Gastroduodenal Ulcers Associated with the Use of Non-steroidal Anti-inflammatory Drugs: A Systematic Review of Preventive Pharmacological Interventions
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Drugs to Prevent Gastroduodenal Ulcers Associated with the Use of NSAIDs

**Technology Name**
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Gastroprotective agents: misoprostol, histamine type-2 receptor antagonists (H2RAs), proton pump inhibitors (PPIs)
- Cyclooxygenase (COX)-2 selective NSAIDs: celecoxib, rofecoxib, meloxicam.

**Disease/Condition**
Traditional NSAIDs, which are used to treat painful arthritic and inflammatory disorders, can produce gastrointestinal (GI) adverse effects. The incidence of serious complications is low, but it is an important clinical issue because of the widespread use of these medications.

**Technology Description**
Gastroprotective agents can help protect the stomach when an NSAID is used. COX is an enzyme. Type 1 COX (COX-1) is involved in protecting the stomach lining, while the second type (COX-2) may be important in promoting the pain of arthritic diseases. Traditional NSAIDs inhibit the effects of COX-1 and COX-2. NSAIDs that selectively inhibit COX-2 theoretically should have little effect on the GI tract.

**The Issue**
The efficacy and safety profiles of available gastroprotective agents should be compared when they are used to protect against NSAID-induced GI damage. The GI safety profiles of COX-2 selective NSAIDs should be compared with those of traditional non-selective NSAIDs.

**Assessment Objectives**
1. To assess how well gastroprotective agents protect against the upper GI damage caused by traditional non-selective NSAIDs.
2. To compare the upper GI damage caused by COX-2 selective NSAIDs with that caused by traditional non-selective NSAIDs.
3. To compare the upper GI damage caused by COX-2 selective NSAIDs with that caused by placebo.

**Method**
For the first objective, a Cochrane Collaboration meta-analysis was updated. For the other objectives, a literature search was used to identify studies that assessed the GI safety of the newer COX-2 selective NSAIDs.

**Conclusions**

**Gastroprotective agents**
- Misoprostol, PPIs and double doses of H2RAs are effective at reducing the risk of endoscopically identified NSAID-induced ulcers.
- Standard doses of H2RAs are ineffective at reducing the risk of endoscopically identified NSAID-induced ulcers.
- Misoprostol is the only agent that has been shown to reduce the risk of NSAID-induced clinically important ulcer complications. Its use, however, is associated with significant adverse effects, particularly at higher doses.

**COX-2 selective NSAIDs**
- COX-2 selective NSAIDs are associated with a lower risk of endoscopically identified ulcers and of clinically important ulcer complications when compared with traditional non-selective NSAIDs in general.
- COX-2 selective NSAIDs were found to be safer than naproxen and ibuprofen (high dose), but no significant difference was found between the COX-2 selective NSAIDs reviewed and diclofenac.
- Preliminary results indicate that the reduced GI complication rate due to celecoxib may be lost when it is administered with acetylsalicylic acid (ASA). This has not been tested for rofecoxib.
- Meloxicam does not seem to be safer than traditional non-selective NSAIDs.
- It is unclear whether the co-administration of a COX-2 selective NSAID and a gastroprotective agent significantly improves safety over the use of a COX-2 selective NSAID alone or the use of a traditional non-selective NSAID with gastroprotection.


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1 Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are used in the management of patients with arthritic and inflammatory conditions.\(^1\) In Canada, these agents are widely prescribed and generate several million dollars in sales every year (Dorothy E. Rhodes, Canadian Compuscript, IMS Health, Montreal: personal communication, 2003 Dec.). NSAIDs, however, have been linked to gastrointestinal (GI) toxicities. Their use is commonly associated with symptoms such as nausea and dyspepsia, but these symptoms correlate poorly with serious adverse GI events.\(^2,3\) Endoscopic ulcers occur in as many as 40% of chronic NSAID users,\(^4\) but up to 85% of these ulcers may never become clinically important.\(^2,5\) Serious NSAID-induced GI complications, such as hemorrhage, perforation or death, are less common, occurring collectively at an incidence rate of about 2% per year in average risk NSAID users and in up to 10% per year in high risk patients.\(^2\)

The unsatisfactory therapeutic profile of classic NSAIDs has prompted the development of three strategies to curtail their adverse effects: substitution of less toxic agents, such as acetaminophen, when possible; use of prophylactic gastroprotective agents, such as misoprostol, histamine type-2 receptor antagonists (H\(_2\)RAs) or proton pump inhibitors (PPIs) with non-selective NSAIDs; and use of newly developed, more selective COX-2 NSAIDs.

The use of prophylactic therapy to prevent NSAID-induced GI complications is common, given the large number of patients using these drugs. Each gastroprotective agent or class of agents has a different mechanism of action. Misoprostol (Cytotec\(^\text{®}\)), which is a synthetic prostaglandin E\(_1\) analogue, has antisecretory and cytoprotective properties. H\(_2\)RAs (cimetidine, famotidine, nizatidine, ranitidine) reduce the secretion of gastric acid by competitively and selectively inhibiting the action of histamine on H\(_2\) receptors of the parietal cells. PPIs (lansoprazole, omeprazole, pantoprazole), which are specific inhibitors of gastric secretion, act by irreversibly binding to K\(^+\)-H\(^+\)-ATPase (an enzyme that transports acid across the parietal cell).\(^6\)

The use of COX-2 selective NSAIDs is an alternative to the combined use of prophylactic gastroprotective therapy and non-selective NSAIDs.\(^6\) When this review was undertaken, three agents were marketed as COX-2 selective NSAIDs in Canada: celecoxib (Celebrex\(^\text{TM}\)), meloxicam (Mobicox\(^\text{TM}\)) and rofecoxib (Vioxx\(^\text{®}\)).

2 Objectives

1. To assess the effectiveness of misoprostol, H\(_2\)RAs and PPIs for the prevention of upper GI toxicity associated with the non-selective NSAIDs.

2. To compare the upper GI toxicity of COX-2 selective NSAIDs with that of the non-selective NSAIDs with or without the concomitant use of gastroprotective agents.

3. To assess the upper GI toxicity of the COX-2 selective NSAIDs available in Canada by comparing these agents with placebo.
3 Methods

A systematic review of randomized controlled trials (RCTs) was conducted to fulfill the three objectives. Addressing the first objective involved the updating of the Cochrane Collaboration systematic review published in 2000 by Rostom et al.\textsuperscript{7,8} For the remaining objectives, the review was expanded to include studies that compare the new COX-2 selective NSAIDs with non-selective NSAIDs or placebo.

Accepted methods of systematic review were used. Published literature and scientific meeting literature were obtained using Dialog\textsuperscript{®} OneSearch\textsuperscript{®} on MEDLINE\textsuperscript{®}, ToxFile, EMBASE\textsuperscript{®}, BIOSIS Previews\textsuperscript{®}, Pharmaceutical News Index (PNI\textsuperscript{®}) and Current Contents Search\textsuperscript{®}. The literature search on the GI safety of the three COX-2 selective NSAIDs was limited to the publication years 1990 to 2002. The original Cochrane review\textsuperscript{8} was updated to cover the period from January 2000 to May 2002. There were no language restrictions. The Cochrane Collaboration Library and Food and Drug Administration (FDA) web site were searched separately. Manufacturers of the three COX-2 selective NSAIDs available in Canada were contacted for any relevant information. All levels of screening, data abstraction and quality assessments were performed in duplicate by independent reviewers.

The primary outcomes examined in this review included the occurrence of endoscopic ulcer (defined as a mucosal defect at least 3 mm in diameter and distinguished from erosions based on the authors’ descriptions), clinical GI events (e.g., upper GI hemorrhage, perforation, pyloric obstruction and death), other measures of toxicity or lack of efficacy, treatment withdrawals and symptoms.

The quantitative analysis was performed using Review Manager (RevMan) version 4.1 and results expressed as relative risk (RR) of the outcome obtained with the intervention compared with outcomes obtained with placebo or active comparators, using a fixed effect model. Heterogeneity was measured using a chi-square test. A p value of <0.10 was considered to be evidence of statistical heterogeneity.\textsuperscript{9} A qualitative analysis was conducted for endpoints and studies that could not be appropriately combined.

4 Results

Of the 898 articles identified by the initial search strategy, 42 studies fulfilled the inclusion criteria. Five studies considered prophylaxis against the GI toxicity of non-selective NSAIDs and 37 articles described COX-2 selective NSAIDs. Some studies considered more than one intervention. As a result, they were used in several analyses.

Prophylactic Gastroprotective Therapy

The five prophylactic studies were used to update the Cochrane Collaboration meta-analysis by Rostom et al.\textsuperscript{7,8} The addition of the new studies, however, did not change the overall results of the original Cochrane Collaboration review.\textsuperscript{7,8}
a) Misoprostol

Misoprostol is the only prophylactic agent that has been shown to reduce the occurrence of clinically important ulcer complications. Its use, however, is associated with significant adverse effects, particularly at high doses.

1. Endoscopic ulcers: In total, 22 studies assessed the effect of misoprostol on the prevention of NSAID-induced endoscopically confirmed ulcers. Eleven studies with 3,687 patients compared the incidence of endoscopic ulcers with misoprostol to that with placebo after at least three months of NSAID exposure. Misoprostol significantly reduced the RR of gastric ulcers by 74% [RR=0.26; 95% confidence interval (CI): 0.17 to 0.39, random effects] and the RR of duodenal ulcers by 53% (RR=0.47; 95% CI: 0.33 to 0.69, random effects), corresponding to absolute risk reductions (ARRs) of 12.0% and 3% for gastric and duodenal ulcers respectively. The observed heterogeneity in these estimates was due to the inclusion of all misoprostol doses in the analyses. Analysis of the misoprostol studies stratified by dose eliminated this heterogeneity.

Subgroup analyses: dose of misoprostol: All the studied doses of misoprostol were associated with a significantly reduced risk of endoscopic ulcers; and a dose-response relationship was demonstrated for endoscopic gastric ulcers. Six of the studies (2,461 patients) used misoprostol 400 µg daily, one study (928 patients) used 600 µg daily and seven studies (2,423 patients) used 800 µg daily. Misoprostol 800 µg daily was associated with the lowest risk (RR=0.17; 95% CI: 0.11 to 0.24) of endoscopic gastric ulcers when compared with placebo, whereas misoprostol 400 µg daily was associated with a RR of 0.42 (95% CI: 0.28 to 0.67, random effects model for heterogeneity). The intermediate misoprostol dose (600 µg daily) was not statistically significantly different from either the low or high dose. The pooled relative risk reduction (RRR) of 78% (4.7% ARR; RR=0.22; 95% CI: 0.09 to 0.49) for the prevention of duodenal ulcers with misoprostol 800 µg daily was not significantly superior to those of the lower daily misoprostol doses.

Subgroup analysis: short-term duration of NSAID exposure: Eight studies, with 2,206 patients, assessed the rates of endoscopic ulcers with misoprostol compared with placebo at 1.0 to 1.5 months. Pooled results from these studies revealed an 83% RRR of gastric ulcers with misoprostol (RR=0.17; 95% CI: 0.09 to 0.31) and a 72% RRR of duodenal ulcers (RR=0.28; 95% CI: 0.14 to 0.56). One study compared misoprostol with a newer cytoprotective agent, dosmafate, for NSAID prophylaxis. No statistically significant difference in ulcer rates between the two agents was found.

2. Clinical ulcer complications: One RCT, the MUCOSA trial, evaluated the efficacy of misoprostol prophylaxis against clinically important NSAID-induced ulcer complications. Among the 8,843 patients studied over six months, the incidence of clinical ulcer complications was about 1.5% per year. Misoprostol 800 µg/day was associated with a statistically significant 40% RRR (odds ratio=0.598; 95% CI: 0.364 to 0.982) of combined clinical ulcer complications (p=0.049), representing a risk difference of 0.38% (from 0.95% to 0.57%).
3. *Adverse effects:* Misoprostol was associated with a small, but statistically significant, 1.6-fold excess risk of treatment withdrawals due to drug-induced adverse events in general; and a statistically significant excess risk of treatment withdrawals due to nausea (RR=1.30; 95% CI: 1.08 to 1.55), diarrhea (RR=2.40; 95% CI: 2.05 to 2.81) and abdominal pain (RR=1.36; 95% CI: 1.20 to 1.55). Overall, 27% of patients on misoprostol experienced one or more side effects.2

When analyzed by dose, only misoprostol 800 µg daily showed a statistically significant excess risk of treatment withdrawals due to diarrhea (RR=2.45; 95% CI: 2.09 to 2.88) and abdominal pain (RR=1.38; 95% CI: 1.17 to 1.63). Both misoprostol doses (800 µg/day and 400 µg/day) were associated with a statistically significant risk of diarrhea (RR=3.25; 95% CI: 2.60 to 4.06 and RR=1.81; 95% CI: 1.52 to 2.16 respectively, p=0.0012).7,8

4. *Analyses by quality:* Both high- and low-quality misoprostol trials demonstrated a statistically significant reduction in endoscopic ulcers.

b) H2RAs

For this review, a standard dose of H2RA was defined as the equivalent of ranitidine 150 mg twice daily, whereas a double dose of H2RA was defined as the equivalent of ranitidine 300 mg twice daily. Double doses of H2RAs are effective at reducing the risk of NSAID-induced gastric and duodenal endoscopic ulcers and are well tolerated. Standard doses of H2RAs are ineffective at reducing the risk of NSAID-induced endoscopic gastric ulcers.

1. *Endoscopic ulcers:* Seven trials with 1,188 patients assessed the effect of a standard dose of H2RAs on the prevention of endoscopic NSAID ulcers at one month.29-35 Five trials with 1,005 patients assessed these outcomes at three months or longer.32,35-38 Standard doses of H2RAs are effective at reducing the risk of duodenal ulcers (RR=0.24; 95% CI: 0.10 to 0.57 and RR=0.36; 95% CI: 0.18 to 0.74 at one and three or more months respectively), but not the risk of gastric ulcers.7,8 One study did not have a placebo comparator and was excluded in the pooled estimate.37

Three RCTs with 298 patients assessed the efficacy of double doses of H2RAs for the prevention of NSAID-induced upper GI toxicity.35,39,40 When compared with placebo, double doses of H2RAs were associated with a statistically significant reduction in the risk of duodenal (RR=0.26; 95% CI: 0.11 to 0.65) and gastric ulcers (RR=0.44; 95% CI: 0.26 to 0.74). This 56% RRR in gastric ulcer corresponds to a 12% ARR (range: 23.1% to 11.3%). Analysis of the secondary prophylaxis studies (i.e., studies that included patients who had previously had NSAID-induced ulcers) alone yielded similar results.

2. *Clinical ulcer complications:* We found no H2RAs studies that assessed clinical ulcer complications.

3. *Symptoms:* H2RAs, in standard or double doses, were not associated with an excess risk of total withdrawals, treatment withdrawals due to side effects or withdrawals due to symptoms when compared with placebo. Symptoms of abdominal pain were significantly reduced, however, with high-dose H2RAs when they were compared with placebo (RR=0.57, 95% CI: 0.33 to 0.98).
4. Analyses by quality: In contrast to high-quality trials, low-quality trials failed to demonstrate a benefit of standard doses of H2RAs for the prevention of endoscopic duodenal ulcers. No significant differences were observed by quality for treatment withdrawals and symptoms.

c) PPIs

PPIs are effective at reducing the risk of NSAID-induced duodenal and gastric endoscopic ulcers and are well tolerated.

1. Endoscopic ulcers: Eight RCTs with 2,181 patients assessed the effect of PPIs on the prevention of NSAID-induced upper GI toxicity. Of the two studies that compared a PPI with placebo and with misoprostol, one studied lansoprazole, whereas the other studied omeprazole as prophylaxis. Chan compared the combination of omeprazole and diclofenac with celecoxib, whereas Jensen compared omeprazole with misoprostol. Another study compared pantoprazole with placebo, whereas the last study compared omeprazole with ranitidine 150 mg.

PPIs versus placebo: PPIs significantly reduced the risk of endoscopic duodenal (RR=0.19; 95% CI: 0.09 to 0.37) and gastric ulcers (RR=0.40; 95% CI: 0.32 to 0.51) compared with placebo. Results were similar for primary and secondary prophylaxis trials; primary studies included patients who did not have an ulcer at initial screening, whereas secondary studies included patients who had previously had NSAID-induced ulcers.

2. Clinical ulcer complications: We found no PPI studies that assessed clinical ulcer complications as a primary outcome.

3. Symptoms: The omeprazole trials used the same composite endpoints to define treatment success. In these trials, omeprazole significantly reduced “dyspeptic symptoms” as defined by the authors. Side effects were not different from placebo.

d) Head-to-head comparisons

1. Misoprostol versus H2RAs: Two trials with 600 patients in total compared misoprostol with ranitidine 150 mg twice daily. Misoprostol seems to be superior to standard doses of ranitidine for the prevention of NSAID-induced gastric ulcers (RR= 0.12; 95% CI: 0.03 to 0.51), but not for duodenal ulcers (RR=1.00; 95% CI: 0.14 to 7.14).

2. PPIs versus ranitidine: In a study of 425 patients, Yeomans et al. compared prophylaxis with omeprazole 20 mg daily to prophylaxis with ranitidine 150 mg twice daily for patients on NSAIDs. In this study, omeprazole was superior to standard doses of ranitidine for the prevention of gastric (RR= 0.32; 95% CI: 0.17 to 0.62) and duodenal ulcers (RR=0.11; 95% CI: 0.01 to 0.89).

3. PPIs versus misoprostol: Two secondary prophylaxis trials with a total of 838 patients compared a PPI with misoprostol. Hawkey et al. compared low-dose misoprostol (400 µg daily) with omeprazole (20 mg daily), whereas the Graham study compared high-dose misoprostol (800 µg) with lansoprazole (15 or 30 mg daily). PPIs were statistically superior to misoprostol for the prevention of duodenal (RR=0.29; 95% CI: 0.15 to 0.56) but not gastric ulcers (random effects model: RR=0.59; 95% CI: 0.27 to 1.25).
4. Symptoms: In the two head-to-head comparisons of omeprazole and misoprostol,\textsuperscript{16,17} omeprazole was associated with significantly fewer treatment withdrawals overall (RR=0.64; 95% CI: 0.45 to 0.91), and significantly fewer treatment withdrawals due to side effects (RR=0.48; 95% CI: 0.29 to 0.78). There were no significant differences between low-dose H\textsubscript{2}RAs and PPIs in treatment withdrawals due to side effects (RR=1.90, 95% CI: 0.77 to 4.67) or symptoms of abdominal pain or diarrhea.\textsuperscript{46} When compared with H\textsubscript{2}RAs used for less than two months, misoprostol caused significantly more treatment withdrawals due to abdominal pain (RR=3.00; 95% CI: 1.11, 8.14) and nausea (RR=3.67; 95% CI: 1.03 to 13.00); and more symptoms of dyspepsia (RR=1.59; 95% CI: 1.01 to 2.49) and diarrhea (RR=2.03; 95% CI: 1.38, 2.99).\textsuperscript{48,49}

\textbf{COX-2Selective NSAIDs}

This review identified 37 studies evaluating the GI toxicity of COX-2 selective NSAIDs. For this review, low-dose COX-2 selective NSAIDs was defined as celecoxib 200 mg bid or less, rofecoxib 25 mg daily or less or meloxicam 7.5 mg daily. High-dose COX-2 was defined as celecoxib 400 mg bid or rofecoxib 50 mg daily or meloxicam 15 mg daily.

\textbf{a) COX-2 selective NSAIDs versus non-selective NSAIDs}

1. \textit{Endoscopic ulcers:} Seven studies with a total of 4,678 patients compared the incidence of endoscopic ulcers in patients taking a COX-2 selective NSAID with patients taking a non-selective NSAID.\textsuperscript{50-55} Of the five studies that assessed celecoxib,\textsuperscript{50-52,55} two studies, which were obtained from the Food and Drug Administration’s web site (FDA studies 21 and 71), remain unpublished.\textsuperscript{50} Two studies assessed rofecoxib.\textsuperscript{53,54}

In the seven studies of patients taking non-selective NSAIDs, 18.9% developed gastric ulcers and 5.6% developed duodenal ulcers; the proportion of patients with gastroduodenal ulcers was 24.2%. Results were similar if only celecoxib studies were considered. Among the patients receiving non-selective NSAIDs in the rofecoxib studies, 39.1% developed gastric ulcers, 5.6% developed duodenal ulcers and 46.3% developed combined gastroduodenal ulcers.

\textit{Gastric ulcers:} Five studies with a total of 2,123 patients compared the safety of low-dose COX-2 selective NSAIDs versus a comparator non-selective NSAID, over three to six months, for endoscopic gastric ulcers.\textsuperscript{51-55} The use of a COX-2 selective NSAID was associated with an 84% RRR in gastric ulcers (RR=0.16; 95% CI: 0.12 to 0.22). Three studies with a total of 981 patients compared the proportions of gastric ulcers with high-dose COX-2 selective NSAIDs versus non-selective NSAIDs.\textsuperscript{53-55} High-dose COX-2 selective NSAIDs were associated with a 77% RRR in gastric ulcers (RR=0.23; 95% CI: 0.16 to 0.32). When low- and high-dose COX-2 selective NSAID studies were considered together (2,613 patients), there was an 82% RRR in gastric ulcers (RR=0.18; 95% CI: 0.14 to 0.23). These RRRs represent an ARR of 22% for gastric ulcers when COX-2 selective NSAIDs are compared with non-selective NSAIDs.

\textit{Duodenal ulcers:} The same five studies also compared the proportions of duodenal ulcers with low-dose COX-2 selective NSAIDs versus non-selective NSAIDs. Low-dose COX-2 selective NSAIDs were associated with a 62% RRR in duodenal ulcers (RR=0.38; 95% CI: 0.25 to 0.60). Likewise, high-dose COX-2 selective NSAIDs were associated with a 57% RRR in duodenal ulcers compared with non-selective NSAIDs (RR=0.43; 95% CI: 0.22 to 0.84).\textsuperscript{53-55}
and high-dose studies were considered, there was a 60% RRR in duodenal ulcers compared with non-selective NSAIDs (RR=0.40; 95% CI: 0.27 to 0.60). This represents a 4% ARR between COX-2 selective NSAIDs and non-selective NSAIDs.

Overall, COX-2 selective NSAIDs were more effective at reducing the risk of gastric ulcers than the risk of duodenal ulcers (RR=0.18 versus 0.40). This difference reached statistical significance (p<0.001). The effect was consistent when celecoxib and rofecoxib were analyzed separately.

**Gastroduodenal ulcers:** The same five studies showed a 76% RRR in combined gastroduodenal ulcers with COX-2 selective NSAIDs versus non-selective NSAIDs (RR=0.24; 95% CI: 0.20 to 0.29). This represents a 26% ARR, which is driven by COX-2 selective NSAIDs’ effect on gastric ulcers. For this analysis, low- and high-dose studies were considered together. The results for the separate low- and high-dose analyses were similar. The RRR is lowered (73%) if FDA studies 21 and 71 are included in the analysis (RR: 0.27; 95% CI: 0.23 to 0.32, ARR: 19%).

**Analysis by COX-2 selective NSAIDs:** Five studies with a total of 3,590 patients compared celecoxib with non-selective NSAIDs, showing a 72% RRR in total gastroduodenal ulcers (RR=0.28; 95% CI: 0.23 to 0.35). Two studies with a total of 1,087 patients compared rofecoxib with non-selective NSAIDs. For rofecoxib, a 75% RRR was observed (RR=0.25; 95% CI: 0.20 to 0.32). This result was not statistically different from that seen with celecoxib.

**Analysis by comparator non-selective NSAIDs:** Three studies (including FDA study 21) compared celecoxib with naproxen and showed a 77% RRR in endoscopic ulcers in favour of celecoxib (RR=0.23; 95% CI: 0.17 to 0.30). Likewise, three studies [two on rofecoxib and one on celecoxib (FDA study 71)] showed a 73% RRR with COX-2 selective NSAIDs compared with ibuprofen (RR=0.27; 95% CI: 0.22 to 0.33). However, two studies that compared celecoxib with diclofenac (including FDA study 71), showed that celecoxib was not statistically different from diclofenac (RR=0.45; 95% CI: 0.15 to 1.29). No study compared rofecoxib with diclofenac.

FDA study 71 compared celecoxib with ibuprofen and diclofenac. In this study, there was no significant RRR between celecoxib and diclofenac for gastric ulcers, but there was a significant 66% RRR when compared with ibuprofen (RR=0.34; 95% CI: 0.23 to 0.51). Unfortunately, this was the only study to compare a COX-2 selective NSAID with more than one non-selective NSAID.

**COX-2 selective NSAIDs versus placebo:** Four studies (including FDA study 21) with a total of 2,576 patients compared low- and high-dose COX-2 selective NSAIDs with placebo. There were no statistically significant differences between COX-2 selective NSAIDs and placebo for all the same analyses that were performed for the COX-2 selective NSAIDs versus non-selective NSAIDs comparison.

2. **Clinical ulcer complications:** Seven studies with a total of 61,282 patients assessed the safety of COX-2 selective NSAIDs using the clinically important endpoint of ulcer complications—
bleeding, perforation and obstruction (POB). Three of these trials used celecoxib,\textsuperscript{57-59} two used rofecoxib\textsuperscript{56,60} and two meloxicam.\textsuperscript{61,62} Two of these studies are combined analyses of the early efficacy and endoscopic studies.\textsuperscript{57,60} One is available only in abstract form.\textsuperscript{59} The two most important studies in this group are the CLASS\textsuperscript{58} and VIGOR studies.\textsuperscript{56}

Overall, COX-2 selective NSAIDs were associated with a 61\% RRR in clinically important GI outcomes compared with non-selective NSAIDs (RR=0.39; 95\% CI: 0.27 to 0.56). This corresponds to a 0.21\% ARR. These results were obtained using the six-month CLASS study data for celecoxib. The same analysis using 12-month CLASS study data obtained from the FDA web site drops the RRR to 55\% (RR= 0.45; 95\% CI: 0.32 to 0.63).\textsuperscript{50} The difference between the RRs obtained from these two analyses was not statistically different.

The same seven articles combined the clinically important GI outcomes with a “symptomatic ulcer” endpoint to make a composite endpoint—ulcer complications and symptomatic ulcers (PUB). Using this endpoint, COX-2 selective NSAIDs were associated with a 53\% RRR in PUBs compared with non-selective NSAIDs (RR=0.47; 95\% CI: 0.38 to 0.57). The same analysis with the 12-month CLASS study data does not significantly alter the results (RR=0.49; 95\% CI: 0.41 to 0.61).\textsuperscript{50} For these analyses, the meloxicam efficacy trials, which did not seek to address ulcer complications, were excluded.

Three studies with 30,306 patients compared celecoxib with various NSAIDs.\textsuperscript{57-59} Significant heterogeneity existed in this analysis, most likely due to differing NSAID comparators. Using a random effects model, celecoxib was associated with a 77\% RRR over non-selective NSAIDs for POBs (RR=0.23; 95\% CI: 0.07 to 0.78). Two studies compared rofecoxib with various NSAIDs.\textsuperscript{56,60} In this analysis, no heterogeneity existed and rofecoxib was associated with a 58\% RRR in POBs (RR=0.42; 95\% CI: 0.24 to 0.73).

Two studies compared meloxicam with a non-selective NSAID.\textsuperscript{61,62} Individually, the Hawkey \textit{et al.}\textsuperscript{62} and Dequeker \textit{et al.}\textsuperscript{61} studies failed to show a statistically significant benefit of meloxicam over diclofenac or piroxicam for either POBs or PUBs. Combining these two studies still failed to show a statistically significant benefit of meloxicam over comparator NSAIDs for these endpoints (RR=0.50; 95\% CI: 0.22 to 1.17 for POBs; RR=0.53; 95\% CI: 0.26 to 1.05 for PUBs).

We identified an additional six studies with a total of 2,300 patients that compared meloxicam with non-selective NSAIDs.\textsuperscript{63-68} From an efficacy perspective, these trials are of good quality, but the reporting of clinical ulcer complications was poor. The criteria by which ulcer complications were adjudicated were not given or poorly described; and all studies but one\textsuperscript{66} had no ulcer complications in at least one group, resulting in empty cell analyses.\textsuperscript{69} These studies were not used in the main analysis, but their data are described in the full report.

Combined analyses studies exist for each COX-2 selective NSAID being considered.\textsuperscript{57,60,70} The combination of varying types of data in these studies is a potential source of bias, but the removal of these combined studies did not significantly alter the results for either the POB or PUB endpoints, using either the six-month or 12-month CLASS data. The removal of the unpublished SUCCESS-1 trial also did not alter the overall results.
Since meloxicam may not possess the same degree of COX-2 selectivity as the others, a sensitivity analysis, with or without the two meloxicam trials, was performed. Removal of the meloxicam trials, however, did not significantly alter the results for either the POB or PUB endpoints, either using the six-month or 12-month CLASS study data.

With regards to PUBs, COX-2 selective NSAIDs seem to be superior to naproxen and ibuprofen, but were not statistically superior to diclofenac (RR=0.73; 95% CI: 0.46 to 1.14). The results were similar when the six-month or 12-month CLASS data was used. COX-2 selective NSAIDs were not statistically superior to piroxicam.

Rofecoxib has not been directly compared with diclofenac in a high-quality clinical ulcer complication trial like VIGOR. The data for rofecoxib versus diclofenac were derived from a subset of the Langman study, so that a high-quality study may show a different result. Nonetheless, from a GI perspective, available data suggest that COX-2 selective NSAIDs are not statistically significantly safer than diclofenac.

b) Head-to-head comparisons: non-selective NSAID plus PPI versus celecoxib

One study compared celecoxib alone (400 mg/day) to a non-selective NSAID with a gastroprotective agent (diclofenac 150 mg/day plus omeprazole 20 mg/day), in 290 high risk arthritic patients who had suffered a recent GI hemorrhage on NSAIDs. The six-month probability of recurrent bleeding was 4.9% for the celecoxib group and 6.4% for the diclofenac-omeprazole group (not statistically different). Similarly, of the 260 patients who were not taking ASA, the six-month probability of recurrent bleeding was 4.5% for the celecoxib group and 5.6% for the diclofenac-omeprazole groups (not statistically different). The authors concluded that the two strategies for recurrent ulcer prevention were equivalent. The annual incidence of NSAID-related ulcer bleeding in this study, however, was high at nearly 10 per 100 person-years. For comparison, the MUCOSA study found a six-month incidence of ulcer complications of 9% in high risk patients taking standard NSAIDs without prophylaxis.

c) Symptoms and treatment withdrawals

1. Treatment withdrawals due to GI side effects: COX-2 selective versus non-selective NSAIDs: The results of comparisons of treatment withdrawals due to side effects (i.e., all side effects or GI side effects only) between COX-2 selective NSAIDs and non-selective NSAIDs are summarized in Table 1. In the previous Cochrane Collaboration meta-analysis, treatment withdrawals due to GI symptoms were the most reliably reported endpoint. Fifteen studies (12 low-dose, two high-dose and one low- plus high-dose) with a total of 49,706 patients assessed this endpoint. Overall, low- or high-dose COX-2 selective NSAIDs reduced the RR of treatment withdrawals due to GI side effects by 27% (RR=0.73; 95% CI: 0.69 to 0.79). This result is driven by the low-dose studies (Table 1).

2. Treatment withdrawals due to GI side effects: COX-2 selective NSAIDs versus placebo: Among eight studies using low- or high-dose COX-2 selective NSAIDs (4,478 patients), there was a slight but not statistically significant increased risk of treatment withdrawals due to GI side effects when compared with placebo (Table 1; RR=1.35; 95% CI: 0.83 to 2.20).
Table 1: Treatment withdrawals and symptoms: COX-2 selective NSAIDs versus non-selective NSAIDs or placebo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Outcome</th>
<th>COX-2 Selective NSAID Versus</th>
<th>COX-2 Selective NSAID Dose</th>
<th>Number of Studies</th>
<th>Number of Patients</th>
<th>RR</th>
<th>95% CI</th>
<th>ARR (%)</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>L and H</td>
<td></td>
<td>22</td>
<td>44,840</td>
<td>0.81*</td>
<td>0.73 to 0.90</td>
<td>2</td>
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<td>Withdrawals</td>
<td>Side effects</td>
<td>NSAID</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GI side effects</td>
<td></td>
<td>L</td>
<td>13</td>
<td>33,444</td>
<td>0.71*</td>
<td>0.65 to 0.77</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>GI side effects</td>
<td></td>
<td>H</td>
<td>3</td>
<td>16,487</td>
<td>0.78*</td>
<td>0.67 to 0.86</td>
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<tr>
<td></td>
<td>GI side effects</td>
<td></td>
<td>L and H</td>
<td>15</td>
<td>49,706</td>
<td>0.73*</td>
<td>0.69 to 0.79</td>
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<td>No</td>
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<tr>
<td></td>
<td>Side effects</td>
<td>Placebo</td>
<td>L</td>
<td>13</td>
<td>6,311</td>
<td>1.13</td>
<td>0.91 to 1.40</td>
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<td>Side effects</td>
<td></td>
<td>H</td>
<td>6</td>
<td>1,863</td>
<td>1.62*</td>
<td>1.16 to 2.25</td>
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<td></td>
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<td></td>
<td>L and H</td>
<td>8</td>
<td>4,478</td>
<td>1.35</td>
<td>0.83 to 2.20</td>
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<tr>
<td>Symptoms</td>
<td>Side effects</td>
<td>NSAID</td>
<td></td>
<td></td>
<td></td>
<td>0.95</td>
<td>0.90 to 1.0</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>GI side effects</td>
<td></td>
<td>L</td>
<td>14</td>
<td>36,564</td>
<td>0.75*</td>
<td>0.72 to 0.78</td>
<td>5</td>
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</tr>
<tr>
<td></td>
<td>GI side effects</td>
<td></td>
<td>H</td>
<td>2</td>
<td>8,411</td>
<td>0.85*</td>
<td>0.80 to 0.90</td>
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<td></td>
<td>Dyspepsia</td>
<td></td>
<td>L</td>
<td>10</td>
<td>35,214</td>
<td>0.75*</td>
<td>0.64 to 0.88</td>
<td>2</td>
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</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td></td>
<td>H</td>
<td>2</td>
<td>8,411</td>
<td>0.89*</td>
<td>0.81 to 0.99</td>
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<tr>
<td></td>
<td>Abdominal pain</td>
<td></td>
<td>L</td>
<td>11</td>
<td>35,567</td>
<td>0.63*</td>
<td>0.52 to 0.76</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td></td>
<td>H</td>
<td>3</td>
<td>8,756</td>
<td>0.75*</td>
<td>0.67 to 0.85</td>
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<tr>
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<td>Nausea</td>
<td></td>
<td>L and H</td>
<td>12</td>
<td>43,490</td>
<td>0.74*</td>
<td>0.68 to 0.81</td>
<td>1</td>
<td>No</td>
</tr>
</tbody>
</table>

*statistically significant
L=low
H=high
3. Symptoms: As described in the Cochrane Collaboration review of NSAID prophylaxis,\textsuperscript{7} the reporting of drug-related symptoms and side effects varied and was often associated with significant heterogeneity. This is partly due to the fact that there is overlap in clinicians’ definitions of dyspepsia, heartburn, indigestion and abdominal pain. Results of the symptom analyses are presented in Table 1.

5 Discussion

Prophylactic Gastroprotective Therapy

Misoprostol is the only prophylactic agent to date that has been evaluated in a true clinical outcome trial. It has been shown to reduce the risk of NSAID-related clinical ulcer complications including bleeding, perforation or hemorrhage. Misoprostol reduces the risk of these events by 51\% (OR=0.487, 95\% CI: 0.268 to 0.886), which represents a 0.38\% ARR. H\(_2\)RAs at standard doses are ineffective at reducing the incidences of endoscopic gastric ulcers. Double doses of H\(_2\)RAs are effective at reducing the occurrence of endoscopic gastric and duodenal ulcers. PPIs are effective at healing NSAID-induced ulcers, despite continued use of the offending NSAIDs. They are also effective at preventing NSAID-induced endoscopic ulcers. Misoprostol, however, may be more effective than PPIs at reducing the risk of NSAID-induced gastric ulcers. Unfortunately, misoprostol is associated with a significant rate of side effects, such as abdominal pain and diarrhea, which are dose-dependent. Hence, at doses shown to be effective at reducing clinically important events, misoprostol is associated with the highest rate of side effects, thus limiting its clinical usefulness.

COX-2 Selective NSAIDs

The results of this meta-analysis demonstrate that COX-2 selective NSAIDs overall are associated with a significant reduction in endoscopic gastric, duodenal and gastroduodenal ulcers when compared with non-selective NSAIDs. The benefit of COX-2 selective NSAIDs seems to be greatest for gastric ulcers. From a GI toxicity perspective, COX-2 selective NSAIDs are safer than naproxen and high-dose ibuprofen. They are better tolerated than NSAIDs in general.

Based on our stratified analyses, rofecoxib was superior to naproxen for POBs and PUBs,\textsuperscript{56} whereas for POBs, celecoxib failed to show a statistically significant benefit over diclofenac and ibuprofen combined or diclofenac alone.\textsuperscript{58} Meloxicam does not show statistically significant benefits over either piroxicam or diclofenac for POBs (RR: 0.50, 95\% CI: 0.22 to 1.17) or PUBs (RR: 0.53, 95\% CI: 0.26 to 1.05). No head-to-head comparisons of the COX-2 selective NSAIDs could be found.

COX-2 selective NSAIDs may not be a different “class” of agents. They may represent a continuum of agents that include the “standard NSAIDs” but with differing GI toxicities and COX-2 selectivities. Based on the results of this review, it cannot be assumed that because a given COX-2 selective NSAID is safer than a specific non-selective NSAID, these data can be extrapolated to mean that COX-2 selective NSAIDs are safer than all non-selective NSAIDs in general (e.g. diclofenac).
Concerns exist about the co-administration of COX-2 selective NSAIDs and ASA. These are based on the apparent absence of any benefit of celecoxib over non-selective NSAIDs when celecoxib was used with ASA in the CLASS study. Also, there are no data regarding the co-administration of rofecoxib and ASA, since patients requiring ASA were excluded from the VIGOR trial. Since COX-2 selective NSAIDs have little anti-platelet effects, the co-administration of ASA with these agents is inevitable in patients with an indication for low-dose ASA. These preliminary concerns will need to be corroborated by the results of ongoing studies. Finally, one Chinese study shows that using a COX-2 selective NSAID (celecoxib) for recurrent ulcer prevention may be equivalent to combining a non-selective NSAID (diclofenac) with a PPI (omeprazole), although these results need to be confirmed in a North American or European population.

6 Conclusion

- Misoprostol reduces the risk of endoscopic gastric and duodenal NSAID-induced ulcers.
- Misoprostol is also the only gastroprotective agent to date that has been evaluated in a true clinical outcome trial and has been shown to reduce the risk of NSAID-related ulcer complications. Its use, however, is associated with significant adverse effects, particularly at higher doses.
- PPIs and double doses of H2RAs are both effective at reducing the risk of endoscopic gastric and duodenal NSAID-induced ulcers and are well tolerated. Misoprostol, however, may be more effective than PPIs at reducing the risk of NSAID-induced gastric ulcers.
- Standard doses of H2RAs are ineffective at reducing the risk of NSAID-induced endoscopic gastric ulcers.

From a GI toxicity perspective, COX-2 selective NSAIDs are safer than naproxen and high-dose ibuprofen; and are better tolerated than non-selective NSAIDs in general. However, we found no significant difference between the COX-2 selective NSAIDs that we considered and diclofenac, so COX-2 selective NSAIDs may not be a different “class” of agents. They may represent a continuum of agents that include the “standard NSAIDs” but with differing GI toxicities and COX-2 selectivity. Showing a superior GI safety profile over one non-selective NSAID does not automatically imply that a given COX-2 selective NSAID is safer than all non-selective NSAIDs. As a result, the characteristics and COX-2 selectivity of the non-selective NSAID comparator should be considered when evaluating the relative safety of COX-2 selective NSAIDs.

Since COX-2 selective NSAIDs have little anti-platelet effects, the co-administration of ASA with these agents is inevitable in patients who need low-dose ASA and raises significant concerns. These preliminary concerns will need to be confirmed by the results of ongoing studies. They are based on the apparent absence of any benefit of celecoxib over non-selective NSAIDs when ASA is co-administered with celecoxib in the CLASS study; and on the absence of data regarding the co-administration of rofecoxib and ASA, since patients requiring ASA are excluded from the VIGOR trial.

Lastly, the benefit of the growing clinical use of COX-2 selective NSAIDs with gastroprotective agents remains untested.
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