studies involving 2,957 cases with a diagnosis of gastroduodenal ulcer, or bleeding or perforation;
- 20 uncontrolled series involving 7,406 patients with a diagnosis of gastroduodenal ulcer, or bleeding or perforation; and
- 4,447 case reports to drug monitoring centres on patients with upper gastrointestinal complications.

Event rate scatter (RCTs and cohort studies): a consistently increased risk was noted with NSAIDs for all three levels of harm (ulcer, bleed or perforation, and death). The L’Abbé plot was presented.

Endoscopically diagnosed ulcer (12 RCTs of 4,111 patients with arthritis): the average absolute risk for an endoscopically diagnosed ulcer with NSAID was 21%. The trials did not report any patients with a more serious level of harm.

Clinically diagnosed (symptomatic) ulcer (3 RCTs and 1 cohort study): the incidence in the RCTs was significantly higher than in the cohort study; the average incidence was 1.48% (range: 1.35 - 1.53) for the RCTs versus 0.39% for the cohort study.

Ulcer bleeding or perforation (4 RCTs and 2 cohort studies): the incidence in the RCTs was significantly higher than in the cohort studies; the average incidence was 0.48% (range: 0.34 - 0.86) for the RCTs versus 0.22% (range: 0.06 - 0.33) for the cohorts.

Death attributable to ulcer bleeding or perforation (2 RCTs and 1 cohort study): the pooled incidence was 0.008% (range: 0.007 - 0.023).

The pooled ulcer bleed/perforation ratio was 3.3 (9 studies involving 1,769 patients with the 3 RCTs (231 patients with ulcer and 84 bleeds/perforations) to 6.0 in the cohort study (131 patients with ulcer and 22 bleeds/perforations).
The pooled bleed/perforation death ratio was 8.3 (50 studies involving 11,040 patients with bleed or perforation). This ranged from 6.3 (23 case reports with 3,669 bleeds/perforations and 585 deaths) to 35.5 (2 RCTs with 71 bleeds/perforations and 2 deaths). <RESULTS OF THE REVIEW> The NNT with NSAID for one patient to die was 1,220 patients (range: 909 - 2,500) when using the first method with data from RCTs for bleed or perforation. The NNT was 1,960 patients (range not reported) when using the second method, based on outcome of symptomatic ulcer.

Authors' conclusions
On average, 1 in 1,200 patients taking NSAIDs for at least 2 months will die from gastroduodenal complications, who would not have died had they not taken NSAIDs. This extrapolates to about 2000 deaths each year in the UK.

CRD commentary
The aims were stated, and the inclusion criteria were defined in terms of intervention and outcome, although the definition of outcome was taken as that stated in individual studies. Two relevant databases were searched, and eligible studies were not restricted to those published in English. Since no attempt was made to locate unpublished studies there was the possibility of publication bias. The methods used to select studies were not described and no systematic assessment of validity was undertaken. Relevant information on the individual studies was presented in tabular format.

The results were grouped and pooled by study design. There was no evaluation of heterogeneity between studies within each study design group, so it was unclear whether pooling was an appropriate method of combining the studies. The NNT was estimated using two different end points. The discussion included consideration of the following potential causes of bias and heterogeneity between study design groups: populations with differing underlying risks necessitating caution in interpreting NNT values; different NSAIDs; concentration of case reports on disasters; ulcers only detected when they bled/perforated; imprecise definitions of drug exposure; very small numbers of deaths in RCTs; and confounding factors such as over-the-counter NSAIDs purchases, which were unrecorded. In view of the above limitations, the conclusion should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors state that patients should receive minimum effective doses for the minimum possible time.

Research: The authors did not state any implications for further research.

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Other publications of related interest
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.