Risk of serious NSAID-related gastrointestinal events during long-term exposure: a systematic review

Delia Schaffer, Timothy Florin, Craig Eagle, Ian Marschner, Gurkirpal Singh, Mendel Grobler, Chris Fenn, Manjula Schou and Kathleen M Curnow

Non-selective non-steroidal anti-inflammatory drugs (NSAIDs) provide effective management of pain and inflammation, but are associated with the formation of peptic ulcers and an increased risk of peptic ulcer haemorrhage and perforations ("serious gastrointestinal events") in the range of 0.3% to 2.5% per year.[1,2] The background rate of serious gastrointestinal (GI) events has been estimated as 0.1%–0.2% per year in non-exposed people.[3,4] This may be higher depending on co-existing factors such as smoking, use of anticoagulants[5] and older age. However, NSAID-related and background serious GI event rates from different studies are not informative for comparison. Studies comparing NSAID users against well-matched controls are more informative, and show NSAIDs to be associated with a 1.5–7.2-fold increase in serious GI events, compared with controls, across various agents.[6-8] Thus, for patients who require long-term therapy, clinicians must weigh the risk of serious GI events relative to other risks.[9-12]

The hypothesis that animals develop mucosal tolerance to the GI-toxic effects of NSAIDs has been proposed repeatedly.[8,13,14] However, the relevance of this to humans and serious GI events is unclear.[15-18] Therefore, we performed a quantitative systematic review to determine whether the occurrence of serious GI events reduces over time in clinical studies of long-term NSAID use. Serious GI events were defined as upper GI ulcers that were complicated by haemorrhage, perforations, obstructions or hospitalisation.

METHODS

Selection of articles

A high-sensitivity search for randomised trials was conducted by searching the Third Quarter 2002 issue of the Cochrane Controlled Trials Register from its start date. The criteria for study selection were:
- study sample included patients exposed to prescription non-selective NSAIDs for a duration greater than 6 months;
- "serious GI event" incidence or risk was reported, by duration of NSAID exposure;

ABSTRACT

Objective: Exposure to non-steroidal anti-inflammatory drugs (NSAIDs) is associated with increased risk of serious gastrointestinal (GI) events compared with non-exposure. We investigated whether that risk is sustained over time.

Data sources: Cochrane Controlled Trials Register (to 2002); MEDLINE, EMBASE, Derwent Drug File and Current Contents (1999–2002); manual searching of reviews (1999–2002).

Study selection: From 479 search results reviewed and 221 articles retrieved, seven studies of patients exposed to prescription non-selective NSAIDs for more than 6 months and reporting time-dependent serious GI event rates were selected for quantitative data synthesis. These were stratified into two groups by study design.

Data extraction: Incidence of GI events and number of patients at specific time points were extracted.

Data synthesis: Meta-regression analyses were performed. Change in risk was evaluated by testing whether the slope of the regression line declined over time. Four randomised controlled trials (RCTs) provided evaluable data from five NSAID arms (aspirin, naproxen, two ibuprofen arms, and diclofenac). When the RCT data were combined, a small significant decline in annualised risk was seen: –0.005% (95% CI, –0.008% to –0.001%) per month. Sensitivity analyses were conducted because there was disparity within the RCT data. The pooled estimate from three cohort studies showed no significant decline in annualised risk over periods up to 2 years: –0.003% (95% CI, –0.008% to 0.003%) per month.

Conclusions: Small decreases in risk over time were observed; these were of negligible clinical importance. For patients who need long-term (> 6 months) treatment, precautionary measures should be considered to reduce the net probability of serious GI events over the anticipated treatment duration. The effect of intermittent versus regular daily therapy on long-term risk needs further investigation.

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- events occurred during current use of medication; and
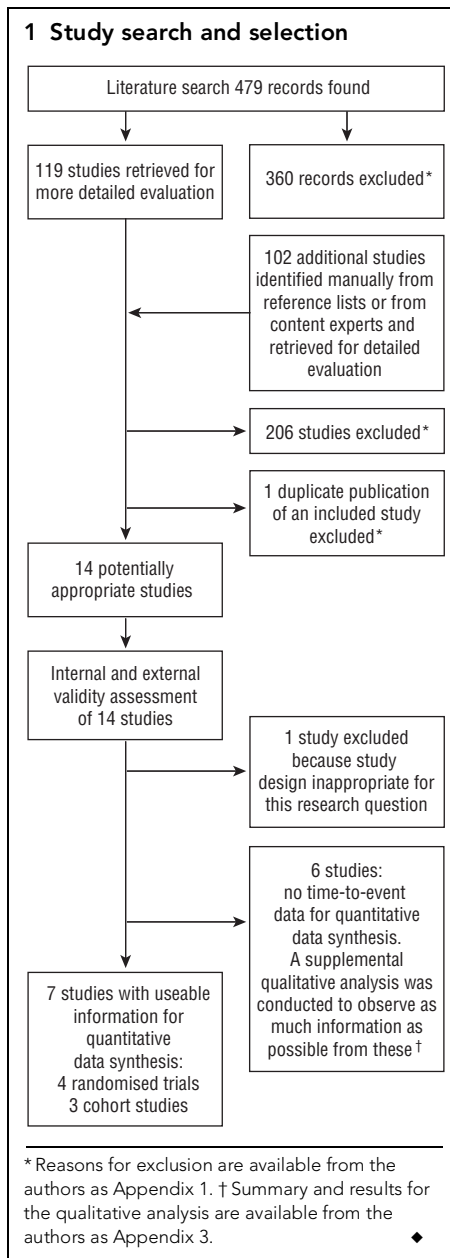- the study was published in full in English, French or German.

Using the same search criteria, a high-specificity search of Current Contents, EMBASE, MEDLINE and Derwent Drug File databases was conducted in July 2002 (limitations: humans, 1999–2002). In this manner, relevant observational studies and further randomised trials were identified either directly (back to 1999) or indirectly (by manual search of systematic reviews from 1999–2002, representing the NSAID literature back to the 1960s). Abstracts of 479 search results were reviewed; 360 records were excluded for not fulfilling the basic criteria, and 119 records plus an additional 102 records identified from manual searches were retrieved for more detailed evaluation (total, 221) (Box 1).

When retrospective cohort studies using the same health care databases (eg, Tennessee Medicaid, UK General Practice Research Database, Tayside, or ARAMIS) were identified, only one study per database was selected; the rest[5,6,19-30] were excluded to avoid potentially redundant patient populations. Meta-analyses were excluded; however, any otherwise unidentified original published studies cited in meta-analyses were retrieved for evaluation against our search criteria. Exclusions were logged with a reason (log available from authors as Appendix 1).

Fourteen studies (represented by 15 publications) were identified as potentially relevant.

Internal and external validity assessments

Individual studies were reviewed to evaluate the presence of a valid statistical association.

1 Study search and selection

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Literature search 479 records found

119 studies retrieved for          360 records excluded*
more detailed evaluation

102 additional studies
identified manually from
reference lists or from
content experts and
retrieved for detailed
evaluation

206 studies excluded*

1 duplicate publication
of an included study
excluded*

14 potentially
appropriate studies

Internal and external
validity assessment
of 14 studies

1 study excluded
because study
design inappropriate for
this research question

6 studies:
no time-to-event
data for quantitative
data synthesis.
A supplemental
qualitative analysis was
conducted to observe as
much information as
possible from these †

7 studies with useable
information for
quantitative
data synthesis:
4 randomised trials
3 cohort studies
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* Reasons for exclusion are available from the authors as Appendix 1. † Summary and results for the qualitative analysis are available from the authors as Appendix 3. ◆

Key parameters affecting internal and external validity were assessed according to standard epidemiological principles and Australian government guidelines.[31-34] Details are available from the authors as Appendix 2. Based on the assessments, seven studies were included in the quantitative data synthesis. These were stratified into two groups according to study design:

• Group 1. Four randomised trials presenting time-to-event data.[35-38] These investigated patients who were using NSAIDs on a regular daily basis and who were subject to protocol-driven constraints (ie, patients were not allowed to switch NSAIDs or to take concomitant anti-ulcer medication;

patients were withdrawn after a serious GI event or other monitored adverse events).

• Group 2. Three cohort studies presenting time-to-event data: one prospective study[2] and two registry studies.[4,39] It is likely that these studies included some patients who used NSAIDs on an "as needed" (prn) basis — detailed compliance information was unavailable.

Box 2 and Box 3 summarise the validity weaknesses identified for the two groups.

Six observational studies,[40-45] classified as Group 3, were excluded for lack of time-to-event data for data synthesis. These reported relative risk or excess risk for NSAID exposure versus non-exposure by duration-of-exposure categories, and were reviewed in a supplemental analysis. Details are available from the authors as Appendix 3.

An additional case–control study[15] nested within a cohort of patients exposed to NSAIDs for up to 1 year was excluded. Odds ratios were not reported, but serious GI bleed rates over time were, so it potentially qualified for quantitative data synthesis inclusion. However, unlike the included studies, that study based rates on estimated exposure duration (derived from a selected subgroup of patients who did not have a serious GI event), rather than actual exposure data from the entire cohort of exposed patients. This led to concerns about bias, as selected patients without bleeds were unlikely to be representative of patients with bleeds. Furthermore, information on numbers at risk over time was not available for that study.

Data extraction and analysis

Data for validity assessment criteria and patient characteristics were extracted from the articles (variables available on request). Outcomes data for serious GI event incidence at specific times were extracted where available, or otherwise were taken from an electronic citation,[46] email correspondence (Dr M Mamdani, Scientist, Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada) and unpublished reports (G Singh, Analysis of a cohort of long-term diclofenac users, 2003; S Morant, Statistician, Cygnus Biostatistics Ltd, Analysis of NSAID exposure duration and GI haemorrhage rates using the UK GP Database, 2002; GD Searle & Co, Final Report for the CLASS trial, 2000). If multiple serious GI event outcome definitions were reported, data were extracted for the strictest definition. Data were only extracted for patients taking non-selective NSAIDs (ie, data from placebo,

COX-2 specific inhibitor, or diclofenac/misoprostol treatment arms found in some studies were outside the scope of our review).

For Group 1 and 2 studies separately, a combined analysis across studies and time points using a generalised estimating equations linear regression model[47] (a form of meta-regression) was conducted using SAS software version 8 (SAS Institute Inc, Cary, NC, USA). The outcome variable was the estimated annualised probability of having an event, for each time point in each study. This was estimated from the conditional probability of having a serious ulcer complication in a specified time interval, given that no event was experienced before the start of that interval, and was derived from the published cumulative probability estimates for each study. The model included time (in months), study and treatment group as explanatory variables. Change in risk was evaluated by estimating and testing the significance of the regression line slope. Weighted analyses were conducted using the inverse variance method, with variance estimated from Greenwood's formula.[48] A sensitivity analysis using inverse standard error weighting was conducted to verify robustness of the estimates. As data were too limited to perform valid heterogeneity testing within the regression model, pre-assessment of heterogeneity was done (details available from the authors as Appendix 4). Lastly, adequacy of the linear model was assessed by including higher-order terms in the model.

RESULTS

Study characteristics

The studies investigated a wide selection of NSAIDs taken in usual clinical doses. One study included aspirin at 1000 mg/day,[37] a dose that is standard for pain management but higher than commonly used in Australia for antithrombotic treatment in patients with myocardial infarction. The studies measured the occurrence of upper GI ulcer bleeds and perforations. In addition to ulcer bleeds, two trials[37,38] and one observational study[43] included hospitalised symptomatic ulcers in the outcome definition.

All studies sampled adult community populations of NSAID users. They included patients with osteoarthritis[36] and rheumatoid arthritis,[2,35,36,38] unspecified NSAID users,[41,42,44,45] or subgroups (>65 years;[4] >40 years;[39,40] and low-income elderly[43]). NSAID use was for pain treatment, or, if

2 Time-to-event results from randomised trials

Study	Analysis	Results	Quality weaknesses
CLASS[36]* Ibuprofen (n = 1985) Diclofenac (n = 1996)	• Time-to-event analysis of ulcer bleed, perforation, or obstruction	• Event rate consistent over 4–6 months (median, 9 months' exposure) • Event rate zero after 4 months in the diclofenac arm‡ and after 6 months in the ibuprofen arm	• Smaller samples compared with the studies in Box 3§ • Diminishing patients over time • High withdrawals in CLASS and Neustadt studies
VIGOR[35]† Naproxen (n = 4029)	• Time-to-event analysis of ulcer bleed, perforation, or obstruction	• Event rate consistent over median 9 months' exposure	• Neustadt study was not peer reviewed
Neustadt[38] Ibuprofen (n = 417) Etodolac 300 mg (n = 620) Etodolac 1000 mg (n = 409)	• Time-to-event analysis of ulcer bleed, or symptomatic ulcer	• Nine events spread out over 3 years in ibuprofen arm • Two events per etodolac arm, both before 4 months	• AMIS patients differ significantly from other trials • Protocol-driven constraints (eg, no anti-ulcer medications and no switching allowed)
AMIS[37] Aspirin (n = 2267)	• Time-to-event analysis of ulcer bleed or ulcer hospitalisation	• Event rate consistent over 4 years	

* Instead of the published 6-month data, we used 12–18-month data from the entire trial (GD Searle & Co, Final report for the CLASS trial, 2000, unpublished; and US Food and Drug Administration [FDA] website: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.pdf). † Instead of the published data, we extracted data for the alternative (stricter) serious GI event endpoint, as provided on the FDA website: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_04_stats.pdf. ‡ With the exception of one event that occurred after 9 months. § All probability estimates from the randomised trials were surrounded by wide 95% confidence intervals, except for the AMIS trial. ◆

unspecified, was assumed most likely for pain. One study enrolled only patients with myocardial infarction.[37] Most patients had taken NSAIDs before study commencement, but one cohort study specifically included NSAID-naïve patients.[4]

Of the randomised trials, the AMIS trial[37] included 100% long-term users (> 6 months) and the VIGOR,[35] Neustadt[38] and CLASS[36] trials included more than 50% long-term users. The prospective cohort study by Singh and Triadafilopoulos[2] included more than 50% long-term users. Although the registry cohort and case–control studies were larger, they included a lower proportion of long-term users (< 12% in Mamdani et al,[4] 12% in UKGPRD,[39] and < 18% in Mellemkjaer et al[42]). Information about the proportion of long-term users was not available for the other three studies.

Group 1 studies: randomised trials

The results of the individual studies are provided in Box 2 and in the Kaplan–Meier curves in the original articles. Four randomised trials provided Kaplan–Meier time-to-event data from seven non-selective NSAID groups (aspirin 1000 mg/day, naproxen 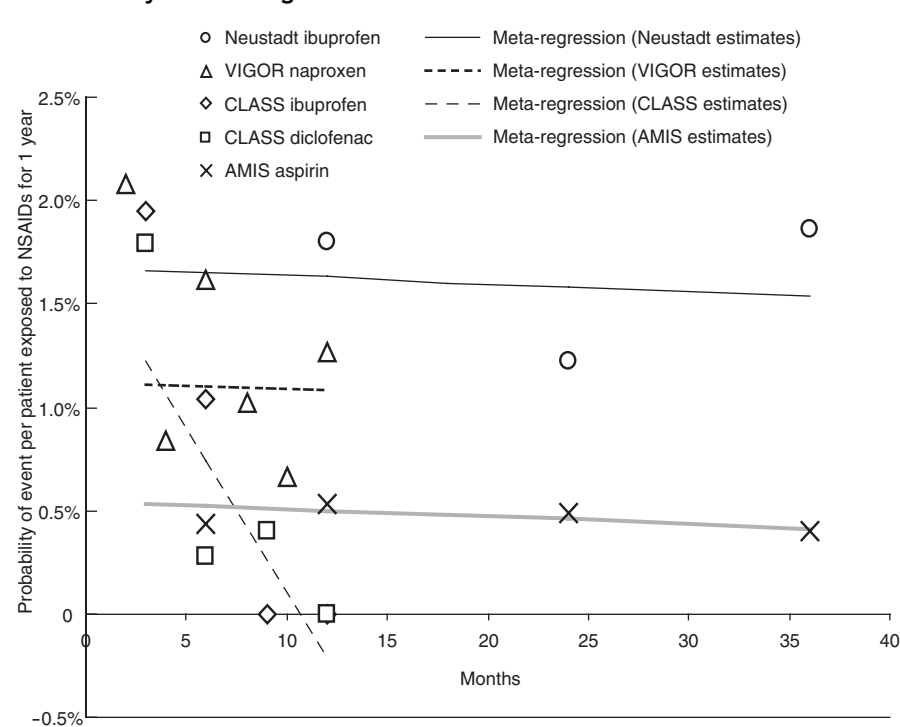1000 mg/day, diclofenac 150 mg/day, two arms with ibuprofen 2400 mg/day, and two arms with etodolac 300 mg/day and 1000 mg/day). Five groups were included in the pooled regression model; the etodolac arms[38] were excluded as time-dependent analysis was not considered valid with only two serious GI events per arm.

When randomised trial data were pooled, a small significant reduction in risk of –0.005% (95% CI, –0.008% to –0.001%) per month was seen (Box 4). Three sensitivity analyses were performed. The first addressed the finding that the slope of the CLASS trial data was significantly different to that of the other studies, mainly driven by
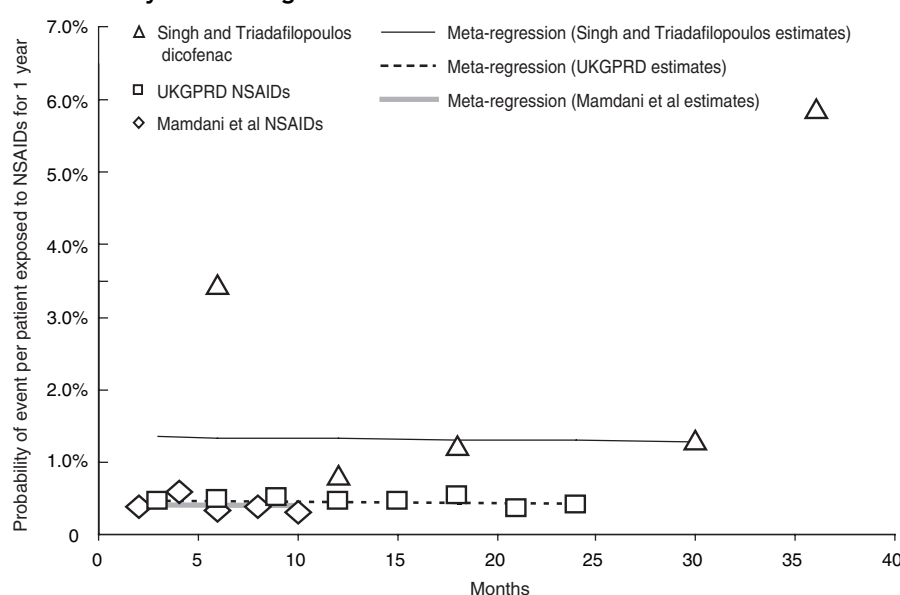
3 Time-to-event results from cohort studies

Study	Analysis	Results	Quality weaknesses
Singh and Triadafilopoulos[2]* NSAIDs (n = 1600) Diclofenac (n = 499)	• Time-to-event analysis of hospitalisation for serious GI events	• Event rate consistent over time up to 10 years in NSAID cohort • Event rate consistent over time over 1 year in diclofenac cohort	• Unblinded exposure and outcome (but bias minimised by verification of records using patient interview) • Small sample in the diclofenac cohort
Mamdani et al[4]† NSAIDs (n = 5391)	• Time-to-event analysis of upper GI bleed hospitalisations	• Event rate consistent over time up to 295 days (maximum length of exposure)	• Retrospectively defined • Unblinded exposure and outcome (but some measures to minimise bias were taken) • Exposure overestimation (based on prescriptions) §
UKGPRD[39]‡ NSAIDs (628 TPY)	• Rate of ulcer bleeds per TPY, by monthly intervals	• Event rate linear over 2 years • No evidence of trend over time for NSAIDs (P = 0.303), diclofenac (P = 0.520) or ibuprofen (P = 0.434)	• Lower proportion of long-term users (12% in UKGPRD; less than 12% in Mamdani et al)

* Instead of the published data, we used unpublished supplemental data (G S, 2003). † We used the published data supplemented by unpublished numbers-at-risk data (Dr M Mamdani, Scientist, Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada, personal communication). ‡ Instead of the published data, we used supplemental unpublished data (Dr S Morant, Statistician, Cygnus Biostatistics Ltd, Haddenham, UK, 2002, personal communication). § This may result in underestimation of incidence, but should not materially affect the relationship between incidence and duration of exposure. TPY = thousand patient-years. ◆

4 Probability of serious gastrointestinal event over time: randomised trials[35-38]

The combined slope for the studies was –0.005% (95% CI, –0.008% to –0.001%), indicating a decline of 0.005% per month on the annualised probability of having an upper gastrointestinal bleed, perforation or obstruction, or being hospitalised for a symptomatic ulcer. One slope was fit, but separate intercepts were allowed in the model. Two slopes were fit (shown above) in the sensitivity analyses (see text) to address disparity in the data. Patient numbers at risk at each time point are available from the authors. ◆

5 Probability of serious gastrointestinal event over time: cohort studies[2,4,39]

The combined slope for the studies was –0.003% (95% CI, –0.008% to 0.003%), indicating a non-significant decline of 0.003% per month on the annualised probability of having an upper gastrointestinal bleed, perforation or obstruction, or being hospitalised for a symptomatic ulcer. One slope was fit, but separate intercepts were allowed in the model. Patient numbers at risk at each time point are available from the authors. ◆

the ibuprofen group. The analysis was re-run allowing different slopes for the CLASS study versus the other studies. The latter studies showed a small decline in annualised risk of serious GI events of –0.004% (95% CI, –0.005% to –0.003%) per month. The disparate CLASS study showed a significant decline in annualised risk of serious GI events of –0.16% (95% CI, –0.223% to –0.096%) per month of exposure. The second sensitivity analysis again allowed different slopes for the CLASS study versus the others, and excluded the AMIS study (because the patient population was very different to those in the other trials). This showed a non-significant decline in annualised risk of –0.018% (95% CI, –0.04% to 0.001%) per month for the VIGOR and Neustadt studies combined. Results were similar when sensitivity analysis was conducted using the alternate weighting method.

Group 2 studies: cohort studies

The results of the individual studies are summarised in Box 3. For the pooled analysis, the NSAID cohort from the study by Singh and Triadafilopoulos[2] was excluded because information on patient numbers over time was not retrievable. Time-to-event data from the diclofenac cohort of the study by Singh and Triadafilopoulos and data from the other two cohort studies were pooled. The slope of the combined regression line shows no significant decline in the annualised probability of serious GI events over time (Box 5). Results were similar when sensitivity analysis was conducted using the alternate weighting method.

Group 3 studies: relative risk and excess risk for NSAID exposure versus non-exposure

Four of six observational studies showed a slight decline in relative risk and excess risk over time, but the risk of serious GI events in NSAID-treated patients did not decline to control-group levels in any of the studies at any time over 1–2 years.

DISCUSSION

Our findings suggest that the probability of having a serious NSAID-related ulcer bleed, perforation or hospitalisation does not meaningfully decline over time. Therefore, duration of treatment should be minimised; if long-term treatment is required, precautionary measures should be considered so as to reduce the risk of serious GI events.

Some of the randomised trial data suggested that risk may decrease over time, but these reductions were not clinically significant. For example, consider a patient with a 1% annual risk of serious GI events at treatment initiation (baseline risk varies by individual patient characteristics). For an expected treatment duration of 3 years, the net risk of a serious GI event is $1-(1-0.01)^3$ $= 2.97\%$. Assuming a 0.005% reduction in annualised risk each month (from the randomised trial results), the risk will be reduced by only 0.26% over the 3 years, to 2.71%. Given disparity in the randomised trial data, alternative estimates of reduced risk should also be considered.

Therefore, although a small risk reduction over time may be a plausible expectation for long-term NSAID users, this is unlikely to have clinical importance. Unlike in some animal models, any significant decreases observed in the randomised trial data more likely reflected depletion of susceptibles rather than marginal adaptation. Depletion of susceptibles, which leads to unmet inflammation-management need, has a vastly different clinical effect than adaptation.

Our findings are difficult to compare with previously published risk-duration meta-analyses,[7,49-51] primarily because previous meta-analyses combined serious and non-serious GI events, and were heavily weighted for short-term studies (7–90 days). Where long-term (> 6 month) studies were cited,[51] the meta-analyses did not meet our criteria for time-to-event data, instead comparing short-term and long-term NSAID users from different studies. These analyses showed no trend for decreasing risk over study durations of 60 days and longer.

This is the first time, to our knowledge, that all available time-to-event data from long-term NSAID studies have been reviewed. Our findings are consistent with three published time-to-event meta-analyses of nabumetone data and non-selective NSAID data (from comparative studies against rofecoxib).[52-54]

Limitations

The primary limitation of our study was the small number of long-term studies. Our analysis is a form of meta-regression, which should generally not be considered when there are fewer than 10 trials.[55] However, because our analysis had multiple time points per study, this guidance is not as relevant. Detailed discussion of other limitations (eg, the studies, except two, were not designed a priori to evaluate this question;

use of high-specificity literature search methods) is available on request. The small number of studies and other limitations mainly affected the precision of the results, but overall, loss of precision would not change the conclusions regarding the nature, direction (slight downward slope) and marginal clinical significance of the risk-over-time relationship.

Implications for future research

Our review provides an overview of the evidence to 2002. Although the trends observed in this analysis may suffice for the purposes of clinical practice, further large trials are needed to address this question with optimal statistical rigour. We are aware of one randomised trial that was completed after the 2002 data cut-off for our project. The trial included very large samples of naproxen and ibuprofen users, and reported the cumulative occurrence of serious GI events over 1 year.[17] Our analysis could not be updated to include the trial because necessary patient numbers at various time points are not publicly available. However, the published Kaplan–Meier results support our findings of consistent risk over time, leading to an accumulation of serious risk over the long term.[17]

If future studies are conducted, these should, if feasible, minimise the effect of rare-event bias[56,57] (which can be amplified over time for pain agents with tolerability issues) and depletion of susceptibles, maximise the numbers of patients remaining in the study long term, and capture potentially important confounding factors such as anticoagulant use, intermittent versus regular therapy, and whether patients continued NSAID treatment after a serious GI event. These were sources of uncertainty in this review and raised new research questions.

COMPETING INTERESTS

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REFERENCES

1 Goldstein JL, Silverstein FE, Agrawal NM, et al. Reduced risk of upper gastrointestinal ulcer complications with celecoxib, a novel COX-2 inhibitor. *Am J Gastroenterol* 2000; 95: 1681-1690.
2 Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. *J Rheumatol Suppl* 1999; 26: 18-24.
3 Hernandez-Diaz S, Garcia Rodriguez LA. Incidence of serious upper gastrointestinal bleeding/perforation in the general population: review of epidemiologic studies. *J Clin Epidemiol* 2002; 55: 157-163.
4 Mamdani M, Rochon PA, Juurlink DN, et al. Observational study of upper gastrointestinal haemorrhage in elderly patients given selective cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs. *BMJ* 2002; 325: 624-629.
5 Shorr RI, Ray WA, Daugherty JR, et al. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. *Arch Intern Med* 1993; 153: 1665-1670.
6 Garcia Rodriguez LA, Hernandez-Diaz S. Relative risk of upper gastrointestinal complications among users of acetaminophen and nonsteroidal anti-inflammatory drugs. *Epidemiology* 2001; 12: 570-576.
7 Henry D, Lim LL, Garcia Rodriguez LA, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996; 312: 1563-1566.
8 Langman MJ, Brooks P, Hawkey CJ, et al. Non-steroidal anti-inflammatory drug associated ulcer: epidemiology, causation and treatment. *J Gastroenterol Hepatol* 1991; 6: 442-449.

9 Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case–control study. *Lancet* 2005; 365: 475-481.

10 Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ* 2005; 330: 1366-1369.

11 Hudson M, Hugues R, Pilote L. Differences in outcomes of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs: population based study. *BMJ* 2005; 330: 1370-1373.

12 Johnsen SP, Larsson H, Tarone RE, et al. Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib, and other NSAIDs: a population-based case-control study. *Arch Intern Med* 2005; 165: 978-984.

13 Shorrock CJ, Prescott RJ, Rees WD. The effects of indomethacin on gastroduodenal morphology and mucosal pH gradient in the healthy human stomach. *Gastroenterology* 1990; 99: 334-339.

14 Skeljo MV, Giraud AS, Yeomans ND. Adaptation of rat gastric mucosa to repeated doses of non-salicylate non-steroidal anti-inflammatory drugs. *J Gastroenterol Hepatol* 1992; 7: 586-590.

15 Carson JL, Strom BL, Soper KA, et al. The association of nonsteroidal anti-inflammatory drugs with upper gastrointestinal tract bleeding. *Arch Intern Med* 1987; 147: 85-88.

16 Elliott SL, Yeomans ND, Buchanan RR, Smallwood RA. Efficacy of 12 months' misoprostol as prophylaxis against NSAID-induced gastric ulcers. A placebo-controlled trial. *Scand J Rheumatol* 1994; 23: 171-176.

17 Schnitzer TJ, Burmester GR, Mysler E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004; 364: 665-674.

18 Paulus HE. Government Affairs. FDA Arthritis Advisory Committee meeting: risks of agranulocytosis/aplastic anemia, flank pain, and adverse gastrointestinal effects with the use of nonsteroidal antiinflammatory drugs. *Arthritis Rheum* 1987; 30: 593-595.

19 Fries JF, Williams CA, Bloch DA, Michel BA. Nonsteroidal anti-inflammatory drug-associated gastropathy: incidence and risk factor models. *Am J Med* 1991; 91: 213-222.

20 Garcia Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; 343: 769-772.

21 Garcia Rodriguez LA, Walker AM, Perez Gutthann S. Nonsteroidal anti-inflammatory drugs and gastrointestinal hospitalizations in Saskatchewan: a cohort study. *Epidemiology* 1992; 3: 337-342.

22 Griffin MR, Ray WA, Schaffner W. Nonsteroidal anti-inflammatory drug use and death from peptic ulcer in elderly persons. *Ann Intern Med* 1988; 109: 359-363.

23 Griffin MR, Piper JM, Daugherty JR, et al. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Ann Intern Med* 1991; 114: 257-263.

24 McMahon AD, Evans JM, White G, et al. A cohort study (with resampled comparator groups) to measure the association between new NSAID use prescribing and upper gastrointestinal hemorrhage and perforation. *J Clin Epidemiol* 1997; 50: 351-356.

25 Perez Gutthann S, Rodriguez LA, Raiford DS. Individual non-steroidal anti-inflammatory drugs and the risk of hospitalisation for upper gastrointestinal bleeding and perforation in Saskatchewan: a nested case–control study. *Pharmacoepidemiol Drug Saf* 1994; 3: S63.

26 Singh G, Fries JF, Spitz PW, et al. Toxic effects of azathioprine in rheumatoid arthritis: a national post-marketing perspective. *Arthritis Rheum* 1989; 32: 837-841.

27 Singh G, Fries JF, Spitz PW, et al. Toxicity profiles of disease modifying antirheumatic drugs in rheumatoid arthritis. *J Rheumatol* 1991; 18: 188-194.

28 Singh G, Ramey DR, Morfeld D, et al. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis: a prospective observational cohort study. *Arch Intern Med* 1996; 156: 1530-1536.

29 Singh G, Terry R, Ramey DR, et al. Epidemiology of serious NSAID-related complications: a prospective multivariate lifetable analysis. *Arthritis Rheum* 1997; 40 (9 Suppl): S213.

30 Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *Am J Med* 1998; 105: 31S-38S.

31 Christie D, Gordon I, Heller H. Randomised controlled trials and longitudinal studies. In: Madjar N, editor. Epidemiology: an introductory text for medical and other health science students. 2nd ed. Sydney: UNSW Press, 1997: 93, 94, 64-78.

32 Australian Government Department of Health and Ageing. Appendices Q and R. In: Guidelines for the pharmaceutical industry on preparation of submissions to the Pharmaceutical Benefits Advisory Committee including major submissions involving economic analyses. Canberra: Department of Health and Ageing, 2002. http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-pubs-guidelines-content.htm (accessed Sep 2002).

33 Jadad AR, Moore A, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1-12.

34 Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999; 354: 1896-1900.

35 Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 2000; 343: 1520-1528.

36 Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib versus nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the Celecoxib Long-Term Arthritis Safety Study: a randomised controlled trial. *JAMA* 2000; 284: 1247-1255.

37 Kurata JJ, Abbey DE. The effect of chronic aspirin use on duodenal and gastric ulcer hospitalizations. *J Clin Gastroenterol* 1990; 12: 260-266.

38 Neustadt DH. Double blind evaluation of the long-term effects of etodolac versus ibuprofen in patients with rheumatoid arthritis. *J Rheumatol Suppl* 1997; 47: 17-22.

39 MacDonald TM, Morant SV, Goldstein JL, et al. Channelling bias and the incidence of gastrointestinal haemorrhage in users of meloxicam, coxib, and older, non-specific non-steroidal anti-inflammatory drugs. *Gut* 2003; 52: 1265-1270.

40 Hallas J, Lauritsen J, Dalsgard Villadsen H, Freng Gram L. Nonsteroidal anti-inflammatory drugs and upper gastrointestinal bleeding, identifying high-risk groups by excess risk estimates. *Scand J Gastroenterol* 1995; 30: 438-444.

41 MacDonald TM, Morant SV, Robinson GC, et al. Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. *BMJ* 1997; 315: 1333-1337.

42 Mellemkjaer L, Blot WJ, Toft Sorensen H, et al. Upper gastrointestinal bleeding among users of NSAIDs: a population-based cohort study in Denmark. *Br J Clin Pharmacol* 2002; 53: 173-181.

43 Smalley WE, Ray WA, Daugherty JR, Griffin MR. Nonsteroidal anti-inflammatory drugs and the incidence of hospitalizations for peptic ulcer disease in elderly persons. *Am J Epidemiol* 1995; 141: 539-545.

44 Perez Gutthann S, Garcia Rodriguez LA, Raiford DS. Individual nonsteroidal antiinflammatory drugs and other risk factors for upper gastrointestinal bleeding and perforation. *Epidemiology* 1997; 8: 18-24.

45 Garcia Rodriguez LA, Cattaruzzi C, Troncon MG, Agostinis L. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. *Arch Intern Med* 1998; 158: 33-39.

46 Li Q. Statistical reviewer briefing document for the advisory committee for NDA # 21-042 s-007. 2000. http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_04_stats.pdf (accessed Nov 2002).

47 Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986; 73: 13-22.

48 Cox DR, Oakes D. Analysis of survival data. London: Chapman and Hall, 1984.

49 Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. *Ann Intern Med* 1991; 115: 787-796.

50 Hernandez-Diaz S, Garcia Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Arch Intern Med* 2000; 160: 2093-2099.

51 Richy F, Bruyere O, Ethgen O, et al. Time dependent risk of gastrointestinal complications induced by non-steroidal anti-inflammatory drug use: a consensus statement using a meta-analytic approach. *Ann Rheum Dis* 2004; 63: 759-766.

52 Freston JW. Rationalizing cyclooxygenase (COX) inhibition for maximal efficacy and minimal adverse events. *Am J Med* 1999; 107(6A): 78S-88S.

53 Lipani JA, Poland M. Clinical update of the relative safety of nabumetone in long-term clinical trials. *Inflammopharmacology* 1995; 3: 351-361.

54 Palmer RH, MacDonald B, DeLapp R. Peptic ulcers with nabumetone: experience in 1677 patients with 4033 years of exposure. *Gastroenterology* 1998; 114 (4 Suppl): A252.

55 Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions 4.2.5 [updated May 2005]. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons, 2005.

56 Fletcher RH, Fletcher SW, Wagner EH. Clinical epidemiology: the essentials. 3rd ed. Baltimore, Md: Williams and Wilkins, 1996.

57 Eypasch E, Lefering R, Kum CK, Troidl H. Probability of adverse events that have not yet occurred: a statistical reminder. *BMJ* 1995; 311: 619-620.