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Prevention of NSAID-induced gastroduodenal ulcers (Review)

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Prevention of NSAID-induced gastroduodenal ulcers.
Cochrane Database of Systematic Reviews 2002, Issue 4. Art. No.: CD002296.
DOI: [10.1002/14651858.CD002296](https://doi.org/10.1002/14651858.CD002296).

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Prevention of NSAID-induced gastroduodenal ulcers (Review)

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[Intervention Review]

Prevention of NSAID-induced gastroduodenal ulcers

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Editorial group: Cochrane Gut Group.

Publication status and date: Edited (no change to conclusions), published in Issue 10, 2021.

Citation: Rostom A, Dube C, Wells GA, Tugwell P, Welch V, Jolicoeur E, McGowan J, Lanas A, Rushton E, Shukla T. Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No.: CD002296. DOI: [10.1002/14651858.CD002296](https://doi.org/10.1002/14651858.CD002296).

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ABSTRACT

Background

Non-steroidal anti-inflammatory drugs (NSAIDs) are important agents in the management of arthritic and inflammatory conditions, and are among the most frequently prescribed medications in North America and Europe. However, there is overwhelming evidence linking these agents to a variety of gastrointestinal (GI) toxicities.

Objectives

To review the effectiveness of common interventions for the prevention of NSAID induced upper GI toxicity.

Search methods

We searched MEDLINE from 1966 to May 2009, Current Contents for six months prior to May 2009, EMBASE to May 2009, and the Cochrane Controlled Trials Register from 1973 to May 2009. Recent conference proceedings were reviewed and content experts and companies were contacted.

Selection criteria

Randomized controlled clinical trials (RCTs) of prostaglandin analogues (PA), H₂-receptor antagonists (H₂RA) or proton pump inhibitors (PPI) for the prevention of chronic NSAID induced upper GI toxicity were included.

Data collection and analysis

Two independent authors extracted data regarding population characteristics, study design, methodological quality and number of participants with endoscopic ulcers, ulcer complications, symptoms, overall drop-outs, drop outs due to symptoms. Dichotomous data were pooled using RevMan 5.0. Heterogeneity was evaluated using a chi square test, and the I square statistic.

Main results

Forty-one RCTs met the inclusion criteria. All doses of misoprostol significantly reduced the risk of endoscopic ulcers. Misoprostol 800 ug/day was superior to 400 ug/day for the prevention of endoscopic gastric ulcers (RR 0.17, and RR 0.39 respectively, P=0.0055). A dose response relationship was not seen with duodenal ulcers. Misoprostol caused diarrhoea at all doses, although significantly more at 800 ug/day than 400 ug/day (P=0.0012). Misoprostol also reduced the risk of clinical ulcer complications.

Standard doses of H2RAs were effective at reducing the risk of endoscopic duodenal (RR 0.36; 95% CI 0.18 to 0.74) but not gastric ulcers (RR 0.73; 95% CI 0.50 to 1.08). Both double dose H2RAs and PPIs were effective at reducing the risk of endoscopic duodenal and gastric ulcers (RR 0.44; 95% CI 0.26 to 0.74) and RR=0.40; 95% CI; 0.32-0.51 respectively for gastric ulcer), and were better tolerated than misoprostol.

Authors' conclusions

Misoprostol, PPIs, and double dose H2RAs are effective at preventing chronic NSAID related endoscopic gastric and duodenal ulcers. Lower doses of misoprostol are less effective and are still associated with diarrhoea. In patients with previous NSAID bleeds, a COX-2 inhibitor alone is equivalent to a tNSAID+PPI, though the re-bleeding rates with both strategies are still relatively high. A strategy of a COX-2 inhibitor +PPI appears to offer the greatest GI safety in high risk patients.

PLAIN LANGUAGE SUMMARY

Medications to prevent NSAID-induced gastroduodenal ulcers

The results of this meta-analysis demonstrate that misoprostol, proton pump inhibitors, and double doses of H2-receptor antagonists are effective at reducing the risk of both gastric and duodenal non steroidal anti-inflammatory (NSAID) medications induced ulcers. In high risk patients, the use of a traditional NSAID + PPI appears equivalent to a COX-2 inhibitor alone. The most effective strategy in high risk GI patients appears to be the combination of a COX-2 inhibitor + PPI.

BACKGROUND

Description of the condition

Non-steroidal anti-inflammatory drugs (NSAIDs) are important agents in the management of arthritic and inflammatory conditions, and are among the most frequently prescribed medications in North America and Europe (Fries 1990; Wallace 1996). However, there is overwhelming evidence linking these agents to a variety of gastrointestinal (GI) toxicities (Fries 1990; Stalnikowicz 1993; Smalley 1996; Fries 1991; Griffin 1988; Bollini 1992; McMahon 1997; Gabriel 1991; Langman 1994; MacDonald 1997; Armstrong 1987; Silverstein 1995). Common side effects such as nausea and dyspepsia correlate poorly with serious adverse GI events (Silverstein 1995; Larkai 1987). While endoscopic ulcers can be documented in up to 40% of chronic NSAID users (Stalnikowicz 1993), it is estimated that as many as 85% of these never become clinically apparent (Silverstein 1995; Maetzel 1998). Serious NSAID induced GI complications such as haemorrhage, perforation or death are much less common, occurring collectively with an incidence of about 1.5% per year (Silverstein 1995). However, the number of individuals prescribed NSAIDs and the potential for life-threatening adverse events make NSAID toxicity an important clinical and economic problem.

Description of the intervention

In the late 1990s, evidence from non-clinical and early clinical trials suggested that the gastrointestinal (GI) safety of the newer cyclooxygenase-2 (COX-2) selective NSAIDs may be such that a fundamental change in clinicians' choice from the use of standard NSAIDs with a gastro-protective agent to monotherapy with a COX-2 selective NSAID (COX-2 inhibitors) was on the horizon.

However, much has changed since then in the NSAID field. The release of the cyclo-oxygenase-2 selective inhibitors (COX-2s) brought about significant changes in the NSAID market place. Traditional nonselective NSAIDs (tNSAIDs) prescription numbers fell rapidly, to be replaced by COX-2 prescriptions. Additionally, overall NSAID prescriptions rose in number suggesting that clinicians were starting COX-2s on patients who were not considered candidates for tNSAIDs. The rise of COX-2s continued until 2004 when greater data regarding their cardiovascular and other toxicities became available, leading to the withdrawal of most of these agents from the market over the following years. Non-naproxen tNSAIDs were also suggested to have important cardiovascular toxicity, leading to considerable uncertainty amongst clinicians treating patients with arthritis and other pain disorders as to the choice of agent to use (Rostom 2009; Rostom 2009b).

How the intervention might work

NSAIDs are believed to cause gastroduodenal mucosal injury through their inhibition of mucosal prostaglandin production. Prostaglandins promote mucosal integrity through several mechanisms including: maintenance of mucosal blood flow; promoting mucosal bicarbonate formation; promoting mucosal mucus formation; and reducing mucosal acid secretion. Three intervention classes were assessed in this review: misoprostol; H2RAs; and PPIs. H2RAs and PPIs are believed to exert their gastro-protective effects from NSAID gastroduodenal injury through the reduction of gastric acid secretion. Prostaglandin analogues such

as misoprostol are believed to exert their gastro-protection by restoring mucosal prostaglandin effects (Rostom 2004).

Why it is important to do this review

NSAIDs are amongst the most commonly prescribed medications worldwide, and are associated with important gastrointestinal harms. The introduction of COX-2s with their greater GI safety resulted in important declines in tNSAID prescriptions. However, with the discovery of cardiovascular (CVS) and other adverse effects associated with COX-2s, practitioners are returning to prescribing tNSAIDs with a gastro-protective agent in an effort to overcome some of the adverse GI effects of tNSAIDs.

OBJECTIVES

The primary objective of this study was to systematically review the available literature on the effectiveness of the prostaglandin analogue (PA) misoprostol, H2-receptor antagonists (H2RA), and proton pump inhibitors (PPI) for the prevention of NSAID induced upper GI toxicity, among patients requiring chronic NSAID use. The secondary objectives were to review the effect of these agents on NSAID induced GI symptoms, and to assess the relationship between the effectiveness of PAs at various doses and their associated drug induced adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials were eligible for this meta-analysis.

Types of participants

Participants were eligible if they had taken NSAIDs for greater than 3 weeks and were enrolled for the prophylaxis of NSAID-induced ulcers.

Types of interventions

Interventions that were examined include: H2-antagonists, proton pump inhibitors and misoprostol each used for the prophylaxis of NSAID induced gastroduodenal ulcers.

Types of outcome measures

Primary outcomes

For each study, the number of participants with: endoscopic ulcers; ulcer complications (haemorrhage, perforation, pyloric obstruction or death); symptoms (nausea, vomiting, dyspepsia, abdominal pain or diarrhoea); overall drop-outs; and drop outs due to symptoms were identified. Included studies were also classified into primary or secondary prophylaxis trials and by the time periods of outcome measures.

The primary outcomes were:

- endoscopic ulcers (gastric, duodenal and gastroduodenal);
- clinical ulcer complications.

Secondary outcomes

The secondary outcomes were:

- symptoms;
- drop-outs and drop outs due to symptoms

Search methods for identification of studies

Electronic searches

Randomized controlled clinical trials (RCTs) of PA, H2RA or PPIs for the prevention of NSAID induced upper GI toxicity were identified in accordance with published recommendations (Haynes 1994; Hunt 1997). This included identification of articles through electronic databases including originally a MEDLINE search from 1966 to June 2002, Current Contents for 6 months prior to June 2002, EMBASE to May 2002, and a search of the Cochrane Controlled Trials Register from 1973 to 2002. These searches were updated from 2002 to Dec 2004 and then from 2004 to May 2009.

Searching other resources

In addition to update searches by the Cochrane UGPD Group, the search strategy for this review was supplemented on two occasions:

1. for the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) review in 2003;
2. for the Canadian Consensus conference on the use of ASA, NSAIDs, and COX-2 Inhibitors in 2007-2008.

The CCOHTA search Description: A Dialog® OneSearch® on MEDLINE®, ToxFile, EMBASE®, BIOSIS Previews®, Pharmaceutical News Index (PNI)® and Current Contents Search® for published and scientific meeting literature was performed. *The Cochrane Library* was searched separately. The web sites for International Agencies for Health Technology Assessment (INAHTA) web sites, specialized databases (e.g. University of York National Health Service (NHS) Center for Reviews and Dissemination (CRD)) and Conference Papers Index, as well as internet searching (i.e. Google searching), were searched in order to identify health technology assessment reports, meeting abstracts, and other grey literature. Trial registries were searched for ongoing trials. Recent conference proceedings were consulted and content experts and companies were contacted. The reference lists of all potentially relevant articles including reviews were reviewed for the identification of other potential studies. The search strategies used are shown in [Appendix 1](#); [Appendix 2](#); [Appendix 3](#); [Appendix 4](#).

The search strategy used to supplement the Canadian NSAID consensus conference is listed in [Appendix 5](#).

Data collection and analysis

Selection of studies

Study selection was performed in duplicate by two independent authors (AR, CD, VW or EJ). A first level screen to obtain a list of potentially relevant articles was performed by reviewing the titles and abstracts of the search results (Rostom 2000). RCTs of PA, H2RAs or PPIs were considered eligible for inclusion if: these drugs were used for the prevention of NSAID induced upper GI toxicity in adults; the duration of NSAID exposure was 4 weeks or greater (equivalent to > 3 weeks); and endoscopic ulcers were defined as at least 3mm in diameter and/or could be distinguished from erosions based on the authors' description. Studies in healthy volunteers were excluded. Double doses of H2RAs were defined as a dose equivalent to or greater than 300mg of ranitidine twice daily.

Data extraction and management

Data extraction was performed independently by two authors (AR,CD, VW, or EJ), with a standardized data extraction sheet. Differences were resolved by consensus.

Assessment of risk of bias in included studies

Studies included in the review were independently assessed for quality by two authors (AR, CD, VW) using a validated quality instrument (Jadad 1996). This instrument rates studies on 3 domains: randomisation; blinding; and completeness of follow-up accounting. Additionally the studies were assessed for the adequacy of allocation concealment. Differences in ratings were resolved by consensus.

Measures of treatment effect

The dichotomous outcomes were analysed with Metaview 5, using the Mantel-Haenszel relative risk (Greenland 1985) using a fixed effects model. The risk difference is also presented. A global chi Square test (1 degree of freedom) was used to assess the difference between the estimated adjusted relative risk (RR) for high and low dose misoprostol.

Unit of analysis issues

The primary analysis unit was the proportion of participants with an outcome over the total number of participants in the group. Mantel-Haenszel relative risks were calculated for treatment groups compared to control. No serious analysis issues arose.

Dealing with missing data

Reporting of a primary outcome was an inclusion criteria of this review. However, some studies did not report on all primary endpoints or all secondary outcomes. In those cases, the studies were used in the analyses of the endpoints they reported. For each endpoint, the studies contributing to the analysis and the total number of participants are indicated in the text. In some cases, missing data could be estimated from survival graphs, or could be calculated by straight forward estimates (e.g. total ulcers from individual reporting of gastric and duodenal ulcer data).

Assessment of heterogeneity

Heterogeneity was tested using a Chi-square test with (N-1) degrees of freedom, where N equals the number of trials contributing data. A P value of less than 0.10 was considered evidence of statistical heterogeneity. Additionally, heterogeneity was deemed to be present if the I square statistic was greater than 50%. Efforts were made *a priori* to reduce clinical and statistical heterogeneity by subdividing analyses by intervention class; dose of intervention used when available; and study durations. Analyses demonstrating heterogeneity were presented using a random effects model only if clinically and statistically appropriate.

Assessment of reporting biases

The presence of publication bias was explored through the use of an inverted funnel plot (studies' effect size vs sample size). A review can be biased if small negative studies are not considered because these studies are often not published. Heterogeneity was tested using a chi square test at an alpha of 0.10, and represented graphically with a L'Abbe plot (L'Abbe 1987). Estimates

of heterogeneous data were obtained using a random effects model (DerSimonian 1986) only if clinically and statistically appropriate.

Data synthesis

Data were analysed using Review Manager (RevMan) version 5.0. Endoscopic, clinical and symptom-based outcomes were analysed separately. The primary analyses were expressed as relative risks using a fixed effects model. A random-effects model was used to combine 'heterogeneous trials' only if it was clinically and statistically appropriate. The absolute risk reduction (ARR) and the number needed to treat (NNT) were calculated for appropriate clinical endpoints.

Subgroup analysis and investigation of heterogeneity

In addition to dividing the data by the intervention and the specific outcome under study, subgroup analyses were performed by the dosages of the intervention used, and the length of follow-up.

Sensitivity analysis

Sensitivity analyses were performed by: the study quality, with the median quality score used as the cut off to define lower and higher quality studies; and by primary vs secondary prophylaxis trials. In the first version of the review, a sensitivity analysis varying the obtained point estimates from efficacy to intention to treat was performed and did not have a significant effect on the estimates. This analysis was not repeated in the updates to the review.

Summary of findings and assessment of the certainty of the evidence

Summary of findings tables and assessments of the certainty of the evidence were not completed for this review.

RESULTS

Description of studies

Thirty-nine RCTs met the inclusion criteria: 23 misoprostol trials; 12 H2RA; and 9 PPI trials. Some studies considered more than one active intervention and seven studies were used for head to head comparisons. See [Characteristics of included studies](#) for a summary of included studies.

A description of the search result updates over time from the original review is detailed below.

Results of the search

Original Cochrane Search Strategy results

Of a total of 970 references identified in the first review, 33 RCTs met the inclusion criteria: 18 misoprostol trials; nine standard dose H2RA; three double dose H2RA trials; and four PPI trials. (See [Rostom 2000](#)).

At the July 2001 update, four potentially relevant articles were found by repeating the electronic searches and reviewing conference proceedings. Of these, two fulfilled the inclusion criteria (misoprostol [Bocanegra 1998](#); 1 PPI-misoprostol abstract [Jensen 2000](#)).

CCOHTA Search Strategy Results (2002)

The updated search identified for tNSAIDs and COX-2s identified 898 references. Of 241 potentially relevant papers, three new studies met the inclusion criteria for this review: two PPI papers ([Graham 2002](#); [Bianchi Porro 2000](#)); and two misoprostol papers ([Graham 2002](#); [Chan 2001a](#)). The Graham study considered two interventions.

Updated Cochrane Searches

An updated search in August 2003 and August 2004 did not reveal any further new studies.

The Cochrane search was updated from 2004 to May 2009. The MEDLINE search identified 235 articles with ten potentially relevant studies ([Desai 2008](#); [Goldstein 2007](#); [Chan 2007](#); [Lanas 2007](#); [Regula 2006](#); [Scheiman 2006](#); [Goldstein 2005](#); [Lai 2005](#); [Miyake 2005](#); [Hawkey 2005](#); [Chan 2004b](#)). While some of these papers provided supporting evidence, none met the inclusion criteria. The EMBASE search identified 549 articles and only identified eight of the eleven potentially relevant studies identified by MEDLINE. Similarly, out of 41 articles identified in the EBM search, only four of the potentially relevant studies were identified. The non-MEDLINE searches did not identify studies that were not identified by MEDLINE. While the [Chan 2004](#) paper did not meet inclusion criteria, the results are presented in the PPI section as indirect evidence.

Canadian Consensus Conference Search Strategy identified two additional studies not identified in the previous searches ([Stupnicki 2003](#); [Lai 2003](#)).

Included studies

See [Characteristics of included studies](#). Thirty-nine studies were included in the review: 23 misoprostol studies (includes six head to head); twelve H2RA trials (nine standard dose; three double dose; one head to head); and nine PPI trials (six direct; five head to head). Some studies considered more than one intervention. All the included studies were RCTs in participants with arthritis who were taking traditional NSAIDs in an outpatient setting.

Excluded studies

See [Characteristics of excluded studies](#). The most common reasons for exclusions were: short term studies <4 weeks; studies not reporting on desired outcomes; studies that were not RCTs.

Risk of bias in included studies

Methodological quality was assessed by two independent authors (AR, VW or EJ) using Jadad's scale ([Jadad 1996](#)) with consideration of allocation concealment. Differences were resolved by consensus. A third reviewer was consulted to resolve any disagreements (CD).

The table of included studies details the Jadad score for the included studies. The majority of the studies were of reasonable quality with a Jadad score of three or greater (20 studies - Q3; ten studies - Q4; two studies Q5). Nine studies received a Jadad Score of two or less.

Allocation

The quality of allocation concealment was unclear in the majority of the included studies.

Blinding

All the included studies were blinded.

Incomplete outcome data

All the included studies reported on one of the primary endpoints (endoscopic ulcer; or clinical ulcer complication).

Selective reporting

The inverted funnel plot reveals a lack of small studies of misoprostol with small effect sizes, suggesting the potential of

publication bias ([Rostom 2000](#)) (please see [Figure 1](#)). However, using the method described by Rosenthal, there would have to be 60 one-month, and 300 three-month small studies averaging null findings to negate the statistically significant reduction in endoscopic gastric ulcers observed with misoprostol ([Rosenthal 1979](#)). The symmetrical distribution of studies of H2RAs suggests the absence of publication bias. Six PPI trials were identified showing similar distribution as seen with misoprostol ([Figure 2](#)).

Figure 1. Funnel plot of comparison: 1 misoprostol vs placebo - Primary Efficacy, outcome: 1.6 Total endoscopic ulcers - 12 weeks or longer studies.

Figure 2. Funnel plot of comparison: 11 PPI vs placebo - 8 weeks or longer studies, outcome: 11.3 Total endoscopic ulcers.

Other potential sources of bias

The observed heterogeneity, based on the estimates for gastric ulcers, is represented graphically (L'Abbe 1987) (see Rostom 2000). Significant heterogeneity was seen only for the three month duodenal ulcer pooled estimate with misoprostol. This disappeared when the studies were grouped by misoprostol dose.

Effects of interventions

Misoprostol

We found twenty-three studies that assessed the long term effect of misoprostol on the prevention of NSAID ulcers (Graham 2002; Chan 2001a; Hawkey 1998; Bocanegra 1998; Raskin 1996; Agrawal 1995; Raskin 1995; Valentini 1995; Delmas 1994; Elliot 1994; Graham 1993; Henriksson 1993; Melo Gomes 1993; Roth 1993; Bolten 1992; Verdickt 1992; Agrawal 1991; Chandresekaran 1991; Saggiaro 1991; Graham 1988; Jensen 2000; Silverstein 1995; Stupnicki 2003). Some of these were head to head studies.

Endoscopic ulcers

Eleven studies with 3,641 participants compared the incidence of endoscopic ulcers, after at least three months, of misoprostol to that of placebo (Graham 2002; Chan 2001a; Hawkey 1998; Agrawal 1995; Raskin 1995; Elliot 1994; Graham 1993; Roth 1993; Verdickt 1992; Agrawal 1991; Graham 1988). The cumulative incidence of endoscopic gastric and duodenal ulcers with placebo were 15% and 6% respectively. Misoprostol significantly reduced the relative

risk of gastric ulcer and duodenal ulcers by 74% (RR 0.26; 95% CI 0.17 to 0.39, random effects; Analysis 1.4), and 58% (RR 0.42; 95% CI 0.22 to 0.81, random effects; Analysis 1.5). These relative risks correspond to a 12.0%, and 3% absolute risk reductions for gastric and duodenal ulcers respectively. The observed heterogeneity in these estimates was due to inclusion of all misoprostol doses in the analyses. Analysis of the misoprostol studies stratified by dose eliminated this heterogeneity.

Analysis by dose

All the studied doses of misoprostol significantly reduced the risk of endoscopic ulcers, and a dose response relationship was demonstrated for endoscopic gastric ulcers. Six studies with 2,461 participants used misoprostol 400 µg (Chan 2001a; Hawkey 1998; Agrawal 1995; Raskin 1995; Verdickt 1992; Graham 1988), one study with 928 participants used 600 µg daily (Raskin 1995), and seven with 2,423 participants used 800 µg daily (Graham 2002; Raskin 1995; Elliot 1994; Graham 1993; Roth 1993; Agrawal 1991; Graham 1988). Misoprostol 800 µg daily was associated with the lowest risk (RR 0.18; 95% CI 0.12 to 0.27; Analysis 4.4) of endoscopic gastric ulcers when compared to placebo, whereas misoprostol 400 µg daily was associated with a relative risk of (RR 0.43; 95% CI 0.28 to 0.67, random effects model for heterogeneity; Analysis 4.4). The observed heterogeneity in the 400 µg dose group was the result of the addition of the Chan study (Chan 2001a). This study compared the relatively more toxic naproxen with low dose misoprostol to nabumatone alone. In this study the risk of ulcers

was inexplicably greater in the misoprostol group, but we feel this result is based on the differences between the safety of the comparator NSAIDS rather than the prophylactic agent. As a sensitivity analysis, removal of the [Chan 2001a](#) study eliminates the observed heterogeneity without significantly altering the results, giving low dose misoprostol prophylaxis a RR of 0.39 (95% CI 0.3 to 0.51; [Analysis 4.5](#)). This difference between high and low dose misoprostol reached statistical significance ($P=0.0055$). The intermediate misoprostol dose (600 µg daily) was not statistically different from either the low or high dose. The pooled relative risk reduction of 78% (4.7% absolute risk difference, (RR 0.21; 95% CI 0.09 to 0.49; [Analysis 4.6](#)) for duodenal ulcers with misoprostol 800 µg daily was not statistically different from those of the lower daily misoprostol dosages.

Studies including data with less than 3 months NSAID exposure

Eight studies, with 2206 participants, assessed the rates of endoscopic ulcers with misoprostol compared to placebo at 1 to 1.5 months ([Bocanegra 1998](#); [Delmas 1994](#); [Elliot 1994](#); [Henriksson 1993](#); [Melo Gomes 1993](#); [Bolten 1992](#); [Chandrasekaran 1991](#); [Saggiaro 1991](#)). The pooling of these studies revealed an 81% relative risk reduction of gastric ulcers with misoprostol (RR 0.17; 95% CI 0.09 to 0.31; [Analysis 1.1](#)) and an 70% relative risk reduction of duodenal ulcers (RR 0.30; 95% CI 0.14 to 0.62; [Analysis 1.2](#)).

One study compared misoprostol to a newer cytoprotective agent, Dosmafate, for NSAID prophylaxis and found no statistically significant difference in ulcer rates between the two agents ([Cohen 2000](#)).

Clinical Ulcers

Only one RCT, the MUCOSA trial, evaluated the efficacy of misoprostol prophylaxis against clinically important NSAID induced ulcer complications. In this study, of 8,843 participants studied over six months, the overall GI event incidence was about 1.5% per year ([Silverstein 1995](#)). Misoprostol 800 µg/day was associated with a statistically significant 40% risk reduction (OR 0.598; 95% CI 0.364 to 0.982) in combined GI events ($P=0.049$), representing a risk difference of 0.38% (from 0.95% to 0.57%). Overall, approximately 260 participants would have to be treated with misoprostol to prevent one clinically important GI event. This NNT would drop as higher risk participants are considered. Misoprostol appeared to be ineffective at preventing endoscopically proven GI haemorrhage alone. However a type II error is likely since the study was not powered to detect a difference in this endpoint ([Silverstein 1995](#)).

Adverse Effects

Misoprostol was associated with a small but statistically significant 1.6 fold excess risk of drop out due to drug induced side effects, and an excess risk of drop-outs due to nausea (RR 1.26; 95% CI 1.07 to 1.48; [Analysis 2.1](#)), diarrhoea (RR 2.36; 95% CI 2.01 to 2.77; [Analysis 2.4](#)), and abdominal pain (RR 1.36; 95% CI 1.20 to 1.55; [Analysis 2.5](#)). In the MUCOSA trial, 732 out of 4404 participants on misoprostol experienced diarrhoea or abdominal pain, compared to 399 out of 4,439 on placebo for a relative risk of 1.82 associated with misoprostol ($p<0.001$). Overall, 27% of participants on misoprostol experienced one or more side-effects ([Silverstein 1995](#)).

When analysed by dose, only misoprostol 800 µg daily showed a statistically significant excess risk of drop-outs due to diarrhoea (RR 2.45; 95% CI 2.09 to 2.88; [Analysis 5.4](#)), and abdominal pain (RR 1.38; 95% CI 1.17 to 1.63; [Analysis 5.5](#)). Both misoprostol doses were associated with a statistically significant risk of diarrhoea. However, the risk of diarrhoea with 800µg/day (RR 3.16; 95% CI 2.33 to 4.29) was significantly higher than that seen with 400 µg/day (RR 1.76 95% CI 1.37 to 2.26) ([Analysis 6.4](#)).

Analyses by Quality

Both high and low quality misoprostol trials demonstrated a statistically significant reduction of endoscopic ulcers.

H2-Receptor Antagonists

Six trials with 942 participants assessed the effect of standard dose H2RAs on the prevention of endoscopic NSAID ulcers at one month ([Berkowitz 1987](#); [Ehsanullah 1988](#); [Robinson 1991](#); [Robinson 1989](#); [Taha 1996](#); [van Groenendaci 1996](#)), and five trials with 1,005 participants assessed these outcomes at 3 months or longer ([Ehsanullah 1988](#); [Taha 1996](#); [Levine 1993](#); [Swift 1989](#); [Simon 1994](#)). Standard dose H2RAs are effective at reducing the risk of duodenal ulcers (RR 0.24; 95% CI 0.10 to 0.57; [Analysis 7.2](#), and RR 0.36; 95% CI 0.18 to 0.74; [Analysis 8.2](#) at one and three or more months respectively), but not of gastric ulcers (NS). One study did not have a placebo comparator and was not included in the pooled estimate ([Simon 1994](#)).

Three RCTs with 298 participants assessed the efficacy of double dose H2RAs for the prevention of NSAID induced upper GI toxicity ([Taha 1996](#); [Hudson 1997](#); [Ten Wolde 1996](#)). Double dose H2RAs when compared to placebo were associated with a statistically significant reduction in the risk of both duodenal (RR 0.26; 95% CI 0.11 to 0.65; [Analysis 8.2](#)) and gastric ulcers (RR 0.44; 95% CI 0.26 to 0.74; [Analysis 8.1](#)). This 56% relative risk reduction in gastric ulcer corresponds to a 12% absolute risk difference (from 23.1% to 11.3%). Analysis of the secondary prophylaxis studies alone yielded similar results.

Symptoms

H2RAs, in standard or double doses, were not associated with an excess risk of total drop-outs, dropouts due to side-effects, or symptoms when compared to placebo. However, high dose H2RAs significantly reduced symptoms of abdominal pain when compared to placebo (RR 0.57; 95% CI 0.33 to 0.98) [Analysis 9.7](#)).

Analyses by Quality

In contrast to high quality trials, low quality trials failed to demonstrate a benefit of standard dose H2RAs for the prevention of endoscopic duodenal ulcers. No significant differences were observed by quality for dropouts and symptoms.

Proton Pump Inhibitors

Six RCTs with 1259 participants assessed the effect of PPIs on the prevention of NSAID induced upper GI toxicity ([Graham 2002](#); [Bianchi Porro 2000](#); [Hawkey 1998](#); [Ekstrom 1996](#); [Cullen 1998](#); [Lai 2003](#)).

PPIs compared to placebo

PPIs significantly reduced the risk of both endoscopic duodenal (RR 0.20; 95% CI 0.10 to 0.39; [Analysis 11.2](#)) and gastric ulcers (RR 0.39;

95% CI 0.31 to 0.50; [Analysis 11.1](#)) compared to placebo ([Bianchi Porro 2000](#); [Cullen 1998](#); [Ekstrom 1996](#); [Graham 2002](#); [Hawkey 1998](#); [Lai 2003](#)). The results were similar for both primary and secondary prophylaxis trials.

Clinical Ulcers

Small studies in relatively high risk participants have emerged that suggest that PPIs can reduce the risk of clinically important ulcer complications. A small 8 week study found that PPIs reduce the risk of endoscopic ulcers but there were also fewer bleeds or symptomatic ulcers in the PPI group compared to placebo ([Lai 2003](#)).

Another study which did not meet the inclusion criteria has shown that a strategy of a COX-2 alone is associated with similar rebleeding rates as a strategy of a tNSAID with a PPI ([Chan 2004b](#)). Several studies have shown that COX-2 inhibitors reduce the risk of clinically important ulcer complications ([Rostom 2007](#)), therefore suggesting that a strategy of a tNSAID with a PPI also reduces the risk of clinical ulcer complications. However, the rate of rebleeding in this study was relatively high suggesting that in high risk participants, neither strategy was sufficient.

Symptoms

Four omeprazole trials used the same composite endpoints to define treatment success ([Cullen 1998](#); [Ekstrom 1996](#); [Hawkey 1998](#); [Yeomans 1998](#)). In these trials omeprazole significantly reduced "dyspeptic symptoms" as defined by the authors. In the combined analysis, drop-outs overall and drop-outs due to side effects were not different from placebo. These results are also supported by a recent study by Hawkey et al that reported statistically significant improvement in dyspeptic symptoms in NSAID participants taking esomeprazole compared to placebo ([Hawkey 2005](#)).

Analyses by Quality

No significant differences were observed with analysis by quality.

Head to Head Comparisons

Misoprostol vs ranitidine

Two trials with 600 participants compared misoprostol to ranitidine 150 mg twice daily ([Raskin 1995](#); [Valentini 1995](#)). Misoprostol appears superior to standard dose ranitidine for the prevention of NSAID induced gastric ulcers (RR 0.12; 95% CI 0.03 to 0.51; [Analysis 18.1](#)) but not for duodenal ulcers (RR 1.00; 95% CI 0.14 to 7.05; [Analysis 18.2](#)).

Omeprazole vs ranitidine

Yeomans et. al. in a study of 425 participants, compared omeprazole 20mg daily to ranitidine 150 mg twice daily for NSAID prophylaxis ([Yeomans 1998](#)). In this study, omeprazole was superior to standard dose ranitidine for the prevention of both gastric (RR 0.32; 95% CI 0.17 to 0.62; [Analysis 14.1](#)) and duodenal ulcers (RR 0.11; 95% CI 0.01 to 0.89; [Analysis 14.2](#)).

PPI vs misoprostol

Four trials with a total of 1478 participants ([Graham 2002](#); [Hawkey 1998](#); [Jensen 2000](#); [Stupnicki 2003](#)) compared a PPI to misoprostol. Two studies compared low dose misoprostol (400 µg) daily to a standard dose PPI ([Hawkey 1998](#); [Stupnicki 2003](#)), while the [Graham 2002](#) study compared high dose misoprostol (800 µg) to

lansoprazole 15 or 30 mg daily. PPIs are statistically superior to misoprostol for the prevention of duodenal ulcer (RR 0.25; 95% CI 0.11 to 0.56; [Analysis 16.2](#) ([Hawkey 1998](#))), but not gastric ulcer (RR 1.61; 95% CI 0.85 to 3.06; random effects [Analysis 16.1](#)) ([Hawkey 1998](#); [Graham 2002](#)) or total gastroduodenal ulcers (RR 0.90; 95% CI 0.47 to 1.72, random effects; [Analysis 16.3](#)). Individually the Hawkey trial showed a non-significant trend towards greater benefit with misoprostol over omeprazole for the prevention of gastric ulcers, while the [Graham 2002](#) study actually showed that misoprostol was superior to lansoprazole for the prevention of gastric ulcers. The pooled results mirror these findings but failed to reach statistical significance (RR 0.62; 95% CI 0.33 to 1.18; [Analysis 15.1](#), random effects). These analyses utilized a small number of studies (duodenal -one study; gastric - two studies; total ulcers - four studies) and demonstrated important clinical and statistical heterogeneity likely stemming in part from differences in intervention doses.

Symptoms

In the two head to head comparisons of omeprazole and misoprostol ([Graham 2002](#); [Hawkey 1998](#)), PPIs were associated with significantly less drop-outs overall (RR 0.71; 95% CI 0.52 to 0.97; [Analysis 17.1](#)), as well as significantly less drop-outs due to side-effects (RR 0.48; 95% CI 0.29 to 0.78; [Analysis 17.2](#)). When compared to H2RA used for less than two months, misoprostol caused significantly more drop-outs due to abdominal pain (RR 3.00, 95% CI 1.11, 8.14; [Analysis 18.6](#)) and more symptoms of diarrhoea (RR 2.03, 95% CI 1.38, 2.99; [Analysis 18.12](#)). There were no significant differences in drop-outs due to side-effects (RR 1.90; 95% CI 0.77 to 4.67; [Analysis 14.5](#)) or symptoms of abdominal pain or diarrhoea between low dose H2RAs and PPIs. Misoprostol also appears to be associated with a lower quality of life amongst chronic NSAID users compared to PPIs ([Yeomans 2001](#)).

DISCUSSION

The results of this meta-analysis demonstrate that misoprostol, PPIs, and double doses of H2RAs are effective at reducing the risk of both endoscopic gastric and duodenal NSAID induced ulcers. Standard doses of H2RAs are not effective at reducing the risk of NSAID induced gastric ulcers. Misoprostol is the only prophylactic 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. However, its use is associated with significant adverse effects particularly at higher doses.

It is difficult to comment on the relative efficacy of the different prophylactic agents since the studies involving head to head comparisons often used doses of the comparator drug that are known to be less effective. For example, misoprostol and omeprazole were compared to standard dose ranitidine, and omeprazole was compared to misoprostol 400 µg/day in one study. However, with these limitations in mind, misoprostol was found to be superior to standard dose H2RAs at reducing endoscopic gastric ulcers. Omeprazole was superior to standard dose ranitidine at reducing the risk of both endoscopic gastric and duodenal ulcers. However, omeprazole was superior to misoprostol at reducing the risk of endoscopic duodenal but not gastric ulcers. In fact based on a single study misoprostol appeared superior to lansoprazole for the secondary prevention of NSAID induced gastric ulcers ([Graham 2002](#)). The true clinical implications of this last point is not clear and may be small, but requires further research.

Overall we found that H2RAs and PPIs were better tolerated than misoprostol, and reduced NSAID related dyspeptic symptoms. Unfortunately, the reporting of symptoms and drug induced side effects were variable in these studies, a problem seen in a variety of other clinical trials. For the current review we concentrated on the reporting of side-effects causing drop-out from the studies. We felt that this end-point would be more reliably reported than side-effects alone. The definitions of dyspepsia, and abdominal pain were also variable or not given in these trials, so we combined these as a composite endpoint. The reporting of diarrhoea was more uniform, likely because it is a common side effect of misoprostol, and this end-point was used as a symptom not causing drop-out. Great care was taken in the abstraction and interpretation of the side-effect data, but the variable reporting of these endpoints may be a potential source of bias.

Because misoprostol is associated with more frequent adverse symptoms than the other agents, we also looked at the effect of dose on the efficacy and tolerability of this agent. Misoprostol 800 µg/day is more effective at reducing gastric ulcers than 400 µg/day. However, both 400 µg and 800 µg daily are associated with significantly more diarrhoea than placebo, and the effectiveness of low doses of misoprostol in the reduction of clinical ulcer complications is not well studied. Therefore, the practice of using lower doses of misoprostol to avoid its associated adverse effects should be questioned.

High risk GI patients represent another area of clinical importance. Several strategies have been evaluated in high risk patients with previous GI bleeding (see GI safety of COX-2 review). The studies focused on comparisons of COX-2 inhibitors (COX-2s) alone and in combination with a PPI, and showed that a strategy of a COX-2 alone was similar to a strategy of using a traditional NSAID with a PPI. However, the rate of re-bleeding with both strategies was still relatively high suggesting that neither strategy was completely effective. However, strategy of a COX-2 + PPI was associated with the greatest protection from recurrent re-bleeding (Chan 2004b; Lai 2005; Chan 2007).

A lot has changed in the NSAID field since the last update of this review. In the early 2000s, it appeared that COX-2s were going to completely replace traditional non selective NSAIDs. In fact, prescriptions, and sales of traditional NSAIDs dropped while COX-2 prescriptions rose to level that suggested that physicians were prescribing COX-2s to patients that were not previously treated with NSAIDs. However, by 2004, greater information regarding the cardiovascular (CVS) safety of COX-2s started to emerge. A large systematic review demonstrated that COX-2 were associated with increased risk of CVS events (Kearney 2006). In addition, one COX-2 was found to be associated with a serious dermatologic disorder while another was associated with higher than expected rates of hepatotoxicity. These factors ultimately led to the withdrawal of most of these agents from the market place. In North America, only celecoxib remains. These events, resulted in a precipitous fall in COX-2 prescriptions, with a resurgence in traditional NSAID use along with a gastro-protective agent such as a PPI. However, traditional NSAIDs were not left unscathed. Several lines of data also suggested that non-naproxen NSAIDs were associated with similar CVS toxicity as the COX-2s, further casting confusion amongst clinicians (Kearney 2006; Rostom 2009). Recently several consensus guidelines have been published to help guide clinicians

in their management of patients with arthritic conditions (Rostom 2009; Bhatt 2008; Chan 2008).

The ideal means of reducing the risk of upper GI toxicity among chronic NSAIDs users is complex. Several factors influence the risk of NSAID related upper GI toxicity: increasing age (>65), previous peptic ulcer disease, co-morbid medical illnesses, the type of NSAID, the use of multiple NSAIDs and the combined use of NSAIDs and corticosteroids (Fries 1991; Bollini 1992; Gabriel 1991; Silverstein 1995; Hallas 1995; Hansen 1996; Laporte 1991; Rodriguez 1997; Hochain 1995). Therefore, younger patients without co-morbidities or previous GI NSAID complications can be treated with a traditional NSAID alone (Rostom 2009; Maetzel 1998).

For patients with low gastrointestinal risk and high cardiovascular risk, naproxen may be preferred because of the potentially lower cardiovascular risk than with other tNSAIDs or COX-2 inhibitors. However, since these patients are assumed to be on low-dose ASA therapy, the combination of naproxen plus ASA would increase the gastrointestinal risk, and therefore, the addition of a gastro-protective agent such as a PPI should be considered (Rostom 2009). For patients at very high risk of upper gastrointestinal events, a combination of a COX-2 inhibitor plus a PPI may offer the best gastrointestinal safety profile. When both gastrointestinal and cardiovascular risks are high, the optimal strategy is to avoid NSAID therapy if at all possible. If the NSAID therapy is deemed necessary, then the clinician must prioritise the cardiovascular and gastrointestinal risks, recognizing that these patients are likely taking ASA for their cardiovascular risk and choose a strategy that addresses the clinical profile recognizing, that there would likely be incomplete protection either on the CVS or GI side with a choice of COX-2 + PPI or naproxen + PPI respectively.

Summary of main results

Misoprostol at 800 µg daily reduces the occurrence of NSAID related clinical ulcer complications. Lower doses of misoprostol are associated with fewer side effects of diarrhoea but are less effective at preventing endoscopic gastric ulcers. The effects of low doses of misoprostol on ulcer complications are unknown, so the use of lower doses may be associated with a significant clinical tradeoff. Standard doses of H2RAs should not be used for prophylaxis against NSAID toxicity. Double doses of H2RAs and standard doses of PPIs are effective at preventing endoscopic duodenal and gastric ulcers, reduce NSAID related dyspepsia and are better tolerated than misoprostol. In high risk GI patients, a COX-2 alone or a traditional NSAID + a PPI offer similar but potentially insufficient protection from recurrent bleeding and a COX-2 + PPI can be considered.

Overall completeness and applicability of evidence

This systematic review includes all the published data that we could identify for the long term prevention (four weeks or greater) of tNSAID related gastroduodenal injury. This field rapidly evolved with the introduction of COX-2 inhibitors, but with the recognition of the toxicity of those agents, clinicians are moving back toward using tNSAIDs with gastro-protection. While there is a single large outcome study for the prevention of clinical ulcer events such as bleeding with misoprostol, and multiple such studies for the COX-2 inhibitors, there is less direct evidence for the PPIs. However, there is data that suggests in high risk GI patients who require NSAIDs, a COX-2 alone and a tNSAID with a PPI offer similar protection from recurrent bleeding. No such data exists for H2RAs, and it is

unlikely that a large outcome study with PPIs or H2RAs would now be conducted in average risk arthritic patients requiring long term tNSAID use.

Quality of the evidence

Overall there is good quality evidence for the interventions assessed in this review. There is good quality endoscopic and clinical ulcer outcome data for misoprostol for the prevention of gastroduodenal ulcers and ulcer complications. There is good quality endoscopic data for the prevention of gastroduodenal endoscopically detected ulcers for H2RAs and PPIs. There is new evidence suggesting that PPIs added to tNSAIDs are as effective as the use of COX-2s for the prevention of recurrent bleeding.

Potential biases in the review process

The review was conducted according to standard systematic review methodology.

Agreements and disagreements with other studies or reviews

The results of this systematic review are in agreement with other reviews and with recent consensus guidelines ([Rostom 2009](#); [Bhatt 2008](#); [Chan 2008](#); [Brown 2006](#)).

AUTHORS' CONCLUSIONS

Implications for practice

- Standard doses of H2RAs should not be used for the prevention of NSAID related Upper GI toxicity, since they are ineffective at preventing NSAID related gastric ulcers.
- Double doses of H2RAs and standard doses of PPIs are effective prophylactic agents based on the results of endoscopic studies.
- Misoprostol is an effective NSAID prophylactic agent based on both a clinical outcome study and multiple endoscopic studies, and may be slightly more effective at reducing NSAID induced

gastric ulcers than PPIs - though the true clinical implications of this last point may be small. Misoprostol use is associated with greater adverse effects than the other agents.

- In high risk GI patients, a strategy of a COX-2 inhibitor or a traditional NSAID + a PPI appear to offer similar though insufficient protection from recurrent NSAID ulcer bleeding. A strategy of a COX-2 inh + a PPI offers the greatest GI safety.
- Gastrointestinal and cardiovascular risk stratification should be undertaken and should inform the decision regarding the choice of a gastro-protective strategy.

Implications for research

- Further study is required to better characterize the relative CVS effects of the various traditional NSAIDs and to determine if naproxen in anti-inflammatory doses also requires the addition of low dose ASA for cardioprotection in those with CVS disease. In patients with CVS disease who require ASA, is the use of low dose COX-2+ASA safer than the naproxen + ASA when either is used with a PPI?
- The comparative cost effectiveness of various strategies for the treatment of arthritic patients including standard NSAIDs with or without prophylaxis with the various agents discussed in this review, compared with treatment with COX-2 inhibitors alone and with the inevitable co-prescribing of COX-2 agents and PPIs would greatly assist clinicians and policy makers alike in rationalizing this rapidly changing field.
- Recent evidence regarding potential harms associated with long term PPI therapy such as possible: increased risk of osteoporosis; increased risk of *Clostridium difficile* colitis; and interaction with antiplatelet agent effects need to be reviewed.

ACKNOWLEDGEMENTS

We would also like to thank the Cochrane UGPD group for their assistance and patience and for updating the search strategies.

REFERENCES

References to studies included in this review

Agrawal 1991 {published data only}

Agrawal N, Roth S, Graham D, White R, Germain B, Brown J et al. Misoprostol compared with sucralfate in the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcer: a randomized, controlled trial. *Annals of Internal Medicine* 1991;**115**:195-200.

Agrawal 1995 {published data only}

Agrawal NM, Van KE, Erhardt LJ, Geis GS. Misoprostol coadministered with diclofenac for prevention of gastroduodenal ulcers. A one-year study. *Digestive Diseases & Sciences* 1995;**40**(5):1125-31.

Berkowitz 1987 {published data only}

Berkowitz JM, Rogenes PR, Sharp JT, Warner CW. Ranitidine protects against gastroduodenal mucosal damage associated with chronic aspirin therapy. *Archives of Internal Medicine* 1987;**147**:2137-2139.

Bianchi Porro 2000 {published data only}

Bianchi Porro G, Lazzaroni M, Imbesi V, Montrone F, Santagada T. Efficacy of pantoprazole in the prevention of peptic ulcers, induced by non-steroidal anti-inflammatory drugs: a prospective double blind, parallel-group study. *Digestive and Liver Disease* 2000;**32**(3):201-8.

Bocanegra 1998 {published data only}

Bocanegra TS, Weaver, AL, Tindall EA, Sikes DH, Ball JA, Wallemark CB et al. Diclofenac/misoprostol compared with diclofenac in the of osteoarthritis of the knee or hip: a randomized placebo controlled trial. Arthrosc Osteoarthritis Study Group. *Journal of Rheumatology* 1998;**28**(8):1602-11.

Bolten 1992 {published data only}

Bolten W, Gomes JA, Stead H, Geis GS. The gastroduodenal safety and efficacy of the fixed combination of diclofenac and misoprostol in the treatment of osteoarthritis. *British Journal of Rheumatology* 1992;**31**(11):753-8.

Chan 2001a {published data only}

Chan FKY, Sung JJY, Ching JYL, Wu JCY, Lee YT, Leung WK, et al. Randomized trial of low dose misoprostol and naproxen vs nabumetone to prevent recurrent upper gastrointestinal hemorrhage in users of non-steroidal anti inflammatory drugs. *Alimentary Pharmacology and Therapeutics* 2001;**15**(1):19-24.

Chan 2001b {unpublished data only}

Chan FKL, Leung WK, Suen BY, Lee YT, et al. A double-blinded randomized comparison of celecoxib versus omeprazole and diclofenac for secondary prevention of ulcer bleeding in chronic NSAID users. *Gastroenterology* 2001;**120**(Suppl 1):A-143.

Chan 2004 {published data only (unpublished sought but not used)}

Chan F, Hung L, Suen B, Wong V, Hui A, Wu J et al. Celecoxib versus diclofenac plus omeprazole in high-risk arthritis patients: results of a randomized double-blind trial. *Gastroenterology* 2004;**127**(4):1038-43.

Chandresekaran 1991 {published data only}

Chandrasekaran AN, Sambandam PR, Lal HM, Ramakrishnan S, Porkodi R, Krishnamurthy V et al. Double blind, placebo controlled trial on the cytoprotective effect of misoprostol in subjects with rheumatoid arthritis, osteoarthritis and seronegative spondarthropathy on NSAIDs [see comments]. *Journal of the Association of Physicians of India* 1991;**39**(12):919-21.

Cullen 1998 {published data only}

Cullen D, Bardhan KD, Eisner M, Kogut DG, Peacock RA, Thomson JM, et al. Primary gastroduodenal prophylaxis with omeprazole for non-steroidal anti-inflammatory drug users. *Alimentary Pharmacology & Therapeutics* 1998;**12**(2):135-40.

Delmas 1994 {published data only}

Delmas PD, Lambert R, Capron MH. [Misoprostol in the prevention of gastric erosions caused by nonsteroidal anti-inflammatory agents]. [French]. *Revue du Rhumatisme. Edition Francaise* 1994;**61**(2):126-31.

Ehsanullah 1988 {published data only}

Ehsanullah RS, Page MC, Tildesley G, Wood JR. Prevention of gastroduodenal damage induced by non-steroidal anti-inflammatory drugs: controlled trial of ranitidine. *BMJ* 1988;**297**:1017-21.

Ekstrom 1996 {published data only}

Ekstrom P, Carling L, Wetterhus S, Wingren PE, Anker-Hansen O, Lundegardh G, et al. Prevention of peptic ulcer and dyspeptic symptoms with omeprazole in patients receiving continuous non-steroidal anti-inflammatory drug therapy. A Nordic multicentre study [see comments]. *Scandinavian Journal of Gastroenterology* 1996;**31**:753-8.

Elliot 1994 {published data only}

Elliot S, Yeomans N, Buchanan R, Smallwood R. Efficacy of 12 months' misoprostol as prophylaxis against NSAID-induced gastric ulcers: a placebo-controlled trial. *Scandinavian Journal of Rheumatology* 1994;**23**:171-6.

Graham 1988 {published data only}

Graham D, Agrawal N, Roth S. Prevention of NSAID-induced gastric ulcer with misoprostol: multicentre, double-blind, placebo-controlled trial. *Lancet* 1988;**2**:1277-80.

Graham 1993 {published data only}

Graham D, White R, Moreland, LW, et al. Duodenal and gastric ulcer prevention with misoprostol in arthritis patients taking NSAIDs. *Annals of Internal Medicine* 1993;**119**:257-62.

Graham 2002 {published data only}

Graham DY, Agrawal NM, Campbell DR, Haber MM, Collis C, Lukasik L, et al. Ulcer prevention in long term users of nonsteroidal anti-inflammatory drugs: results of a double-blind randomized, multicenter, active and placebo-controlled study of misoprostol vs lansoprazole. *Archives of Internal Medicine* 2002;**162**(2):169-75.

Hawkey 1998 {published data only}

Hawkey C, Karrasch J, Szczepanski L, Walker D, Barkun A, Swannell A et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. *New England Journal of Medicine* 1998;**338**:727-34.

Henriksson 1993 {published data only}

Henriksson K, Uribe A, Sandstedt B, Nord CE. Helicobacter pylori infection, ABO blood group, and effect of misoprostol on gastroduodenal mucosa in NSAID-treated patients with rheumatoid arthritis. *Digestive Diseases & Sciences* 1993;**38**(9):1688-96.

Hudson 1997 {published data only}

Hudson N, Taha AS, Russell RI, Trye P, Cottrell J, Mann SG, et al. Famotidine for healing and maintenance in nonsteroidal anti-inflammatory drug-associated gastroduodenal ulceration [see comments]. *Gastroenterology* 1997;**112**:1817-22.

Jensen 2000 {unpublished data only}

Jensen DM, Ho S, Hamamah S, Frankl H, Faigel D, DeMarco D, et al. A randomized study of omeprazole compared to misoprostol for prevention of recurrent ulcers and ulcer hemorrhage in high risk patients ingesting aspirin or NSAIDs. In: *Gastroenterology*. Vol. 118. 2000:A892.

Lai 2003 {published data only}

Lai KC, Lam SK, Chu KM, Hui WM, Kwok KF, Wong BC et al. Lansoprazole reduces ulcer relapse after eradication of Helicobacter pylori in nonsteroidal anti-inflammatory drug users – a randomized trial. *Alimentary Pharmacology and Therapeutics* 2003;**18**(8):829-36.

Levine 1993 {published data only}

Levine LR, Cloud ML, Enas NH. Nizatidine prevents peptic ulceration in high-risk patients taking nonsteroidal anti-inflammatory drugs [see comments]. *Archives of Internal Medicine* 1993;**153**:2449-54.

Melo Gomes 1993 {published data only}

Melo Gomes JA, Roth SH, Zeeh J, Bruyn GA, Woods EM, Geis GS. Double-blind comparison of efficacy and gastroduodenal safety of diclofenac/misoprostol, piroxicam, and naproxen in the treatment of osteoarthritis. *Annals of the Rheumatic Diseases* 1993;**52**(12):8 81-5.

Raskin 1995 {published data only}

Raskin J, White R, Jackson J, Weaver A, Tindall E, Lies R et al. Misoprostol dosage in the prevention of nonsteroidal anti-inflammatory drug-induced gastric and duodenal ulcers: A comparison of three regimens. *Annals of Internal Medicine* 1995;**123**:344-50.

Raskin 1996 {published data only}

Raskin JB, White RH, Jaszewski R, Korsten MA, Schubert TT, Fort JG. Misoprostol and ranitidine in the prevention of NSAID-induced ulcers: a prospective, double-blind, multicenter study. *American Journal of Gastroenterology* 1996;**91**(2):223-7.

Robinson 1989 {published data only}

Robinson MG, Griffin JW, Bowers J, Kogan FJ, Kogut DG, Lanza FL et al. Effect of ranitidine on gastroduodenal mucosal damage induced by non-steroidal anti-inflammatory drugs. *Digestive Diseases and Sciences* 1989;**34**:424-8.

Robinson 1991 {published data only}

Robinson M, Mills RJ, Euler AR. Ranitidine prevents duodenal ulcers associated with non-steroidal anti-inflammatory drug therapy. *Alimentary Pharmacology and Therapeutics* 1991;**5**:143-50.

Roth 1987 {published data only}

Roth SH, Bennett RE, Mitchell CS, Hartman RJ. Cimetidine therapy in nonsteroidal anti-inflammatory drug gastropathy. Double-blind long-term evaluation. *Archives of Internal Medicine* 1987;**147**:1798-1801.

Roth 1993 {published data only}

Roth S, Tindall E, Jain A, McMahon F, April P, Bockow B et al. A controlled study comparing the effects of nabumetone, ibuprofen, and ibuprofen plus misoprostol on the upper gastrointestinal tract mucosa. *Archives of Internal Medicine* 1993;**153**:2565-71.

Saggioro 1991 {published data only}

Saggioro A, Alvisi V, Blasi A, Dobrilla G, Fioravanti A, Marcolongo R. Misoprostol prevents NSAID-induced gastroduodenal lesions in patients with osteoarthritis and rheumatoid arthritis [published erratum appears in Ital J Gastroenterol 1991 Jun;**23**(5):273]. *Italian Journal of Gastroenterology* 1991;**23**:119-123.

Silverstein 1995 {published data only}

Silverstein F, Graham D, Senior J, Davies H, Struthers B, Bittmann R et al. Misoprostol reduces gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: A randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine* 1995;**123**:241-9.

Simon 1994 {published data only}

Simon B, Muller P. Nizatidine in therapy and prevention of non-steroidal anti-inflammatory drug-induced gastroduodenal ulcer in rheumatic patients. *Scandinavian Journal of Gastroenterology - Supplement* 1994;**206**:25-28.

Stupnicki 2003 {published data only}

Stupnicki T, Dietrich K, Gonzalez-Carro P, Straszak A, Terjung KA, Thomas B et al. Efficacy and tolerability of pantoprazole compared with misoprostol for the prevention of NSAID-related gastrointestinal lesions and symptoms in rheumatic patients. *Digestion* 2003;**68**:198-208.

Swift 1989 {published data only}

Swift GL, Heneghan M, Williams GT, Williams BD, O'Sullivan MM, Rhodes J. Effect of ranitidine on gastroduodenal mucosal damage in patients on long-term non-steroidal anti-inflammatory drugs. *Digestion* 1989;**44**:86-94.

Taha 1996 {published data only}

Taha AS, Hudson N, Hawkey CJ, Swannell AJ, Trye PN, Cottrell J, et al. Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. *New England Journal of Medicine* 1996;**334**:1435-9.

Ten Wolde 1996 {published data only}

Wolde S, Dijkmans BA, Janssen M, Hermans J, Lamers CB. High-dose ranitidine for the prevention of recurrent peptic ulcer disease in rheumatoid arthritis patients taking NSAIDs. *Alimentary Pharmacology & Therapeutics* 1996;**10**:347-51.

Valentini 1995 {published data only}

Valentini M, Cannizzaro R, Poletti M, Bortolussi R, Fracasso A, Testa V, et al. Nonsteroidal antiinflammatory drugs for cancer pain: comparison between misoprostol and ranitidine in prevention of upper gastrointestinal damage. *Journal of Clinical Oncology* 1995;**13**(10):2637-42.

van Groenendael 1996 {published data only}

Van Groenendael JH, Markusse HM, Dijkmans BA, Breedveld FC. The effect of ranitidine on NSAID related dyspeptic symptoms with and without peptic ulcer disease of patients with rheumatoid arthritis and osteoarthritis. *Clinical Rheumatology* 1996;**15**:450-6.

Verdict 1992 {published data only}

Verdict W, Moran C, Hantzel H, Fraga A, Stead H, Geis G. A double-blind comparison of the gastroduodenal safety and efficacy of diclofenac and a fixed dose combination of diclofenac and misoprostol in the treatment of rheumatoid arthritis. *Scandinavian Journal of Rheumatology* 1992;**21**(2):85-91.

Yeomans 1998 {published data only}

Yeomans ND, Tulassay Z, Juhasz L, Racz I, Howard J. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. *New England Journal of Medicine* 1998;**338**:719-26.

References to studies excluded from this review
Agrawal 1999 {published data only}

Agrawal NM, Caldwell J, Kivitz AJ, Weaver AL, Bocanegra TS, Ball J, et al. Comparison of the upper gastrointestinal safety of Arthrotec 75 and nabumatone in osteoarthritis patients at high risk for developing nonsteroidal anti-inflammatory drug induced gastrointestinal ulcers. *Clinical Therapeutics* 1999;**21**(4):659-74.

Agrawal 2000 {published data only}

Agrawal NM, Campbell DR, Safdi MA, Lukasik NL, Huang B, Haber MM, . Superiority of lansoprazole vs ranitidine NSAID drug associated gastric ulcers. *Archives of Internal Medicine* 2000;**160**(10):1455-61.

Bianchi Porro 1997 {published data only}

Bianchi Porro G, Lazzaroni M, Petrillo M. Double blind, double dummy endoscopic comparison of the mucosal protective effect of misoprostol versus ranitidine on naproxen-

induced mucosal injury to the stomach and duodenum in rheumatic patients. *American Journal of Gastroenterology* 1997;**92**(4):663-7.

Bianchi Porro 1998 {published data only}

Bianchi Porro G, Lazzaroni M, Petrillo M, Manzionna G, Montrone F, Caruso I. Prevention of gastroduodenal damage with omeprazole in patients receiving continuous NSAIDs treatment: a double blind placebo controlled study. *Italian Journal of Gastroenterology and Hepatology* 1998;**30**(1):43-7.

Caldwell 1989 {published data only}

Caldwell JR, Weaver AL, Brown SK, McCormack GH. Endoscopic evaluation of rioprostil in the management of non-steroidal anti-inflammatory drug-induced gastritis: an interim analysis. *Scandinavian Journal of Gastroenterology. Supplement* 1989;**24**(164):239-41.

Ryan JR, Vargas R, Clay GA, McMahon FG. Role of misoprostol in reducing aspirin-induced gastrointestinal blood loss in arthritic patients. *American Journal of Medicine* 1987;**83**(1A):41-6.

Cohen de Lara 2000 {published data only}

Cohen de Lara A, Gompel H. Two comparative studies of dosmalfate vs misoprostol in the prevention of NSAID-induced gastric ulcers in rheumatic patients. *Drugs Of Today* 2000;**36**(supplement A):73-8.

Daneshmend 1990 {published data only}

Daneshmend TK, Stein AG, Bhaskar NK, Hawkey CJ. Abolition by omeprazole of aspirin induced gastric mucosal injury in man. *Gut* 1990;**31**(5):514-7.

Desai 2008 {published data only}

Desai J, Sanyal S, Goo T, Benson A, Bodian C, Miller K et al. Primary prevention of adverse gastroduodenal effects from short-term use of non-steroidal anti-inflammatory drugs by omeprazole 20 mg in healthy subjects: a randomized, double-blind, placebo-controlled study. *Digestive Diseases & Sciences* 2008;**58**(8):2059.

Donnelly 2000 {published data only}

Donnelly MT, Goddard AF, Filipowicz B, Moran SV, Sheild MJ, Hawkey CJ. Low-dose misoprostol for the prevention of low dose aspirin induced gastroduodenal injury. *Alimentary Pharmacology and Therapeutics* 2000;**14**(5):529-34.

Geis 1991 {published data only}

Geis G, Stead MWC, Nicholson P. Prevalence of mucosal lesions in the stomach and duodenum due to chronic use of NSAID in patients with rheumatoid arthritis or osteoarthritis, and interim report on prevention by misoprostol of diclofenac-associated lesions. *Journal of Rheumatology* 1991;**28**(March Supplement):11-4.

Geis 1992 {published data only}

Geis GS. Overall safety of Arthrotec. *Scandinavian Journal of Rheumatology. Supplement* 1992;**96**:33-6.

Goldstein 2004 {published data only}

Goldstein J, Huang B, Amer F, Christopoulos N. Ulcer recurrence in high-risk patients receiving nonsteroidal anti-inflammatory drugs plus low-dose aspirin: results of a post hoc subanalysis. *Clinical Therapeutics* 2004;**26**:1637-43.

Goldstein 2005 {published data only}

Goldstein J, Johanson J, Suchower L, Brown K. Healing of gastric ulcers with esomeprazole versus ranitidine in patients who continued to receive NSAID therapy: a randomized trial. *American Journal of Gastroenterology* 2005;**100**:2650-7.

Goldstein 2007 {published data only}

Goldstein J, Johanson J, Hawkey C, Suchower L, Brown K. Clinical trial: healing of NSAID-associated gastric ulcers in patients continuing NSAID therapy - a randomized study comparing ranitidine with esomeprazole. *Alimentary Pharmacology & Therapeutics* 2007;**26**(8):1101-11.

Lanas 2007 {published data only}

Lanas A, Garcia-Rodriguez L, Arroyo M, Bujanda L, Gomollon F, Forne M et al, Investigators of the Asociacion Espanola de Gastroenterologia (AEG). Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. *American Journal of Gastroenterology* 2007;**102**(3):507-15.

Melo Gomes 1992 {published data only}

Melo Gomes JA. The safety of Arthrotec in patients with rheumatoid arthritis or osteoarthritis: an assessment of the upper gastrointestinal tract by endoscopy. *Scandinavian Journal of Rheumatology. Supplement* 1992;**96**:23-31.

Miyake 2005 {published data only}

Miyake K, Ueki N, Suzuki K, Shinji Y, Kusunoki M, Hiratsuka T et al. Preventive therapy for non-steroidal anti-inflammatory drug-induced ulcers in Japanese patients with rheumatoid arthritis: the current situation and a prospective controlled-study of the preventive effects of lansoprazole or famotidine. *Alimentary Pharmacology and Therapeutics* 2005;**21**(Suppl 2):67-72.

Regula 2006 {published data only}

Regula J, Butruk E, Dekkers CP, de Boer SY, Raps D, Simon L et al. Prevention of NSAID-associated gastrointestinal lesions: a comparison study pantoprazole versus omeprazole. *American Journal of Gastroenterology* 2006;**101**(8):1747-55.

Rose 1999 {published and unpublished data}

Rose P, Huang B, Lukasik N, Collis C. Evidence that lansoprazole is effective in preventing NSAID induced ulcers. *Gastroenterology* 1999;**116**:A295.

Rugstad 1994 {published data only}

Rugstad HE, Giercksky KE, Husby G, Holme I. Effect of cimetidine on gastrointestinal symptoms in patients taking nonsteroidal anti-inflammatory drugs: a large double-blind placebo controlled study. *Scandinavian Journal of Rheumatology* 1994;**23**:177-82.

Ryan 1987 {published data only}

Ryan JR, Vargas R, Clay GA, McMahon FG. Role of misoprostol in reducing aspirin-induced gastrointestinal blood loss in arthritic patients. *American Journal of Medicine* 1987;**83**(Supplement 1A):41-4.

Scheiman 2006 {published data only}

Scheiman J, Yeomans N, Talley N, Vakil N, Chan F, Tulassay Z et al. Prevention of ulcers by esomeprazole in at-risk patients using non-selective NSAIDs and COX-2 inhibitors. *American Journal of Gastroenterology* 2006;**12**(36):5913-15.

Walan 1984 {published data only}

Walan A, Bader J, Classen M, Lamers CBHW, Piper DW, Rutgersson K et al. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. *New England Journal of Medicine* 1989;**320**(2):69-75.

Yilmaz 2007 {published data only}

Yilmaz S, Bayan K, Dursun M, Canoruç F, Kiliç N, Tüzün Y et al. Does adding misoprostol to standard intravenous proton pump inhibitor protocol improve the outcome of aspirin/NSAID induced upper gastrointestinal bleeding? *Digestive Diseases and Sciences* 2007;**110**(8):110-8.

Additional references
Armstrong 1987

Armstrong CP, Blower AL. Nonsteroidal antiinflammatory drugs and life threatening complications of peptic ulceration. *Gut* 1987;**28**:527-32.

Bhatt 2008

Bhatt DL, Scheiman J, Abraham NS, Antman EM, Chan FK, Furberg CD et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2008;**118**(18):1894-909.

Bollini 1992

Bollini P, Rodriguez G, Gutthann S. The impact of research quality and study design on epidemiologic estimates of the effect of nonsteroidal anti-inflammatory drugs on upper gastrointestinal tract disease. *Archives of Internal Medicine* 1992;**152**:1289-95.

Brown 2006

Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C et al. A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling. *Health Technology Assessment (Winchester, England)* 2006;**10**(38):1-202.

Chan 2002

Chan FK, Hung LC, Suen BY, Wu JC, Lee KC, Leung VK, et al. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. *New England Journal of Medicine* 2002;**347**:2104-10.

Chan 2004b

Chan FK, Hung LC, Suen BY, Wong VW, Hui AJ, Wu JC et al. Celecoxib versus diclofenac plus omeprazole in high-risk arthritis patients: results of a randomized double-blind trial. *Gastroenterology* 2004;**127**(4):1038-43.

Chan 2007

Chan FK, Wong VW, Suen BY, Wu JC, Ching JY, Hung LC, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. *Lancet* 2007;**369**:1621-6.

Chan 2008

Chan FK, Abraham NS, Scheiman JM, Laine L. Management of patients on nonsteroidal anti-inflammatory drugs: a clinical practice recommendation from the First International Working Party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal Anti-inflammatory Drugs and Anti-platelet Agents. *American Journal of Gastroenterology* 2008;**103**:2908-18.

Cohen 2000

Cohen de Lara A, Gompel H. Two comparative studies of Dismalate vs Misoprostol in the prevention of NSAID-induced gastric ulcers in rheumatic patients. *Drugs Of Today* 2000;**36**(supplement A):73-8.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177-88.

FDA 2010

Food and Drug Administration (US). Summary Minutes of the Gastrointestinal Drugs Advisory Committee (4 November 2010). <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM235452.pdf> (accessed 12 April 2011).

Fries 1990

Fries JF, Miller SR, Spitz PW, Williams CA, Hubert HB, Bloch DA. Identification of patients at risk for gastropathy associated with NSAID use. *Journal of Rheumatology* 1990;**20**(supplement):12-19.

Fries 1991

Fries JF. NSAID gastropathy: the second most deadly rheumatic disease? Epidemiology and risk appraisal. *Journal of Rheumatology* 1991;**28**(supplement):6-10.

Gabriel 1991

Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of non-steroidal anti-inflammatory drugs: a meta-analysis. *Annals of Internal Medicine* 1991;**115**:787-96.

Graham 2009

Graham DY. Endoscopic ulcers are neither meaningful nor validated as a surrogate for clinically significant upper gastrointestinal harm. *Clinical Gastroenterology and Hepatology* 2009;**7**(11):1147-50.

Greenland 1985

Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. *Biometrics* 1985;**41**(1):55-68.

Griffin 1988

Griffin MR, Ray WA, Schaffner W. Nonsteroidal anti-inflammatory drug use and death from peptic ulcer in elderly persons. *Annals of Internal Medicine* 1988;**109**:359-63.

Hallas 1995

Hallas J, Lauritsen J, Villadsen HD, Gram LF. Nonsteroidal anti-inflammatory drugs and upper gastrointestinal bleeding, identifying high-risk groups by excess risk estimates. *Scandinavian Journal of Gastroenterology* 1995;**30**:438-44.

Hansen 1996

Hansen JM, Hallas J, Lauritsen JM, Bytzer P. Non-steroidal anti-inflammatory drugs and ulcer complications: a risk factor analysis for clinical decision-making. *Scandinavian Journal of Gastroenterology* 1996;**31**:126-30.

Hawkey 2005

Hawkey C, Talley NJ, Yeomans ND, Jones R, Sung JJ, Langstrom G et al. Improvements with esomeprazole in patients with upper gastrointestinal symptoms taking non-steroidal anti-inflammatory drugs, including selective COX-2 inhibitors. *American Journal of Gastroenterology* 2005;**100**(5):1028-36.

Haynes 1994

Haynes RB, Wilczynski N, McKibbon KA, Walker CJ, Sinclair JC. Developing optimal search strategies for detecting clinically sound studies in MEDLINE. *Journal of the American Medical Informatics Association* 1994;**1**:447-58.

Hochain 1995

Hochain P, Berkelmans I, Czernichow P, Duhamel C, Tranvouez JL, Lerebours E et al. Which patients taking non-aspirin non-steroidal anti-inflammatory drugs bleed? A case-control study. *European Journal of Gastroenterology & Hepatology* 1995;**7**:419-26.

Hunt 1997

Hunt D, McKibbon K. Locating and appraising systematic reviews. *Annals of Internal Medicine* 1997;**126**:532-8.

Jadad 1996

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996;**17**:1-12.

Kearney 2006

Kearney PM, Baigent C, Godwin J et al. Do selective cyclooxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherosclerosis? Meta-analysis of randomised trials. *British Medical Journal* 2006;**332**:1302-8.

L'Abbe 1987

L'Abbe KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. *Annals of Internal Medicine* 1987;**107**:224-33.

Lai 2005

Lai K, Chu K, Hui W, Wong B, Hu W, Wong W et al. Celecoxib compared with lansoprazole and naproxen to prevent gastrointestinal ulcer complications. *American Journal of Medicine* 2005;**118**(11):1271-8.

Langman 1994

Langman MJ, Weil J, Wainwright P, Lawson DH, Rawlins MD, Logan RF et al. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994;**343**:1075-8.

Laporte 1991

Laporte JR, Carne X, Vidal X, Moreno V. Upper gastrointestinal bleeding in relation to previous use of analgesics and non-steroidal anti-inflammatory drugs. *Lancet* 1991;**337**:85-9.

Larkai 1987

Larkai EN, Smith JL, Lidsky MD. Gastroduodenal mucosa and dyspeptic symptoms in arthritic patients during chronic non-steroidal anti-inflammatory drug use. *American Journal of Gastroenterology* 1987;**82**:1153-8.

MacDonald 1997

MacDonald TM, Morant SV, Robinson GC. Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. *BMJ* 1997;**315**:1333-7.

Maetzel 1998

Maetzel A, Ferraz MB, Bombardier C. The cost-effectiveness of misoprostol in preventing serious gastrointestinal events associated with the use of nonsteroidal antiinflammatory drugs. *Arthritis and Rheumatism* 1998;**41**:16-25.

McGauran 2010

McGauran N, Wieseler B, Kreis J, Schuler YB, Kolsch H, Kaiser T. Reporting bias in medical research? A narrative review. *Trials* 2010;**11**(37):1-15.

McMahon 1997

McMahon AD, Evans JM, White G, Murray FE, McGilchrist MM, McDevitt DG et al. A cohort study (with re-sampled comparator groups) to measure the association between new NSAID prescribing and upper gastrointestinal hemorrhage and perforation. *Journal of Clinical Epidemiology* 1997;**50**:351-6.

Moore 2009

Moore A, Bjarnason I, Cryer B, Garcia-Rodriguez L, Goldkind L, Lanas A, et al. Evidence for endoscopic ulcers as meaningful surrogate endpoint for clinically significant upper gastrointestinal harm. *Clinical Gastroenterology and Hepatology* 2009;**7**(11):1156-63.

Rodriguez 1997

Rodriguez LA. Nonsteroidal anti-inflammatory drugs, ulcers and risks: a collaborative meta-analysis. *Seminars in Arthritis and Rheumatism* 1997;**26**:16-20.

Rosenthal 1979

Rosenthal R. The "file drawer problem" and tolerance for null results. *Psychological Bulletin* 1979;**86**:638-41.

Rostom 2004

Alaa Rostom, Catherine Dubé, Emilie Jolicoeur, Michel Boucher, Peter Tugwell, George Wells et al. Chapter 6: Non-steroidal anti-inflammatory drug-induced gastroduodenal toxicity. In: Edited by J McDonald, A Burroughs, B Feagan, editors(s). Evidence Based Gastroenterology. Second Edition. Vol. **Chapter 6**. Oxford, UK: BMJ Books, 2004:117-138. [ISBN: 978-0-7279-1751-5]

Rostom 2007

Rostom A, Muir K, Dubé C, Jolicoeur E, Boucher M, Joyce J, Tugwell P, Wells GW. The Gastrointestinal toxicity of COX-2 inhibitors a Cochrane Collaboration Systematic Review. *Clinical Gastroenterology and Hepatology* 2007;**5**:818-828.

Rostom 2009

Rostom A, Moayyedi P, Hunt R, for the Canadian Association of Gastroenterology Consensus group. Canadian consensus guidelines on long-term nonsteroidal anti-inflammatory drug therapy and the need for gastroprotection: benefits versus risks.. *Alimentary Pharmacology and Therapeutics* 2009;**29**(5):481-96.

Rostom 2009b

Alaa Rostom, Catherine Dubé, Emilie Jolicoeur, Michel Boucher, Peter Tugwell, George Wells et al. Chapter 6: Non-steroidal anti-inflammatory drug-induced gastroduodenal toxicity. *Evidence Based Gastroenterology. Second Edition. Edited by J. McDonald, A. Burroughs, B. Feagan* 2009 - In press;**Chapter 6**:Chapter 6.

Rostom 2009c

Rostom A, Muir C, Dube C, Lanas A, Jolicoeur J, Tugwell P. Prevention of NSAID-related upper gastrointestinal toxicity: a meta-analysis of traditional NSAIDs with gastroprotection and COX-2 inhibitors. *Drug Healthcare and Patient Safety* 2009;**1**:47-71.

Smalley 1996

Smalley WE, Griffin MR, Fought RL, Ray WA. Excess costs from gastrointestinal disease associated with nonsteroidal anti-inflammatory drugs. *Journal of General Internal Medicine* 1996;**11**:461-9.

Stalnikowicz 1993

Stalnikowicz R, Rachmilewitz D. NSAID-induced gastroduodenal damage: is prevention needed? A review and metaanalysis. *Journal of Clinical Gastroenterology* 1993;**17**:238-43.

Wallace 1996

Wallace JL. NSAID gastroenteropathy: past, present and future. *Canadian Journal of Gastroenterology* 1996;**10**:451-9.

Yeomans 2001

Yeomans N, Wilson I, Långström G, Hawkey C, Naesdal J, Walan A et al. Quality of life in chronic NSAID users: a comparison of the effect of omeprazole and misoprostol. *Scandinavian Journal of Rheumatology* 2001;**30**:328–34.

toxicity: a Cochrane collaboration metaanalysis of randomized controlled trials. *Journal of Rheumatology* 2000;**27**(9):2203-14.

Rostom 2002

Rostom A, Dube C, Wells GA, Tugwell P, Welch V, Jolicoeur E, et al. Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No: CD002296. [DOI: [10.1002/14651858.CD002296](https://doi.org/10.1002/14651858.CD002296)]

References to other published versions of this review

Rostom 2000

Rostom A, Wells G, Tugwell P, Welch V, Dubé C, McGowan J. The prevention of chronic NSAID induced upper gastrointestinal

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Agrawal 1991

Study characteristics		
Methods	Randomized controlled trial Double-blind Sample size at entry: misoprostol: 179; sucralfate: 177 Study duration: 12 weeks	
Participants	Patient: osteoarthritis Median age (yrs): misoprostol: 60; sucralfate: 60 Sex % F: misoprostol: 56; sucralfate: 59 Type of NSAID: ibuprofen, naproxen, piroxicam Previous peptic ulcers (%): misoprostol: 22; sucralfate: 27 Primary vs secondary prophylaxis: primary H pylori positive(%): not mentioned	
Interventions	1) misoprostol 200µg x 4 = 800µg 2) sucralfate 1g x 4 = 4g	
Outcomes	Endoscopic gastric ulcers (>3 mm) Endoscopic duodenal ulcers (>3 mm) Gastric ulcers (>5 mm) Withdrawals overall Withdrawals due to side effects Drop out due to diarrhea Drop out due to dyspepsia	
Notes	Quality = 2	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Agrawal 1995

Study characteristics		

Prevention of NSAID-induced gastroduodenal ulcers (Review)

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Agrawal 1995 (Continued)

Methods	Randomized controlled trial Single-blind Sample size at entry: misoprostol: 193; placebo: 191 Study duration: up to 52 weeks
Participants	Patient: rheumatoid arthritis and osteoarthritis Mean age (yrs): misoprostol: 57.3; placebo: 57.5 Sex % F: Misoprostol: 66; placebo: 70 Type of NSAID: diclofenac Previous peptic ulcers (%): all Primary vs secondary prophylaxis: secondary H pylori positive (%): not mentioned
Interventions	1) misoprostol 200 µg 2-3/day (400-600 µg) + diclofenac 2) placebo + diclofenac 50 mg BID/ TID
Outcomes	Gastric endoscopic ulcers Duodenal endoscopic ulcers Total gastroduodenal ulcers Drop-outs due to side-effects Abdominal pain Diarrhea Dyspepsia Nausea
Notes	Quality = 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Berkowitz 1987
Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: ranitidine: 25; placebo: 25 Study duration: 4 weeks
Participants	Patient: rheumatic Mean age (yrs): ranitidine: 28.5; placebo: 26.2 Sex % F: ranitidine: 0; placebo: 0 Type of NSAID: aspirin Previous peptic ulcers (%): 0 Primary vs secondary prophylaxis: primary H pylori positive (%): not mentioned
Interventions	1) ranitidine 150 mg bid and 650 mg aspirin qid 2) placebo bid and 650 mg aspirin qid
Outcomes	Endoscopic gastric ulcer (>3 mm)

Prevention of NSAID-induced gastroduodenal ulcers (Review)

Berkowitz 1987 (Continued)

Endoscopic duodenal ulcer (>3 mm)
Withdrawals overall
Withdrawals due to side effects

Notes Quality = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Bianchi Porro 2000

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: Pantoprazole: 70; placebo: 34 Study duration: 12 weeks
Participants	Patient: rheumatoid arthritis and osteoarthritis Mean age (yrs): Pantoprazole: 58; placebo: 59 Sex % F: pantoprazole: 82.9; placebo: 82.4 Type of NSAID: diclofenac, ketoprofen, Indocid Previous peptic ulcers (%): pantoprazole: 25; placebo: 5 Primary vs secondary prophylaxis: primary H pylori positive (%): pantoprazole: 37; placebo: 50
Interventions	1) placebo 2) pantoprazole 40mg /day
Outcomes	Lanza Score Endoscopic ulcer = 4 Adverse effects
Notes	Quality = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Bocanegra 1998

Study characteristics

Methods	Randomized controlled trial Double-blind
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Bocanegra 1998 (Continued)

Sample size at entry: diclofenac 50mg+misoprostol 200µg tid: 154, diclofenac 75mg+misoprostol 200µg bid: 152, diclofenac 75mg Bid: 175, placebo: 91

Study duration: 6 weeks

Participants	<p>Patient: osteoarthritis</p> <p>Mean age (yrs): diclofenac 50mg+misoprostol 200µg tid: 62.9, diclofenac 75mg+misoprostol 200µg bid: 62.3, diclofenac 75mg Bid: 62.8, placebo: 61.5</p> <p>Sex % F: diclofenac 50mg+misoprostol 200µg tid: 71, diclofenac 75mg+misoprostol 200µg bid: 68, diclofenac 75mg Bid: 67, placebo: 68</p> <p>Type of NSAID: diclofenac, misoprostol</p> <p>Previous peptic ulcers (%): not mentioned</p> <p>Primary vs secondary prophylaxis: primary</p> <p>H pylori positive (%): not mentioned</p>
Interventions	<p>1) diclofenac 75mg bid</p> <p>2) diclofenac 75mg+misoprostol 200µg bid</p> <p>3) diclofenac 50mg+misoprostol 200µg tid</p> <p>4) placebo</p>
Outcomes	<p>Endoscopic gastric ulcers (>3mm)</p> <p>Endoscopic duodenal ulcers (>3mm)</p> <p>Side-effects</p> <p>Side-effects causing withdrawal</p> <p>Withdrawal overall</p>
Notes	Quality=3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Bolten 1992

Study characteristics

Methods	<p>Randomized controlled trial</p> <p>Double-blind</p> <p>Sample size at entry: misoprostol: 178; placebo: 183</p> <p>Study duration: 4 weeks</p>
Participants	<p>Patient: osteoarthritis</p> <p>Mean age (yrs): misoprostol: 59.2; placebo: 61.3</p> <p>Sex % F: misoprostol: 75.8; placebo: 70.5</p> <p>Type of NSAID: diclofenac</p> <p>Previous peptic ulcers (%): misoprostol: 0; placebo: 4</p> <p>Primary vs secondary prophylaxis: primary</p> <p>H pylori positive (%): not mentioned</p>
Interventions	<p>1) misoprostol 400-600µg/day (Arthrotec) 2) placebo</p>
Outcomes	<p>Endoscopic ulcers (gastric, duodenal, total) at 1 month</p> <p>Dropouts overall</p>

Bolten 1992 (Continued)

Notes

Quality = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Chan 2001a
Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: misoprostol: 45; nabumetone: 45 Study duration: 24 weeks
Participants	Patient: high risk NSAID ulcers user Mean age (yrs): misoprostol: 75; nabumetone: 74 Sex % F: misoprostol: 62; nabumetone: 67 Type of NSAID: naproxen Previous peptic ulcers (%): all Primary vs secondary prophylaxis: secondary H pylori positive (%): 0
Interventions	1) naproxen+misoprostol 200 bid 2) 1000-1500mg
Outcomes	Ucers or bleeding Adverse events
Notes	Quality=4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Chan 2001b
Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: omeprazole: 66; celecoxib: 64 Study duration: 24 weeks
Participants	Patient: arthritis Mean age (yrs): omeprazole: 68; celecoxib: 66 Sex % F: omeprazole: 58; celecoxib: 55

Prevention of NSAID-induced gastroduodenal ulcers (Review)

Chan 2001b (Continued)

Type of NSAID: diclofenac
Previous peptic ulcers (%): all
Primary vs secondary prophylaxis: secondary
H pylori positive (%): 0

Interventions	1) diclofenac 75mg bid + omeprazole 20mg daily 2) celecoxib 200 mg bid
Outcomes	Recurrent ulcer bleeding
Notes	quality=3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Chan 2004

Study characteristics

Methods	Randomized controlled trial Double blind Sample size at entry: omeprazole: 106; celecoxib: 116 Study duration: 6 months
Participants	Patient: arthritis Mean age (yrs): omeprazole: 68; celecoxib: 68 Sex % F: omeprazole: 50.9; celecoxib: 53.4 Type of NSAID: diclofenac Previous peptic ulcers (%): all Primary vs secondary prophylaxis: secondary H pylori positive (%): 0
Interventions	1) diclofenac 75mg bid + omeprazole 20mg daily 2) celecoxib 200 mg bid
Outcomes	Recurrent ulcer bleeding
Notes	Quality=3

Chandresekaran 1991

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: misoprostol: 45; placebo: 45 Study duration: 4 weeks
Participants	Patient: rheumatoid arthritis, osteoarthritis and spondyloarthropathy Mean age (yrs): 39.9

Chandresekaran 1991 (Continued)

Sex % F: 47%
Type of NSAID: ASA, ibuprofen, diclofenac, indomethacin
Previous peptic ulcers (%): n/a - but no history of gastroduodenal surgery
Primary vs secondary prophylaxis: primary
H pylori positive (%): n/a

Interventions	1) misoprostol 200 µg tid 2) placebo
Outcomes	Endoscopic ulcers
Notes	Quality = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Cullen 1998
Study characteristics

Methods	Randomized controlled trial Double blind Sample size at entry: omeprazole: 83; placebo: 85 Study duration: up to 6 months
Participants	Patient: rheumatoid arthritis, osteoarthritis Mean age (yrs): omeprazole: 55; placebo: 56 Sex % F: omeprazole: 64.7; placebo: 68.7 Type of NSAID: naproxen Previous peptic ulcers (%): omeprazole: 27; placebo: 21 Primary vs secondary prophylaxis: primary H pylori positive (%): omeprazole: 35.5; placebo: 27.3
Interventions	1) omeprazole 20 mg daily 2) placebo
Outcomes	Endoscopic ulcers
Notes	Quality = 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Delmas 1994

Study characteristics

Methods	Randomized controlled trial Double blind Sample size at entry:256 Study duration:4 weeks
Participants	Patient: osteoarthritis, rheumatoid arthritis, or other rheumatic diseases and prior NSAID use in last 10 days Median age (yrs): n/a Sex % F:n/a Type of NSAID:diclofenac, naproxen, piroxicam, ibuprofen, indomethacin, ketoprofen, or tiaprofenic acid Previous peptic ulcers (%): n/a but none on entry had ulcers Primary vs secondary prophylaxis:primary H pylori positive (%):n/a
Interventions	1) misoprostol 400 2) misoprostol 800 3) placebo (any NSAID)
Outcomes	Gastric ulcers Duodenal ulcers
Notes	Quality = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Ehsanullah 1988

Study characteristics

Methods	Randomized controlled trial Double blind Sample size at entry: ranitidine: 137; placebo: 126 Study duration: up to 8 weeks
Participants	Patient: rheumatoid arthritis and osteoarthritis Mean age (yrs): ranitidine: 57.7; placebo: 60 Sex % F: ranitidine: 57.7; placebo: 62.7 Type of NSAID: not mentioned Previous peptic ulcers (%): ranitidine: 11; placebo: 11 Primary vs secondary prophylaxis: primary H pylori positive (%): not mentioned
Interventions	1) ranitidine 150 mg bid 2) placebo
Outcomes	Endoscopic ulcers

Ehsanullah 1988 (Continued)

adverse events

Notes Quality = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Ekstrom 1996

Study characteristics

Methods	Randomized controlled trial Double blind Sample size at entry: omeprazole: 86; placebo: 91 Study duration: 3 months
Participants	Patient: osteoarthritis, rheumatoid arthritis, spondylarthritis, ankylosing spondylitis Mean age (yrs): omeprazole: 58; placebo: 59 Sex % F: omeprazole: 63.5; placebo: 74.4 Type of NSAID: naproxen Previous peptic ulcers (%): omeprazole: 27; placebo: 21 Primary vs secondary prophylaxis: primary H pylori positive (%): omeprazole: 53; placebo: 51
Interventions	1) omeprazole 20 mg daily 2) placebo
Outcomes	Endoscopic ulcers
Notes	Quality = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Elliot 1994

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: misoprostol: 40; placebo: 43 Study duration: 12 months
Participants	Patient: rheumatic arthritis, osteoarthritis

Prevention of NSAID-induced gastroduodenal ulcers (Review)

Elliot 1994 (Continued)

Mean age (yrs): misoprostol: 65; placebo: 65
Sex % F: misoprostol: 37.5, placebo: 51.2
Type of NSAID: piroxicam, ibuprofen, naproxen
Previous peptic ulcers (%): misoprostol: 28; placebo: 28
Primary vs secondary prophylaxis: primary
H pylori positive (%): not mentioned

Interventions	1) misoprostol 200 µg qid or bd or td depending on frequency of NSAID use 2) placebo (same protocol as misoprostol, with NSAID)
Outcomes	Endoscopic gastric ulcers (>3 mm), mean size 6 mm Endoscopic duodenal ulcers (>3 mm) Clinical ulcers Withdrawals overall Withdrawals due to side effects Drop out due to diarrhea
Notes	Quality=4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Graham 1988
Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: isoprotol 100: 143; misoprostol 200: 139; placebo: 138 Study duration: 12 weeks
Participants	Patient: osteoarthritis Mean age (yrs): 58.9 Sex % F: 65 Type of NSAID: ibuprofen; piroxicam; naproxen Previous peptic ulcers (%): 13 Primary vs secondary prophylaxis: primary H pylori positive (%): not mentioned
Interventions	1) placebo x 4 2) misoprostol 100 µg x 4 3) misoprostol 200 µg x 4
Outcomes	Endoscopic gastric ulcers (>3 mm) Endoscopic gastric ulcers (>5 mm) Clinical ulcers: Withdrawals overall Withdrawals due to side effects
Notes	Quality=3

Graham 1988 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Graham 1993

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: misoprostol: 320; placebo: 323 Study duration: 12 weeks
Participants	Patient: rheumatoid arthritis, osteoarthritis, Reiter syndrome, psoriatic arthritis, ankylosing spondylitis Median age (yrs): misoprostol: 59; placebo: 61 Sex % F: misoprostol: 47; placebo: 50 Type of NSAID: ibuprofen, piroxicam, naproxen, sulindac, tolmetin, indomethacin, diclofenac Previous peptic ulcers (%): misoprostol: 25; placebo: 26 Primary vs secondary prophylaxis: primary H pylori positive (%): not mentioned
Interventions	1) misoprostol 800 µg (200 µg x 4) 2) placebo
Outcomes	Endoscopic gastric ulcers (>5 mm) Endoscopic duodenal ulcers (>5 mm) Clinical ulcers: Withdrawals overall Withdrawals due to side effects Diarrhea drop out Nausea drop out Abdominal pain drop out
Notes	Quality=3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Graham 2002

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: misoprostol:134; lansoprazole 15mg: 136; lansoprazole 30mg: 133; placebo: 134
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Graham 2002 (Continued)

Study duration: 12 weeks

Participants	Patient: History of endoscopically documented gastric ulcer with or without GI bleeding Mean age (yrs): misoprostol:59.4; lansoprazole 15mg : 61.6; lansoprazole 30mg: 60.2; placebo: 60.5 Sex % F: misoprostol:68; lansoprazole 15mg: 63; lansoprazole 30mg: 64; placebo: 65 Type of NSAID: ibuprofen, naproxen, diclofenac, aspirin, piroxicam Previous peptic ulcers (%): all Primary vs secondary prophylaxis: secondary H pylori positive (%): 15
Interventions	1) placebo 2) misoprostol 800µg 3) lansoprazole 15 mg 4) lansoprazole 30 mg
Outcomes	Endoscopic gastric ulcers
Notes	Quality=4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Hawkey 1998
Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: omeprazole: 274; misoprostol: 296; placebo: 155 Study duration: 6 months
Participants	Patient: rheumatoid arthritis, osteoarthritis Mean age (yrs): omeprazole: 58; misoprostol: 58; placebo: 57 Sex % F: omeprazole: 63; misoprostol: 60; placebo: 69 Type of NSAID: diclofenac, ketoprofen, naproxen Previous peptic ulcers (%): omeprazole: 29; misoprostol: 27; placebo: 31 Primary vs secondary prophylaxis: primary H pylori positive (%):omeprazole: 42; misoprostol: 41; placebo: 38
Interventions	1) omeprazole 20 mg 2) misoprostol 200 µg bid = 400 µg 3) placebo
Outcomes	Endoscopic gastric ulcers (>3 mm) Endoscopic gastric ulcers (>5 mm) Endoscopic duodenal ulcers (>3 mm) Endoscopic duodenal ulcers (>5 mm) Clinical ulcers: ? Withdrawals overall Withdrawals due to side effects

Hawkey 1998 (Continued)

Notes

Quality = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Henriksson 1993

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: misoprostol: 19; placebo: 20 Study duration: 30 months
Participants	Patient: rheumatoid arthritis Mean age (yrs): misoprostol: 60; placebo: 54 Sex % F: misoprostol: 84; placebo: 66 Type of NSAID: diclofenac, naproxen, ibuprofen, ketoprofen, piroxicam Previous peptic ulcers (%): misoprostol: 0; placebo: 5 Primary vs secondary prophylaxis: primary H pylori positive (%): 33
Interventions	1) misoprostol 200 µg tid 2) placebo tid
Outcomes	Endoscopic gastric ulcers Endoscopic duodenal ulcers Drop-outs overall Abdominal pain Diarrhea GI symptoms
Notes	Quality = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Hudson 1997

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: famotidine: 39; placebo: 39
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Hudson 1997 (Continued)

Study duration: up to 24 weeks

Participants	Patient: rheumatoid arthritis and osteoarthritis Median age (yrs): famotidine: 58; placebo: 55 Sex % F: famotidine: 64.1; placebo: 49.1 Type of NSAID: diclofenac Previous peptic ulcers (%): famotidine: 31; placebo: 28 Primary vs secondary prophylaxis: primary H pylori positive (%): 46
Interventions	1) famotidine 40 mg bid (high dose) 2) placebo bid
Outcomes	Endoscopic ulcers
Notes	Quality = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Jensen 2000
Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: omeprazole: 23; misoprostol: 23 Study duration: 32 weeks
Participants	Patient: high risk with previous NSAID or ASA ulcer who need continuation of NSAID Mean age (yrs): n/a Sex % F: n/a Type of NSAID: ASA $\geq$ 325mg, or 'moderate dose' NSAIDs Previous peptic ulcers (%): all Primary vs secondary prophylaxis: secondary H pylori positive (%): n/a
Interventions	1) omeprazole 20mg bid 2) misoprostol 200µg qid
Outcomes	UGI bleeding Symptomatic ulcer recurrence Unrelieved UGI symptoms
Notes	Abstract - Can't determine some results

Risk of bias

Bias	Authors' judgement	Support for judgement
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Jensen 2000 (Continued)

Allocation concealment (selection bias)	Unclear risk	D - Not used
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Lai 2003
Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: lansoprazole: 22; no treatment: 21 Study duration: 5 weeks
Participants	Patient: rheumatoid arthritis and osteoarthritis Mean age (yrs): lansoprazole: 67.1; No treatment: 70.2 Sex % F: lansoprazole: 36.4; No treatment: 52.4 Type of NSAID: naproxen Previous peptic ulcers (%): all Primary vs secondary prophylaxis: secondary H pylori positive (%): 54
Interventions	1) naproxen 750 mg tid + either 30 mg of lansoprazole 2) no treatment for 8 weeks
Outcomes	Primary: symptomatic and complicated ulcers secondary: cumulative Relapse of all ulcers
Notes	Quality = 3

Levine 1993
Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: nizatidine: 248; placebo: 248 Study duration: 3 months
Participants	Patient: osteoarthritis Mean age (yrs): nizatidine: 56.9; placebo: 51.5 Sex % F: nizatidine: 64.9; placebo: 66.1 Type of NSAID: piroxicam, ibuprofen, naproxen, diclofenac Previous peptic ulcers (%): nizatidine: 17.3; placebo: 18.1 Primary vs secondary prophylaxis: primary H pylori positive: nizatidine: 38.3; placebo: 56.2
Interventions	1) nizatidine 150 mg bid 2) placebo
Outcomes	Endoscopic ulcers Symptoms

Levine 1993 (Continued)

Notes Quality =3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Melo Gomes 1993

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: diclofenac/misoprostol: 216; piroxicam: 217; naproxen: 210 Study duration: 4 weeks
Participants	Patient: osteoarthritis Mean age (yrs): diclofenac/misoprostol: 60.7; piroxicam: 58.7; naproxen: 59.5 Sex % F: diclofenac/misoprostol: 76; piroxicam: 75; naproxen: 77 Type of NSAID: diclofenac, misoprostol, piroxicam, naproxen Previous peptic ulcers (%): 0 Primary vs secondary prophylaxis: primary H pylori positive (%): not mentioned
Interventions	1) diclofenac/misoprostol 2) piroxicam 3) naproxen
Outcomes	Endoscopic ulcers Endoscopic gastric ulcers Endoscopic duodenal ulcers Abdominal pain Diarrhea Dyspepsia Nausea
Notes	Quality = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Raskin 1995

Study characteristics

Methods	Randomized controlled trial Double-blind
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Prevention of NSAID-induced gastroduodenal ulcers (Review)

Raskin 1995 (Continued)

Sample size at entry: misoprostol 400: 462; misoprostol 600: 474; misoprostol 800: 228; placebo: 454

Study duration: 3 months

Participants	<p>Patient: rheumatoid arthritis, osteoarthritis, psoriatic arthritis, ankylosing spondylitis, Reiter syndrome</p> <p>Median age (yrs): misoprostol 400: 58; misoprostol 600: 58; misoprostol 800: 58; placebo: 58</p> <p>Sex % F: misoprostol 400: 56; misoprostol 600: 60; misoprostol 800: 60; placebo: 59</p> <p>Type of NSAID: diclofenac, ketoprofen; naproxen</p> <p>Previous peptic ulcers (%): 0</p> <p>Primary vs secondary prophylaxis: primary</p> <p>H pylori positive (%): not mentioned</p>
Interventions	<p>1) placebo: 4 x day</p> <p>2) misoprostol 200 µg x 2 = 400 µg</p> <p>3) misoprostol 200 µg x 3 = 600 µg</p> <p>4) misoprostol 200 µg x 4 = 800 µg</p>
Outcomes	<p>Endoscopic gastric ulcers (>3 mm)</p> <p>Endoscopic duodenal ulcers (>3 mm)</p> <p>Clinical ulcers: not mentioned</p> <p>Withdrawals overall</p> <p>Withdrawals due to side effects</p> <p>All adverse events</p>
Notes	Quality = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Raskin 1996

Study characteristics

Methods	<p>Randomized controlled trial</p> <p>Double-blind</p> <p>Sample size at entry: misoprostol: 269; ranitidine: 269</p> <p>Study duration: 8 weeks</p>
Participants	<p>Patient: rheumatoid arthritis, osteoarthritis, psoriatic arthritis, ankylosing spondylitis, Reiter syndrome</p> <p>Mean age (yrs): misoprostol: 61; ranitidine: 60</p> <p>Sex % F: misoprostol: 53; ranitidine: 57</p> <p>Type of NSAID: ibuprofen, naproxen, piroxan, sulindac</p> <p>Previous peptic ulcers (%): misoprostol: 23; ranitidine: 21</p> <p>Primary vs secondary prophylaxis: primary</p> <p>H pylori positive (%): not mentioned</p>
Interventions	<p>1) misoprostol 200 µg qid</p> <p>2) ranitidine 150 mg bid</p>
Outcomes	<p>Endoscopic gastric ulcer (>3 mm)</p> <p>Endoscopic duodenal ulcers (>3 mm)</p> <p>Clinical ulcers</p>

Raskin 1996 (Continued)

Withdrawals overall
Withdrawals due to side effects
Nausea

Notes Quality = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Robinson 1989

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: ranitidine 150 mg bid: 72; placebo: 72 Study duration: 8 weeks
Participants	Patient: arthritis Mean age (yrs): ranitidine 150 mg bid: 48.9; placebo: 44.5 Sex % F: ranitidine 150 mg bid: 60; placebo: 69 Type of NSAID: naproxen, sulindac, ibuprofen, piroxicam, indomethacin Previous peptic ulcers (%): 0 Primary vs secondary prophylaxis: primary H pylori positive (%): not mentioned
Interventions	1) ranitidine 150 mg bid 2) placebo bid
Outcomes	Endoscopic duodenal ulcers Endoscopic gastric ulcers Adverse events
Notes	Quality = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Robinson 1991

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: placebo: 330; ranitidine: 343
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Robinson 1991 (Continued)

Study duration: 4 & 8 weeks

Participants	Patient: with no ulcers, confirmed by endoscopy Mean age (yrs): placebo: 50.7; ranitidine: 51.2 Sex % F: placebo: 64; ranitidine: 58 Type of NSAID: aspirin, diclofenac, ibuprofen, indomethacin, naproxen, piroxicam, sulindac Previous peptic ulcers (%): none Primary vs secondary prophylaxis: primary H pylori positive (%): not mentioned
Interventions	ranitidine 150 mg bid placebo
Outcomes	Duodenal ulcers (unspecified criteria)
Notes	Quality=2

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Roth 1987
Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: placebo: 46; cimetidine: 48 Study duration: 2 months
Participants	Patient: rheumatoid arthritis, osteoarthritis Mean age (yrs): not mentioned Sex % F: not mentioned Type of NSAID: various Previous peptic ulcers (%): all Primary vs secondary prophylaxis: secondary H pylori positive (%): not mentioned
Interventions	Cimetidine 400 mg per day placebo
Outcomes	Total endoscopic ulcers
Notes	Quality =1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Roth 1993

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: nabumetone: 58; ibuprofen: 53; ibuprofen and misoprostol: 60 Study duration: 12 weeks
Participants	Patient: rheumatoid arthritis, osteoarthritis Mean age (yrs): nabumetone: 70; ibuprofen: 70; ibuprofen and misoprostol: 70 Sex % F: nabumetone: 67; ibuprofen: 77; ibuprofen and misoprostol: 82 Type of NSAID: nabumetone, ibuprofen Previous peptic ulcers (%): nabumetone: 17; ibuprofen: 26; ibuprofen and misoprostol: 23 Primary vs secondary prophylaxis: primary H pylori positive (%): not mentioned
Interventions	1) nabumetone 1000 mg x? 2) ibuprofen 600 mg x 4/day 3) ibuprofen and misoprostol 600 mg/200 mg x 4/day
Outcomes	Endoscopic gastric ulcers (>3 mm) Endoscopic duodenal ulcers (>3 mm) Clinical ulcers Withdrawals overall Withdrawals due to side effects GI Side Effects
Notes	Quality = 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Saggioro 1991

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: misoprostol: 82; placebo: 84 Study duration: 4 weeks
Participants	Patient: rheumatoid arthritis, osteoarthritis Mean age (yrs): 56 Sex % F: 59.5 Type of NSAID: piroxicam, diclofenac, naproxen, ibuprofen Previous peptic ulcers (%): none Primary vs secondary prophylaxis: H pylori positive (%): n/a
Interventions	1) misoprostol 200 µg qid

Prevention of NSAID-induced gastroduodenal ulcers (Review)

Saggioro 1991 (Continued)

2) placebo

Outcomes	Endoscopic ulcers Symptoms
Notes	Quality = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Silverstein 1995

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: misoprostol: 440; placebo: 443 Study duration: 6 months
Participants	Patient: rheumatoid arthritis Median age (yrs): misoprostol: 67.6; placebo: 67.6 Sex % F: misoprostol: 71.1; placebo: 70.6 Type of NSAID: diclofenac, indomethacin; ketoprofen ; naproxen, piroxicam, sulindac Previous peptic ulcers (%): misoprostol: 14.6; placebo: 14.4 Primary vs secondary prophylaxis: primary H pylori positive (%): not mentioned
Interventions	1) misoprostol 200 µg x 4/day or 100 µg x 4 if poorly treated 2) placebo
Outcomes	Endoscopic gastric ulcers (>3 mm) Endoscopic duodenal ulcers (>3 mm) Clinical ulcers: category 1-6 Withdrawals overall Withdrawals due to side effects
Notes	Quality = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Simon 1994

Study characteristics

Prevention of NSAID-induced gastroduodenal ulcers (Review)

Simon 1994 (Continued)

Methods	Randomized controlled trial Double-blind Sample size at entry: nizatidine 300mg daily: 93; nizatidine 150mg bid: 151; nizatidine 300mg bid: 90 Study duration: 3 weeks	
Participants	Patient: rheumatoid arthritis with an ulcer Median age (yrs): nizatidine 300mg daily: 58; nizatidine 150mg bid: 55; nizatidine 300mg bid: 57 Sex % F: nizatidine 300mg daily: 45.3; nizatidine 150mg bid: 37.6; nizatidine 300mg bid: 38.9 Type of NSAID: Previous peptic ulcers (%): all Primary vs secondary prophylaxis: secondary H pylori positive (%): not mentioned	
Interventions	1) Nizatidine 150 mg daily 2) Nizatidine 150 mg bid	
Outcomes	Endoscopic ulcers	
Notes	Quality =2	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Stupnicki 2003

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: pantoprazole: 257; misoprostol: 258 Study duration: 4 weeks	
Participants	Patient: rheumatoid arthritis Mean age (yrs): pantoprazole: 55; misoprostol: 55 Sex % F: pantoprazole: 64; misoprostol: 64 Type of NSAID: diclofenac Previous peptic ulcers (%): pantoprazole: 23; misoprostol: 22.5 Primary vs secondary prophylaxis: primary H pylori positive (%): pantoprazole: 33; misoprostol: 31	
Interventions	1) misoprostol 400µg/day 2) pantoprazole 40mg/day	
Outcomes	Endoscopic ulcers Serious adverse events	
Notes	Quality: randomisation 2; blinding 1; follow up 1:	

Swift 1989

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: famotidine: 51; cimetidine: 54 Study duration: 7 weeks
Participants	Patient: rheumatoid arthritis + 4 osteoarthritis Mean age (yrs): famotidine: 45; cimetidine: 39 Sex % F: famotidine: 25.5; cimetidine: 25.9 Type of NSAID: indomethacin sulindac, naproxen, ibuprofen, piroxicam, ketoprofen, + others Previous peptic ulcers (%): n/a Primary vs secondary prophylaxis: primary H pylori positive (%): n/a
Interventions	1) ranitidine 150 mg bid for 7 weeks then ranitidine 300 mg bid for 7 weeks 2) placebo for 14 weeks
Outcomes	Gastritis Lanza score Gastric ulcers Faecal blood loss
Notes	Quality = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Taha 1996

Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: famotidine 20 mg bid: 95, famotidine 40 mg bid: 97, placebo: 93 Study duration: 24 weeks
Participants	Patient: rheumatoid, osteoarthritis Mean age (yrs): famotidine 20 mg bid: 57.2, famotidine 40 mg bid: 55, placebo: 53.4 Sex % F: famotidine 20 mg bid: 73, famotidine 40 mg bid: 70, placebo: 76 Type of NSAID: diclofenac, naproxen, indomethacin, ketoprofen, ibuprofen, febufen Previous peptic ulcers (%): famotidine 20 mg bid: 16, famotidine 40 mg bid: 13, placebo: 10 Primary vs secondary prophylaxis: primary H pylori positive (%): 20 mg bid: 51, famotidine 40 mg bid: 49, placebo: 49
Interventions	1) famotidine 20 mg bid 2) famotidine 40 mg bid 3) placebo
Outcomes	Endoscopic ulcers

Taha 1996 (Continued)

Symptoms

Notes Quality =4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Ten Wolde 1996
Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: ranitidine: 15; placebo: 15 Study duration: 12 months
Participants	Patient: rheumatic arthritis Mean age (yrs): ranitidine: 67; placebo: 58 Sex % F: ranitidine: 40; placebo: 60 Type of NSAID: diclofenac Previous peptic ulcers (%): all Primary vs secondary prophylaxis: secondary H pylori positive (%): 45
Interventions	1) ranitidine 300 mg bid + NSAIDs 2) placebo bid + NSAIDs
Outcomes	Gastric duodenal ulcers Duodenal endoscopic ulcers Total endoscopic ulcers
Notes	Quality = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Valentini 1995
Study characteristics

Methods	Randomized controlled trial Single-blind Sample size at entry: misoprostol: 23; ranitidine: 26 Study duration: not mentioned
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Valentini 1995 (Continued)

Participants	Patient: cancer Mean age (yrs): misoprostol: 59.2; ranitidine: 59.8 Sex % F: misoprostol: 56; ranitidine: 54 Type of NSAID: diclofenac Previous peptic ulcers (%): 0 Primary vs secondary prophylaxis: primary H pylori positive (%): not mentioned
Interventions	1) misoprostol 200 µg bid and diclofenac 200 mg/day 2) ranitidine 150 mg bid and diclofenac 200 mg/day
Outcomes	Gastric ulcers >6 mm Duodenal ulcers, > 6 mm Gastric erosions Duodenal erosions Nausea, abdominal pain, vomiting, diarrhea
Notes	Quality = 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

van Groenendaci 1996
Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: ranitidine 150mg: 47, placebo: 47; ranitidine 300mg: 30 Study duration: 4 weeks
Participants	Patient: rheumatoid arthritis, osteoarthritis Mean age (yrs): ranitidine 150mg: 57.5, placebo: 56; ranitidine 300mg: 55 Sex % F: ranitidine 150mg: 76.6, placebo: 74.5; ranitidine 300mg: 73.3 Type of NSAID: ketoprofen, indomethacin, naproxen, piroxicam, salicylates Previous peptic ulcers (%): not mentioned Primary vs secondary prophylaxis: primary H pylori positive (%): not mentioned
Interventions	1) ranitidine 150 mg bid 2) placebo bid
Outcomes	Endoscopic ulcers and erosions GI symptoms
Notes	Quality = 1

Risk of bias

Bias	Authors' judgement	Support for judgement
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van Groenendaci 1996 (Continued)

Allocation concealment (selection bias)	Unclear risk	D - Not used
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Verdict 1992
Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: diclofenac and misoprostol: 164; diclofenac and placebo: 175 Study duration: 12 weeks
Participants	Patient: rheumatoid arthritis Mean age (yrs): diclofenac and misoprostol: 53.2; diclofenac and placebo: 53.4 Sex % F: diclofenac and misoprostol: 75; diclofenac and placebo: 78 Type of NSAID: diclofenac Previous peptic ulcers (%): not mentioned Primary vs secondary prophylaxis: primary H pylori positive (%): not mentioned
Interventions	50 mg diclofenac and misoprostol (200 mcg) 50 mg diclofenac and placebo
Outcomes	Endoscopic gastric ulcers (>3 mm), ulcer of any size Endoscopic duodenal ulcers (>3 mm), ulcer of any size Clinical ulcers: Withdrawals overall Withdrawals due to side effects Worse arthritis withdrawal
Notes	Quality = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Yeomans 1998
Study characteristics

Methods	Randomized controlled trial Double-blind Sample size at entry: omeprazole: 210; ranitidine: 215 Study duration: 4 & 8 weeks
Participants	Patient: rheumatoid arthritis, osteoarthritis Mean age (yrs): omeprazole: 56; ranitidine: 56 Sex % F: omeprazole: 69.5; ranitidine: 69.3 Type of NSAID: diclofenac, indomethacin, naproxen

Prevention of NSAID-induced gastroduodenal ulcers (Review)

Yeomans 1998 *(Continued)*

Previous peptic ulcers (%): omeprazole: 25.3; ranitidine: 31.6
Primary vs secondary prophylaxis: primary
H pylori positive (%): omeprazole: 49.5; ranitidine: 46.5

Interventions	1) omeprazole 20 mg 2) ranitidine 150 mg bid
Outcomes	Endoscopic ulcers
Notes	Quality = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agrawal 1999	Compared diclofenac + misoprostol to nabumetone - study differences partially due to NSAID differences
Agrawal 2000	NSAID ulcer treatment not prophylaxis
Bianchi Porro 1997	Acute - only 14 days of treatment
Bianchi Porro 1998	Acute - only 3 week study
Caldwell 1989	Healing study
Cohen de Lara 2000	Misoprostol vs dosmalfate not placebo
Daneshmend 1990	Acute < 2 weeks of NSAID exposure
Desai 2008	Acute and in healthy volunteers
Donnelly 2000	Only assessed erosions and not ulcers
Geis 1991	Required data could not be extracted
Geis 1992	Duplicate data
Goldstein 2004	Post hoc analysis of previous study
Goldstein 2005	Healing phase study not prevention
Goldstein 2007	Healing phase not prevention
Lanas 2007	Not RCT

Study	Reason for exclusion
Melo Gomes 1992	Duplicate publication of Bolten 1992 in OA patients and Verdickt 1992 in rheumatoid arthritis patients
Miyake 2005	Study does not appear to be randomised
Regula 2006	PPI vs PPI study - no placebo or separate control group
Rose 1999	Abstract incomplete, group sizes not stated May be included in future revision when published in full
Rugstad 1994	No ulcer outcomes, only GI symptoms
Ryan 1987	< 3 weeks of prophylaxis
Scheiman 2006	participants were on both tNSAIDs and COX-2 inhibitors
Walan 1984	Prophylaxis phase cannot be extracted
Yilmaz 2007	Healing phase study on acute bleed

DATA AND ANALYSES

Comparison 1. Misoprostol vs placebo - primary efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Gastric ulcers - 4 - 11 week studies	8	2033	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.09, 0.31]
1.2 Duodenal ulcers - 4 - 11 week studies	6	1546	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.14, 0.62]
1.3 Total ulcers - 4 - 11 week studies	4	1323	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.14, 0.42]
1.4 Gastric ulcers - 12 weeks or longer studies	11	3641	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.17, 0.39]
1.5 Duodenal ulcers - 12 weeks or longer studies	8	2785	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.22, 0.81]
1.6 Total endoscopic ulcers - 12 weeks or longer studies	6	1791	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.20, 0.59]
1.7 Total endoscopic ulcers Chan 2001 removed - 12 weeks or longer studies	5	1701	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.20, 0.38]
1.8 Clinical ulcers - 12 weeks or longer studies	2	9276	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.27, 0.87]

Analysis 1.1. Comparison 1: Misoprostol vs placebo - primary efficacy, Outcome 1: Gastric ulcers - 4 - 11 week studies

Analysis 1.2. Comparison 1: Misoprostol vs placebo - primary efficacy, Outcome 2: Duodenal ulcers - 4 - 11 week studies

Analysis 1.3. Comparison 1: Misoprostol vs placebo - primary efficacy, Outcome 3: Total ulcers - 4 - 11 week studies

Analysis 1.4. Comparison 1: Misoprostol vs placebo - primary efficacy, Outcome 4: Gastric ulcers - 12 weeks or longer studies

Analysis 1.5. Comparison 1: Misoprostol vs placebo - primary efficacy, Outcome 5: Duodenal ulcers - 12 weeks or longer studies

Analysis 1.6. Comparison 1: Misoprostol vs placebo - primary efficacy, Outcome 6: Total endoscopic ulcers - 12 weeks or longer studies

Analysis 1.7. Comparison 1: Misoprostol vs placebo - primary efficacy, Outcome 7: Total endoscopic ulcers Chan 2001 removed - 12 weeks or longer studies

Analysis 1.8. Comparison 1: Misoprostol vs placebo - primary efficacy, Outcome 8: Clinical ulcers - 12 weeks or longer studies

Comparison 2. Misoprostol vs placebo - toxicity causing withdrawal

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Nausea	6	11021	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.07, 1.48]
2.2 Dyspepsia	7	10634	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.95, 1.36]
2.3 Constipation	2	9199	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.38, 1.06]
2.4 Diarrhea	10	11793	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [2.01, 2.77]
2.5 Abdominal pain	6	11098	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.20, 1.55]
2.6 Flatulence	3	9638	Risk Ratio (M-H, Random, 95% CI)	2.46 [0.91, 6.65]
2.7 Vomiting	2	9525	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.36, 7.31]
2.8 Drop-outs due to side-effects	12	12146	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.31, 1.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.9 Drop-outs overall	15	13239	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.11, 1.86]

Analysis 2.1. Comparison 2: Misoprostol vs placebo - toxicity causing withdrawal, Outcome 1: Nausea

Analysis 2.2. Comparison 2: Misoprostol vs placebo - toxicity causing withdrawal, Outcome 2: Dyspepsia

Analysis 2.3. Comparison 2: Misoprostol vs placebo - toxicity causing withdrawal, Outcome 3: Constipation

Analysis 2.4. Comparison 2: Misoprostol vs placebo - toxicity causing withdrawal, Outcome 4: Diarrhea

Analysis 2.5. Comparison 2: Misoprostol vs placebo - toxicity causing withdrawal, Outcome 5: Abdominal pain

Analysis 2.6. Comparison 2: Misoprostol vs placebo - toxicity causing withdrawal, Outcome 6: Flatulence

Analysis 2.7. Comparison 2: Misoprostol vs placebo - toxicity causing withdrawal, Outcome 7: Vomiting

Analysis 2.8. Comparison 2: Misoprostol vs placebo - toxicity causing withdrawal, Outcome 8: Drop-outs due to side-effects

Analysis 2.9. Comparison 2: Misoprostol vs placebo - toxicity causing withdrawal, Outcome 9: Drop-outs overall

Comparison 3. Misoprostol vs placebo - toxicity symptoms only

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Nausea	10	2835	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.81, 2.45]
3.2 Dyspepsia	10	2696	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.85, 1.63]
3.3 Constipation	2	469	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.22, 1.57]
3.4 Diarrhea	13	3409	Risk Ratio (M-H, Random, 95% CI)	2.59 [1.89, 3.55]
3.5 Abdominal pain	9	2621	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.87, 1.65]
3.6 Flatulence	5	1542	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.97, 1.91]

Analysis 3.1. Comparison 3: Misoprostol vs placebo - toxicity symptoms only, Outcome 1: Nausea

Analysis 3.2. Comparison 3: Misoprostol vs placebo - toxicity symptoms only, Outcome 2: Dyspepsia

Analysis 3.3. Comparison 3: Misoprostol vs placebo - toxicity symptoms only, Outcome 3: Constipation

Analysis 3.4. Comparison 3: Misoprostol vs placebo - toxicity symptoms only, Outcome 4: Diarrhea

Analysis 3.5. Comparison 3: Misoprostol vs placebo - toxicity symptoms only, Outcome 5: Abdominal pain

Analysis 3.6. Comparison 3: Misoprostol vs placebo - toxicity symptoms only, Outcome 6: Flatulence

Comparison 4. Misoprostol vs placebo - efficacy by dosage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Gastric ulcers - 1 month	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1.1 Low dose (400-600 ug)	5	1555	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.11, 0.41]
4.1.2 Mid-range dose (600 ug)	2	370	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.07, 0.69]
4.1.3 High dose (800 ug)	4	710	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.03, 0.32]
4.2 Duodenal ulcers - 1 month	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.2.1 Low dose (400-600 ug)	4	1274	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.08, 0.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2.2 Mid-range dose (600 ug)	3	410	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.25, 1.58]
4.2.3 High dose (800 ug)	1	183	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.06, 6.97]
4.3 Total ulcers - 1 month	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.3.1 Low dose (400-600 ug)	3	1091	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.11, 0.43]
4.3.2 Mid-range dose (600 ug)	2	370	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.17, 0.79]
4.3.3 High dose (800 ug)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.4 Gastric ulcers - 3-24 months	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.4.1 Low dose (400-600 ug)	6	2461	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.28, 0.67]
4.4.2 Mid-range dose (600 ug)	1	928	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.13, 0.44]
4.4.3 High dose (800 ug)	7	2377	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.12, 0.27]
4.5 Gastric ulcers - 3-24 months (sensitivity analysis excluding Chan 2001)	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.5.1 Low dose (400-600 ug)	5	2371	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.30, 0.51]
4.5.2 Mid-range dose (600 ug)	1	928	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.13, 0.44]
4.5.3 High dose (800 ug)	7	2377	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.11, 0.24]
4.6 Duodenal ulcers - 3-24 months	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.6.1 Low dose (400-600 ug)	5	2180	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.39, 0.81]
4.6.2 Mid-range dose (600 ug)	1	928	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.23, 0.93]
4.6.3 High dose (800 ug)	4	1521	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.09, 0.49]
4.7 Total endoscopic ulcers 3-24 months	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.7.1 Low dose (400-600 ug)	3	813	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.27, 1.31]
4.7.2 Mid-range dose (600 ug)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.7.3 High dose (800 ug)	3	978	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.14, 0.34]
4.8 Clinical ulcers - 3-24 months	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.8.1 Low dose (400-600 ug)	1	433	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.8.2 Mid-range dose (600 ug)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.8.3 High dose (800 ug)	1	8843	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.27, 0.89]

Analysis 4.1. Comparison 4: Misoprostol vs placebo - efficacy by dosage, Outcome 1: Gastric ulcers - 1 month

Analysis 4.2. Comparison 4: Misoprostol vs placebo - efficacy by dosage, Outcome 2: Duodenal ulcers - 1 month

Analysis 4.3. Comparison 4: Misoprostol vs placebo - efficacy by dosage, Outcome 3: Total ulcers - 1 month

Analysis 4.4. Comparison 4: Misoprostol vs placebo - efficacy by dosage, Outcome 4: Gastric ulcers - 3-24 months

0.005 0.1 1 10 200
Favours Misoprostol Favours Control

Analysis 4.5. Comparison 4: Misoprostol vs placebo - efficacy by dosage, Outcome 5: Gastric ulcers - 3-24 months (sensitivity analysis excluding Chan 2001)

Analysis 4.6. Comparison 4: Misoprostol vs placebo - efficacy by dosage, Outcome 6: Duodenal ulcers - 3-24 months

Analysis 4.7. Comparison 4: Misoprostol vs placebo - efficacy by dosage, Outcome 7: Total endoscopic ulcers 3-24 months

Analysis 4.8. Comparison 4: Misoprostol vs placebo - efficacy by dosage, Outcome 8: Clinical ulcers - 3-24 months

Comparison 5. Misoprostol vs placebo - toxicity causing withdrawal - by dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Nausea	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1.1 Misoprostol 400 ug/day	3	1629	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.44, 1.74]
5.1.2 Misoprostol 600 ug/day	2	1234	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.06, 2.93]
5.1.3 Misoprostol 800 ug/day	4	10281	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.00, 1.48]
5.2 Dyspepsia	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.2.1 Misoprostol 400 ug/day	3	1629	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.20, 1.11]
5.2.2 Misoprostol 600 ug/day	2	1214	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.32, 1.47]
5.2.3 Misoprostol 800 ug/day	5	10157	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.96, 1.39]
5.3 Constipation	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.3.1 Misoprostol 400 ug/day	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3.2 Misoprostol 600 ug/day	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3.3 Misoprostol 800 ug/day	2	9199	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.38, 1.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.4 Diarrhea	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.4.1 Misoprostol 400 ug/day	4	2062	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.78, 2.90]
5.4.2 Misoprostol 600 ug/day	2	1234	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [1.20, 5.95]
5.4.3 Misoprostol 800 ug/day	7	10886	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [2.09, 2.88]
5.5 Abdominal pain	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.5.1 Misoprostol 400 ug/day	3	1733	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.90, 2.59]
5.5.2 Misoprostol 600 ug/day	1	928	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.04, 3.51]
5.5.3 Misoprostol 800 ug/day	4	10291	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.17, 1.63]
5.6 Flatulence	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.6.1 Misoprostol 400 ug/day	1	916	Risk Ratio (M-H, Random, 95% CI)	1.97 [0.60, 6.48]
5.6.2 Misoprostol 600 ug/day	1	928	Risk Ratio (M-H, Random, 95% CI)	4.31 [1.47, 12.64]
5.6.3 Misoprostol 800 ug/day	3	9638	Risk Ratio (M-H, Random, 95% CI)	2.46 [0.91, 6.65]
5.7 Vomiting	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.7.1 Misoprostol 400 ug/day	1	916	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.04, 5.40]
5.7.2 Misoprostol 600 ug/day	1	928	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.24, 8.56]
5.7.3 Misoprostol 800 ug/day	2	9525	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.34, 6.25]
5.8 Dropouts due to side effects	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.8.1 Misoprostol 400 ug/day	5	2176	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.88, 1.51]
5.8.2 Misoprostol 600 ug/day	1	928	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.76, 1.57]
5.8.3 Misoprostol 800 ug/day	9	11521	Risk Ratio (M-H, Random, 95% CI)	1.68 [1.31, 2.17]
5.9 Dropouts overall	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.9.1 Misoprostol 400 ug/day	5	2073	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.82, 1.14]
5.9.2 Misoprostol 600 ug/day	2	968	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.88, 1.36]
5.9.3 Misoprostol 800 ug/day	8	10703	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.10, 1.65]

Analysis 5.1. Comparison 5: Misoprostol vs placebo - toxicity causing withdrawal - by dose, Outcome 1: Nausea

Analysis 5.2. Comparison 5: Misoprostol vs placebo - toxicity causing withdrawal - by dose, Outcome 2: Dyspepsia

Analysis 5.3. Comparison 5: Misoprostol vs placebo - toxicity causing withdrawal - by dose, Outcome 3: Constipation

Analysis 5.4. Comparison 5: Misoprostol vs placebo - toxicity causing withdrawal - by dose, Outcome 4: Diarrhea

Analysis 5.5. Comparison 5: Misoprostol vs placebo - toxicity causing withdrawal - by dose, Outcome 5: Abdominal pain

Analysis 5.6. Comparison 5: Misoprostol vs placebo - toxicity causing withdrawal - by dose, Outcome 6: Flatulence

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Analysis 5.7. Comparison 5: Misoprostol vs placebo - toxicity causing withdrawal - by dose, Outcome 7: Vomiting

Analysis 5.8. Comparison 5: Misoprostol vs placebo - toxicity causing withdrawal - by dose, Outcome 8: Dropouts due to side effects

Analysis 5.9. Comparison 5: Misoprostol vs placebo - toxicity causing withdrawal - by dose, Outcome 9: Dropouts overall

Comparison 6. Misoprostol vs placebo - symptoms - by dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Nausea	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1.1 Misoprostol 400 ug/day	7	3043	Risk Ratio (M-H, Random, 95% CI)	1.46 [1.13, 1.89]
6.1.2 Misoprostol 600 ug/day	2	1234	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.01, 1.60]
6.1.3 Misoprostol 800 ug/day	5	1576	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.54, 1.75]
6.2 Dyspepsia	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2.1 Misoprostol 400 ug/day	8	3219	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.80, 1.23]
6.2.2 Misoprostol 600 ug/day	5	1539	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.70, 0.97]
6.2.3 Misoprostol 800 ug/day	6	1849	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.83, 1.82]
6.3 Constipation	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.3.1 Misoprostol 400 ug/day	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.3.2 Misoprostol 600 ug/day	2	469	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.22, 1.57]
6.3.3 Misoprostol 800 ug/day	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.4 Diarrhea	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.4.1 Misoprostol 400 ug/day	8	3219	Risk Ratio (M-H, Random, 95% CI)	1.76 [1.37, 2.26]
6.4.2 Misoprostol 600 ug/day	4	1363	Risk Ratio (M-H, Random, 95% CI)	2.13 [1.28, 3.55]
6.4.3 Misoprostol 800 ug/day	9	2580	Risk Ratio (M-H, Random, 95% CI)	3.16 [2.33, 4.29]
6.5 Abdominal pain	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.5.1 Misoprostol 400 ug/day	7	2943	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.07, 1.60]
6.5.2 Misoprostol 600 ug/day	3	1273	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.85, 1.60]
6.5.3 Misoprostol 800 ug/day	5	1845	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.57, 1.64]
6.6 Flatulence	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.6.1 Misoprostol 400 ug/day	4	1897	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.06, 2.52]
6.6.2 Misoprostol 600 ug/day	1	928	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.06, 1.71]
6.6.3 Misoprostol 800 ug/day	3	1411	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.24, 1.96]
6.7 Vomiting	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.7.1 Misoprostol 400 ug/day	1	916	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.04, 5.40]
6.7.2 Misoprostol 600 ug/day	1	928	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.24, 8.56]
6.7.3 Misoprostol 800 ug/day	2	9525	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.34, 6.25]
6.8 Dropouts due to side effects	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.8.1 Misoprostol 400 ug/day	5	2176	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.88, 1.51]
6.8.2 Misoprostol 600 ug/day	1	928	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.76, 1.57]
6.8.3 Misoprostol 800 ug/day	9	11521	Risk Ratio (M-H, Random, 95% CI)	1.68 [1.31, 2.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.9 Dropouts overall	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.9.1 Misoprostol 400 ug/day	5	2073	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.82, 1.14]
6.9.2 Misoprostol 600 ug/day	2	968	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.88, 1.36]
6.9.3 Misoprostol 800 ug/day	8	10703	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.10, 1.65]
6.10 Headache	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.10.1 Misoprostol 400 ug/day	2	700	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.38, 1.06]
6.10.2 Misoprostol 600 ug/day	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.10.3 Misoprostol 800 ug/day	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 6.1. Comparison 6: Misoprostol vs placebo - symptoms - by dose, Outcome 1: Nausea

Analysis 6.2. Comparison 6: Misoprostol vs placebo - symptoms - by dose, Outcome 2: Dyspepsia

Analysis 6.3. Comparison 6: Misoprostol vs placebo - symptoms - by dose, Outcome 3: Constipation

Analysis 6.4. Comparison 6: Misoprostol vs placebo - symptoms - by dose, Outcome 4: Diarrhea

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Analysis 6.5. Comparison 6: Misoprostol vs placebo - symptoms - by dose, Outcome 5: Abdominal pain

Analysis 6.6. Comparison 6: Misoprostol vs placebo - symptoms - by dose, Outcome 6: Flatulence

Analysis 6.7. Comparison 6: Misoprostol vs placebo - symptoms - by dose, Outcome 7: Vomiting

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Favours treatment Favours control

Analysis 6.8. Comparison 6: Misoprostol vs placebo - symptoms - by dose, Outcome 8: Dropouts due to side effects

Analysis 6.9. Comparison 6: Misoprostol vs placebo - symptoms - by dose, Outcome 9: Dropouts overall

Analysis 6.10. Comparison 6: Misoprostol vs placebo - symptoms - by dose, Outcome 10: Headache

Comparison 7. H2 Receptor vs placebo - 4 - 11 week studies by dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Gastric ulcer	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1.1 High dose	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.04, 0.85]
7.1.2 Low dose	5	715	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.31, 1.13]
7.2 Duodenal ulcer	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.2.1 High dose	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.30]
7.2.2 Low dose	6	942	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.10, 0.57]
7.3 Total endoscopic ulcers	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.3.1 High dose	2	268	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.11, 0.53]
7.3.2 Low dose	5	597	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.23, 0.71]

Analysis 7.1. Comparison 7: H2 Receptor vs placebo - 4 - 11 week studies by dose, Outcome 1: Gastric ulcer

Analysis 7.2. Comparison 7: H2 Receptor vs placebo - 4 - 11 week studies by dose, Outcome 2: Duodenal ulcer

Analysis 7.3. Comparison 7: H2 Receptor vs placebo - 4 - 11 week studies by dose, Outcome 3: Total endoscopic ulcers

Comparison 8. H2 Receptor vs placebo 12 weeks or longer - by dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Gastric ulcer	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1.1 High dose	3	298	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.26, 0.74]
8.1.2 Low dose	4	1005	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.50, 1.08]
8.2 Duodenal ulcer	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.2.1 High dose	3	298	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.11, 0.65]
8.2.2 Low dose	3	981	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.18, 0.74]
8.3 Total endoscopic ulcers	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.3.1 High dose	3	298	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.26, 0.63]
8.3.2 Low dose	3	981	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.45, 0.88]

Analysis 8.1. Comparison 8: H2 Receptor vs placebo 12 weeks or longer - by dose, Outcome 1: Gastric ulcer

Analysis 8.2. Comparison 8: H2 Receptor vs placebo 12 weeks or longer - by dose, Outcome 2: Duodenal ulcer

Analysis 8.3. Comparison 8: H2 Receptor vs placebo 12 weeks or longer - by dose, Outcome 3: Total endoscopic ulcers

Comparison 9. H2 Receptor vs placebo - toxicity - by dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Total drop-outs	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1.1 High dose	3	292	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.41, 1.70]
9.1.2 Low dose	6	1199	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.66, 1.01]
9.2 Drop-outs due to side effects	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.2.1 High dose	2	102	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.21, 4.65]
9.2.2 Low dose	5	1011	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.58, 1.28]
9.3 Dropouts due to GI symptoms	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.3.1 High dose	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.3.2 Low dose	2	793	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.41, 1.23]
9.4 Dropouts due to abdominal pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.4.1 High dose	1	190	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.4.2 Low dose	1	188	Risk Ratio (M-H, Fixed, 95% CI)	2.94 [0.12, 71.20]
9.5 Dropouts due to diarrhea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.5.1 High dose	1	190	Risk Ratio (M-H, Fixed, 95% CI)	2.88 [0.12, 69.76]
9.5.2 Low dose	1	188	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.6 Diarrhea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.6.1 High dose	1	190	Risk Ratio (M-H, Fixed, 95% CI)	2.88 [0.12, 69.76]
9.6.2 Low dose	1	188	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.7 Abdominal pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.7.1 High dose	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.33, 0.98]
9.7.2 Low dose	1	188	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.39, 1.10]
9.8 GI symptoms	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.8.1 High dose	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.8.2 Low dose	2	520	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.29, 1.19]
9.9 Flatulence	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.9.1 High dose	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.9.2 Low dose	1	496	Risk Ratio (M-H, Fixed, 95% CI)	2.43 [1.03, 5.75]
9.10 Dyspepsia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.10.1 High dose	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.10.2 Low dose	2	520	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.29, 1.19]
9.11 Rash	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.11.1 High dose	1	190	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.11.2 Low dose	2	684	Risk Ratio (M-H, Fixed, 95% CI)	3.85 [1.20, 12.33]

Analysis 9.1. Comparison 9: H2 Receptor vs placebo - toxicity - by dose, Outcome 1: Total drop-outs

Analysis 9.2. Comparison 9: H2 Receptor vs placebo - toxicity - by dose, Outcome 2: Drop-outs due to side effects

Analysis 9.3. Comparison 9: H2 Receptor vs placebo - toxicity - by dose, Outcome 3: Dropouts due to GI symptoms

Analysis 9.4. Comparison 9: H2 Receptor vs placebo - toxicity - by dose, Outcome 4: Dropouts due to abdominal pain

Analysis 9.5. Comparison 9: H2 Receptor vs placebo - toxicity - by dose, Outcome 5: Dropouts due to diarrhea

Analysis 9.6. Comparison 9: H2 Receptor vs placebo - toxicity - by dose, Outcome 6: Diarrhea

Analysis 9.7. Comparison 9: H2 Receptor vs placebo - toxicity - by dose, Outcome 7: Abdominal pain

Analysis 9.8. Comparison 9: H2 Receptor vs placebo - toxicity - by dose, Outcome 8: GI symptoms

Analysis 9.9. Comparison 9: H2 Receptor vs placebo - toxicity - by dose, Outcome 9: Flatulence

Analysis 9.10. Comparison 9: H2 Receptor vs placebo - toxicity - by dose, Outcome 10: Dyspepsia

Analysis 9.11. Comparison 9: H2 Receptor vs placebo - toxicity - by dose, Outcome 11: Rash

Comparison 10. PPI vs placebo - 4 - 11 week studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Endoscopic gastric ulcer	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.02]
10.2 Endoscopic duodenal ulcer	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.05, 4.88]
10.3 Total endoscopic ulcers	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.05, 0.87]
10.4 Clinical Ulcer (POB)	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.86]
10.5 Clinical Ulcer - PUB (POB + symptomatic ulcer)	1	43	Odds Ratio (M-H, Fixed, 95% CI)	0.06 [0.01, 0.56]

Analysis 10.1. Comparison 10: PPI vs placebo - 4 - 11 week studies, Outcome 1: Endoscopic gastric ulcer

Analysis 10.2. Comparison 10: PPI vs placebo - 4 - 11 week studies, Outcome 2: Endoscopic duodenal ulcer

Analysis 10.3. Comparison 10: PPI vs placebo - 4 - 11 week studies, Outcome 3: Total endoscopic ulcers

Analysis 10.4. Comparison 10: PPI vs placebo - 4 - 11 week studies, Outcome 4: Clinical Ulcer (POB)

Analysis 10.5. Comparison 10: PPI vs placebo - 4 - 11 week studies, Outcome 5: Clinical Ulcer - PUB (POB + symptomatic ulcer)

Comparison 11. PPI vs placebo - 8 weeks or longer studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Endoscopic gastric ulcer	6	1230	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.31, 0.50]
11.2 Endoscopic duodenal ulcer	5	883	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.10, 0.39]
11.3 Total endoscopic ulcers	6	1259	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.28, 0.42]

Analysis 11.1. Comparison 11: PPI vs placebo - 8 weeks or longer studies, Outcome 1: Endoscopic gastric ulcer

Analysis 11.2. Comparison 11: PPI vs placebo - 8 weeks or longer studies, Outcome 2: Endoscopic duodenal ulcer

Analysis 11.3. Comparison 11: PPI vs placebo - 8 weeks or longer studies, Outcome 3: Total endoscopic ulcers

Comparison 12. PPI vs placebo - 12 weeks or longer studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Endoscopic gastric ulcer	5	1187	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.32, 0.51]
12.2 Endoscopic duodenal ulcer	4	840	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.09, 0.37]
12.3 Total endoscopic ulcers	5	1216	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.28, 0.43]

Analysis 12.1. Comparison 12: PPI vs placebo - 12 weeks or longer studies, Outcome 1: Endoscopic gastric ulcer

Analysis 12.2. Comparison 12: PPI vs placebo - 12 weeks or longer studies, Outcome 2: Endoscopic duodenal ulcer

Analysis 12.3. Comparison 12: PPI vs placebo - 12 weeks or longer studies, Outcome 3: Total endoscopic ulcers

Comparison 13. PPI vs placebo - toxicity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Dropouts overall	2	833	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.62, 1.29]
13.2 Dropouts due to side effects	4	1113	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.66, 2.15]
13.3 Diarrhea	2	832	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [0.85, 3.22]
13.4 Abdominal pain	2	832	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.39, 1.98]
13.5 Flatulence	1	430	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.25, 2.44]
13.6 Dyspepsia	2	345	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.30, 0.82]

Analysis 13.1. Comparison 13: PPI vs placebo - toxicity, Outcome 1: Dropouts overall

Analysis 13.2. Comparison 13: PPI vs placebo - toxicity, Outcome 2: Dropouts due to side effects

Analysis 13.3. Comparison 13: PPI vs placebo - toxicity, Outcome 3: Diarrhea

Analysis 13.4. Comparison 13: PPI vs placebo - toxicity, Outcome 4: Abdominal pain

Analysis 13.5. Comparison 13: PPI vs placebo - toxicity, Outcome 5: Flatulence

Analysis 13.6. Comparison 13: PPI vs placebo - toxicity, Outcome 6: Dyspepsia

Comparison 14. PPI vs H2-antagonist - 12 weeks or longer studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Endoscopic gastric ulcers	1	425	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.17, 0.62]
14.2 Endoscopic duodenal ulcers	1	425	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 0.89]
14.3 Total endoscopic ulcers	1	425	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.15, 0.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.4 Total clinical ulcers	1	425	Risk Ratio (M-H, Fixed, 95% CI)	3.07 [0.13, 74.96]
14.5 Toxicity- dropouts due to side effects	1	425	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [0.77, 4.67]
14.6 Vomiting	1	2	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14.7 Abdominal pain	1	2	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14.8 Diarrhea	1	2	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 14.1. Comparison 14: PPI vs H2-antagonist - 12 weeks or longer studies, Outcome 1: Endoscopic gastric ulcers

Analysis 14.2. Comparison 14: PPI vs H2-antagonist - 12 weeks or longer studies, Outcome 2: Endoscopic duodenal ulcers

Analysis 14.3. Comparison 14: PPI vs H2-antagonist - 12 weeks or longer studies, Outcome 3: Total endoscopic ulcers

Analysis 14.4. Comparison 14: PPI vs H2-antagonist - 12 weeks or longer studies, Outcome 4: Total clinical ulcers

Analysis 14.5. Comparison 14: PPI vs H2-antagonist - 12 weeks or longer studies, Outcome 5: Toxicity- dropouts due to side effects

Analysis 14.6. Comparison 14: PPI vs H2-antagonist - 12 weeks or longer studies, Outcome 6: Vomiting

Study or Subgroup	Treatment		Control		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Yeomans 1998	0	1	0	1		Not estimable	
Total (95% CI)		1		1		Not estimable	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable

Analysis 14.7. Comparison 14: PPI vs H2-antagonist - 12 weeks or longer studies, Outcome 7: Abdominal pain

Study or Subgroup	Treatment		Control		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Yeomans 1998	0	1	0	1		Not estimable	
Total (95% CI)		1		1		Not estimable	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable

Analysis 14.8. Comparison 14: PPI vs H2-antagonist - 12 weeks or longer studies, Outcome 8: Diarrhea

Study or Subgroup	Treatment		Control		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Yeomans 1998	0	1	0	1		Not estimable	
Total (95% CI)		1		1		Not estimable	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable

Comparison 15. Misoprostol Vs PPI (as control) - 12 weeks or longer studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Endoscopic gastric ulcer	2	917	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.33, 1.18]
15.2 Endoscopic duodenal ulcer	1	570	Risk Ratio (M-H, Fixed, 95% CI)	3.97 [1.77, 8.88]
15.3 Total endoscopic ulcers	4	1478	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.58, 2.13]

Analysis 15.1. Comparison 15: Misoprostol Vs PPI (as control) - 12 weeks or longer studies, Outcome 1: Endoscopic gastric ulcer

Analysis 15.2. Comparison 15: Misoprostol Vs PPI (as control) - 12 weeks or longer studies, Outcome 2: Endoscopic duodenal ulcer

Analysis 15.3. Comparison 15: Misoprostol Vs PPI (as control) - 12 weeks or longer studies, Outcome 3: Total endoscopic ulcers

Comparison 16. PPI Vs Misoprostol (as control) - 12 weeks or longer studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Endoscopic gastric ulcer	2	917	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.85, 3.06]
16.2 Endoscopic duodenal ulcer	1	570	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.11, 0.56]
16.3 Total endoscopic ulcers	4	1478	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.47, 1.72]

Analysis 16.1. Comparison 16: PPI Vs Misoprostol (as control) - 12 weeks or longer studies, Outcome 1: Endoscopic gastric ulcer

Analysis 16.2. Comparison 16: PPI Vs Misoprostol (as control) - 12 weeks or longer studies, Outcome 2: Endoscopic duodenal ulcer

Analysis 16.3. Comparison 16: PPI Vs Misoprostol (as control) - 12 weeks or longer studies, Outcome 3: Total endoscopic ulcers

Comparison 17. Misoprostol vs PPI - toxicity - 12 weeks or longer studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Dropouts overall	2	974	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.52, 0.97]
17.2 Dropouts due to side effects	3	1019	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.29, 0.78]

Analysis 17.1. Comparison 17: Misoprostol vs PPI - toxicity - 12 weeks or longer studies, Outcome 1: Dropouts overall

Analysis 17.2. Comparison 17: Misoprostol vs PPI - toxicity - 12 weeks or longer studies, Outcome 2: Dropouts due to side effects

Comparison 18. Misoprostol vs ranitidine 150 mg bid - 1-2 month

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Endoscopic gastric ulcers	2	599	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.03, 0.51]
18.2 Endoscopic duodenal ulcers	2	599	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.14, 7.05]
18.3 Dropouts due to side effects	2	599	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [1.16, 3.37]
18.4 Total endoscopic ulcers	1	538	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.07, 0.80]
18.5 Dropouts overall	2	599	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.94, 1.54]
18.6 Dropouts due to abdominal pain	1	538	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [1.11, 8.14]
18.7 Dropouts due to nausea	1	538	Risk Ratio (M-H, Fixed, 95% CI)	3.67 [1.03, 13.00]
18.8 Dyspepsia	2	599	Risk Ratio (M-H, Random, 95% CI)	2.49 [0.39, 15.92]
18.9 Abdominal pain symptoms	1	538	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.01, 1.52]
18.10 Flatulence symptoms	1	538	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [1.10, 1.99]
18.11 Nausea symptoms	1	538	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.81, 1.50]
18.12 Diarrhea symptoms	1	538	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.38, 2.99]

Analysis 18.1. Comparison 18: Misoprostol vs ranitidine 150 mg bid - 1-2 month, Outcome 1: Endoscopic gastric ulcers

Analysis 18.2. Comparison 18: Misoprostol vs ranitidine 150 mg bid - 1-2 month, Outcome 2: Endoscopic duodenal ulcers

Analysis 18.3. Comparison 18: Misoprostol vs ranitidine 150 mg bid - 1-2 month, Outcome 3: Dropouts due to side effects

Analysis 18.4. Comparison 18: Misoprostol vs ranitidine 150 mg bid - 1-2 month, Outcome 4: Total endoscopic ulcers

Analysis 18.5. Comparison 18: Misoprostol vs ranitidine 150 mg bid - 1-2 month, Outcome 5: Dropouts overall

Analysis 18.6. Comparison 18: Misoprostol vs ranitidine 150 mg bid - 1-2 month, Outcome 6: Dropouts due to abdominal pain

Analysis 18.7. Comparison 18: Misoprostol vs ranitidine 150 mg bid - 1-2 month, Outcome 7: Dropouts due to nausea

Analysis 18.8. Comparison 18: Misoprostol vs ranitidine 150 mg bid - 1-2 month, Outcome 8: Dyspepsia

Analysis 18.9. Comparison 18: Misoprostol vs ranitidine 150 mg bid - 1-2 month, Outcome 9: Abdominal pain symptoms

Analysis 18.10. Comparison 18: Misoprostol vs ranitidine 150 mg bid - 1-2 month, Outcome 10: Flatulence symptoms

Analysis 18.11. Comparison 18: Misoprostol vs ranitidine 150 mg bid - 1-2 month, Outcome 11: Nausea symptoms

Analysis 18.12. Comparison 18: Misoprostol vs ranitidine 150 mg bid - 1-2 month, Outcome 12: Diarrhea symptoms

Comparison 19. Nizatidine 150 mg vs 300 mg efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 Total endoscopic ulcers	1	237	Risk Ratio (M-H, Fixed, 95% CI)	2.88 [0.59, 13.96]
19.2 Dropouts overall	1	237	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.26, 2.01]

Analysis 19.1. Comparison 19: Nizatidine 150 mg vs 300 mg efficacy, Outcome 1: Total endoscopic ulcers

Analysis 19.2. Comparison 19: Nizatidine 150 mg vs 300 mg efficacy, Outcome 2: Dropouts overall

Comparison 20. NSAID + PPI vs COX 2

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 Clinical Ulcer (POB)	1	130	Odds Ratio (M-H, Fixed, 95% CI)	2.03 [0.49, 8.51]

Analysis 20.1. Comparison 20: NSAID + PPI vs COX 2, Outcome 1: Clinical Ulcer (POB)

APPENDICES

Appendix 1. MEDLINE search strategy

- RCT filter updated
- Lines 15-17 deleted: redundant (included in 'exp peptic ulcer/')
- Lines 27 and 28 deleted: redundant (see line 25)
- Line 37 amended to '(pylor\$ adj3 stenosis).tw' to pick up eg 'stenosis of the pylorus'
- Line 45 amended to 'lan?oprazole.tw'
- (After line 61) inserted 'exp proton pump inhibitors/'
- Line 70 amended to 'nonsteroid\$ anti-inflammator\$.tw'
- Line 71 amended to 'non-steroid\$ anti-inflammator\$.tw'
- (After line 71) inserted 'nonsteroid\$ antiinflammator\$.tw' and 'non-steroid\$ antiinflammator\$.tw'
- (After line 79) inserted 'exp fenoprofen/'
- (After line 80) inserted 'exp flurbiprofen/'
- Line 82 amended to 'exp indomethacin/' (correct spelling of subject heading)
- Line 83 amended to 'indomet?acin\$.tw'
- (After line 100) inserted 'phenazone.tw' (synonym for 'antipyrene')
- (After line 105) inserted 'exp aminopyrine/'
- (After line 106) inserted 'exp curcumin/'
- (After line 107) inserted 'exp clofazimine/'

Search as run 07/05/09

RCT filter updated 26/03/09

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. humans.sh.
11. 9 and 10
12. exp peptic ulcer/
13. exp peptic ulcer hemorrhage/
14. (pep\$ adj5 ulcer\$).tw.
15. (stomach adj5 ulcer\$).tw.
16. (duoden\$ adj5 ulcer\$).tw.
17. (gastr\$ adj5 ulcer\$).tw.
18. exp gastritis/
19. gastritis.tw.

20. gastropathy.tw.
21. (bleed\$ adj5 ulcer\$).tw.
22. (rebleed\$ adj5 ulcer\$).tw.
23. (gastrointestinal adj5 bleed\$).tw.
24. (gastrointestinal adj5 rebleed\$).tw.
25. (gastrointestinal adj5 hemorrhag\$).tw.
26. (gastrointestinal adj5 haemorrhag\$).tw.
27. (ulcer adj5 hemorrhag\$).tw.
28. (ulcer adj5 haemorrhag\$).tw.
29. (mucos\$ adj5 injur\$).tw.
30. exp pyloric stenosis/
31. (pylor\$ adj3 stenosis).tw.
32. (gastrointestinal adj3 perforat\$).tw.
33. (gi adj3 perforat\$).tw.
34. (ulcer\$ adj3 perforat\$).tw.
35. or/12-34
36. exp anti-ulcer agents/
37. exp omeprazole/
38. omeprazole.tw.
39. lan?oprazole.tw.
40. pantoprazole.tw.
41. rabeprazole.tw.
42. esomeprazole.tw.
43. exp histamine H2 antagonists/
44. exp cimetidine/
45. cimetidine.tw.
46. exp ranitidine/
47. ranitidine.tw.
48. exp famotidine/
49. famotidine.tw.
50. exp nizatidine/
51. nizatidine.tw.
52. (histamine adj3 H2 adj3 antagonist\$).tw.
53. (antiulcer adj5 agent\$).tw.
54. (anti\$ adj3 ulcer\$ adj3 agent\$).tw.

55. (H2 adj5 receptor adj5 antagonist\$.tw.
56. exp proton pump inhibitors/
57. (proton adj3 pump adj3 inhibitor\$.tw.
58. exp misoprostol/
59. exp sucralfate/
60. misoprostol.tw.
61. sucralfate.tw.
62. or/36-61
63. Anti-inflammatory agents, non-steroidal/
64. nsaid\$.tw.
65. nonsteroid\$ anti-inflammator\$.tw.
66. non-steroid\$ anti-inflammator\$.tw.
67. nonsteroid\$ antiinflammator\$.tw.
68. non-steroid\$ antiinflammator\$.tw.
69. exp ibuprofen/
70. ibuprofen\$.tw.
71. aceclofenac\$.tw.
72. acetamin\$.tw.
73. dexketoprofen\$.tw.
74. exp diclofenac/
75. diclofenac\$.tw.
76. fenbufen\$.tw.
77. exp fenoprofen/
78. fenoprofen\$.tw.
79. exp flurbiprofen/
80. flurbiprofen\$.tw.
81. exp indomethacin/
82. indomet?acin\$.tw.
83. exp ketoprofen/
84. ketoprofen\$.tw.
85. exp mefenamic acid/
86. (mefenamic adj3 acid\$.tw.
87. nabumetone\$.tw.
88. exp naproxen/
89. naproxen\$.tw.

90. exp phenylbutazone/
91. phenylbutazone\$.tw.
92. exp piroxicam/
93. piroxicam\$.tw.
94. exp sulindac/
95. sulindac\$.tw.
96. exp tolmetin/
97. tolmetin.tw.
98. exp antipyrine/
99. antipyrine.tw.
100. phenazone.tw.
101. tenoxicam\$.tw.
102. (tiaprofenic adj3 acid\$.tw.
103. exp aspirin/
104. aspirin\$.tw.
105. (acetylsalicylic adj3 acid\$.tw.
106. exp aminopyrine/
107. aminopyrine.tw.
108. exp curcumin/
109. curcumin.tw.
110. exp clobazamine/
111. clobazamine.tw.
112. or/63-111
113. 35 and 62 and 112
114. 11 and 113
115. limit 114 to yr="2004-2009"

Appendix 2. CCOHTA Search Strategy

Literature Search Strategy

Search Legend

In Dialog®

De = descriptor, ie. Medical Subject Heading (a controlled, thesaurus term)

Ti = title (i.e. word has to occur in title field of the bibliographic record)

Ab = abstract (ie word has to occur in abstract field of bibliographic record)

! = explode; picks up narrower terms as well, i.e. terms which are conceptually subsets of a broader term. For instance, gastritis! also retrieves gastritis, atrophic and gastritis, hypertrophic

() = words must be adjacent

? = truncation symbol

DATABASES LIMITS KEY WORDS AND STRATEGY

Dialog® OneSearch®

MEDLINE® (File 155,

1966-2002/Apr W4);
ToxFile(File 156, 1966-
2002/Feb W4))
2000-2002
for the update
of the
Cochrane
Review;
1990-2002
for the COX-
2/GI safety
review
Search done
May 3, 2002
1. gastritis!
2. (gastritis OR gastropathy)/ti,ab
3. gastrointestinal hemorrhage!
4. gi(w2)hemorrhage?/ti,ab
5. gi(w2)haemorrhage?/ti,ab
6. gastrointestinal(w2)hemorrhage?/ti,ab
7. gastrointestinal(w2)haemorrhage?/ti,ab
8. gi(w2)bleed?/ti,ab
9. gastrointestinal(w2)bleed?/ti,ab
10. ulcer(w2)hemorrhage?/ti,ab
11. ulcer(w2)haemorrhage?/ti,ab
12. peptic ulcer perforation/de
13. ulcer(w2)perforation?/ti,ab
14. gi(w2)perforation?/ti,ab
15. gastrointestinal(w2)perforation?/ti,ab
16. mucosa?(w2)injur?/ti,ab
17. peptic ulcer!
18. peptic(w2)ulcer?/ti,ab
19. stomach(w2)ulcer?/ti,ab
20. duodenal(w2)ulcer?/ti,ab
21. gastroduodenal(w2)ulcer?/ti,ab
22. gastric(w2)ulcer?/ti,ab
23. pyloric stenosis/de
24. pyloric(w)stenos?s/ti,ab
25. Set 1:Set 24
26. anti-inflammatory agents, non-steroidal/de
27. non()steroidal()antiflammar?ti,ab
28. nonsteroidal()antiflammar?/ti,ab
58
DATABASES LIMITS KEY WORDS AND STRATEGY
29. nsaid?/ti,ab
30. meclofenamic acid/de
31. meclofenamic()acid/ti,ab OR rn= 644-62-2
32. sulindac/de OR rn=38194-50-2 OR
sulindac/ti,ab
33. tolmetin/de OR tolmetin/ti,ab OR rn=26171-
23-3
34. naproxen/de OR naproxen/ti,ab OR
rn=22204-53-1
35. phenylbutazone! OR rn = 50-33-9 OR
phenylbutazone/ti,ab
36. rn=129-20-4 OR rn=30748-29-9 OR 57-96-5
OR (oxyphenbutazone OR prenazone OR
sulfinpyrazone)/ti,ab
37. ketoprofen/de OR ketoprofen/ti,ab OR rn =
22071-15-4
38. indomethacin! OR indomethacin/ti,ab OR
rn=53-86-1

39. ketorolac/de OR ketorolac/ti,ab OR rn=66635-83-4
40. ibuprofen/de OR ibuprofen/ti,ab OR rn=15687-27-1
41. curcumin/de OR curcumin./ti,ab OR rn=458-37-7
42. flurbiprofen/de OR flurbiprofen/ti,ab OR rn=5104-49-4
43. diclofenac/de OR diclofenac/ti,ab OR rn=15307-86-5
44. clofazimine/de OR clofazimine/ti,ab OR rn=2030-63-9
45. aspirin/de OR [acetylsalicylic()]acid OR aspirin]/ti,ab OR rn=50-78-2
46. antipyrine/de OR antipyrine/tia,b OR rn=60-80-0
47. aminopyrine! OR (aminopyrine OR dipyrone)/ti,ab OR rn=58-15-1 OR rn= 68-89-3 OR dipyrone/de
48. oxaprozin/ti,ab OR rn=21256-18-8
49. diflunisal/de OR diflunisal/ti,ab OR rn=22494-42-4
50. choline()magnesium()salicylate?/ti,ab OR rn=64425-90-7
51. choline()salicylate?/ti,ab OR rn=2016-36-659
- DATABASES LIMITS KEY WORDS AND STRATEGY
52. floctafenine/ti,ab OR rn=23779-99-9
53. piroxicam/de OR piroxicam/ti,ab OR rn=36322-90-4
54. tenoxicam/ti,ab OR rn=59804-37-4
55. nabumetone/ti,ab OR rn=42924-53-8
56. tiaprofenic()acid?/ti,ab OR rn=33005-95-7
57. fenoprofen/de OR fenoprofen/ti,ab OR rn=31879-05-7
58. mefenamic acid/de OR mefenamic()acid?/ti,ab or rn= 61-68-7
59. etodolac/de OR etodolac/ti,ab OR rn=41340-25-4
60. Set 26:Set 59
61. anti-ulcer agents/de
62. sucralfate/de OR sucralfate/ti,ab OR rn=54182-58-0
63. Set 61:Set 62
64. prostaglandin antagonists/de
65. prostaglandin()antagonist?/ti,ab
66. misoprostol/de OR misoprostol/ti,ab OR rn=59122-46-2
67. Set 64:Set 66
68. proton pumps!(!ai
69. proton()pump?()inhibit?/ti,ab OR PPI?/ti,ab
70. omeprazole/de OR omeprazole/ti,ab OR rn=73590-58-6
71. pantoprazole/ti,ab OR rn=102625-70-7
72. lansoprazole/tia,b OR rn=103577-45-3
73. timoprazole?/ti,ab OR 57237-97-5
74. rabeprazole /ti,ab OR rn=117976-89-3
75. esomeprazole/ti,ab OR Nexium/ti,.ab
76. Set 68:Set 75
77. histamine H2 antagonists/de
78. histamine()H2()antagonist?/ti,ab OR

H2RA/ti,ab OR
[histamine()H2()receptor()antagonist? OR
histamine()type()2()receptor()antagonist?]/ti,
ab
79. cimetidine/de OR cimetidine/ti,ab OR rn=
51481-61-9
80. famotidine/de OR famotidine/ti,ab OR rn=
76824-35-6
81. nizatidine/de OR nizatidine/.ti,ab OR
82. ranitidine/de OR ranitidine/ti,ab OR
60
DATABASES LIMITS KEY WORDS AND STRATEGY
rn=66357-35-5
83. Set 77:Set 82
84. Set 25 AND Set 60
85. Set 84 AND (Set 63 OR Set 67 OR Set 76 OR
Set 83)
86. dt= (clinical trial OR clinical trial, phase i OR
clinical trial, phase ii OR clinical trial, phase
iii OR clinical trial, phase iv OR metaanalysis
OR controlled clinical trial OR
randomized controlled trial OR multicenter
study OR review)
87. clinical trials!
88. (comparative study OR double-blind method
OR random
allocation)/de
89. (random? OR controlled trial? OR controlled
clinical trial? OR clinical trial? OR double
blind?)/ti,ab
90. (multicent? trial? OR multi cent? trial? OR
meta analy? OR metaanaly? OR metaanalysis)/
ti,ab
91. (research integration OR research overview?
OR quantitative review? OR quantitative
overview? OR methodologic review?
OR methodologic overview?)/ti,ab
92. (systematic overview? OR systematic review?
OR integrative research OR quantitative
synthesis OR comparative stud? OR
prospective stud? OR retrospective stud? OR
single blind? OR triple blind? OR treble
blind? OR dummy OR sham OR rct?)/ti,ab
93. Set 86:Set 92
94. Set 85 AND Set 93
95. Set 94/2000:2002
96. Set 95 from 155
97. Set 95 from 156
98. Set 94/1990:2002
99. Set 98 from 155
100. S98 from 156
101. [cyclo()oxygenase()2()inhibit? OR
cyclooxygenase()2()inhibit? OR
cox()2()inhibit?]/ti,ab
102. [celecoxib OR celebrex]/ti,ab OR rn=
169590-42-5
61
DATABASES LIMITS KEY WORDS AND STRATEGY
103. [rofecoxib OR vioxx]/ti,ab OR rn=162011-
90-7
104. (meloxicam OR mobic OR movalis OR
mobec OR movicox OR parocin OR uticox

OR mobicox)/ti,ab OR rn=71125-38-7
105. etodolac/de OR etodolac/ti,ab OR rn=41340-25-4
106. Set 101:Set 105
107. Set 25 AND Set 106 AND Set 93
108. Set 107/1990:2002
109. Set 108 from 155
110. Set 109 from 156
EMBASE® (File 73, 1974-2002/Apr W4)
111. ulcer perforation/de
112. stomach mucosa injury/de
113. pylorus stenosis!
114. Set 111:Set 113
115. Set 1: 11
116. Set 13:16
117. Set 18:22
118. Set 114:Set 117
119. Set 17 OR Set 24 OR Set 118
120. nonsteroid antiinflammatory agent!
121. Set 120 OR Set 60
122. Set 119 AND Set 121
123. antiulcer agent! OR Set 62 OR gastrointestinal mucosa protective agent!
124. prostaglandin receptor blocking agent!
125. stomach secretion inhibitor!
126. Set 123: Set 125
127. Set 69:Set 75
128. Set 65 OR Set 127 OR Set 83 OR Set 126
129. Set 122 AND Set 128
130. (comparative study OR randomized controlled trial OR prospective study OR retrospective study OR meta analysis OR clinical trial OR multicenter study OR phase 1 clinical trial OR phase 2 clinical trial OR phase 3 clinical trial OR phase 4 clinical trial OR prospective study OR retrospective study OR double blind procedure OR conference paper! OR longitudinal study /de
131. Set 129 AND (Set 130 OR Set 89 OR Set 90 OR Set 91 OR Set 92)
132. Set 131/2000:2001
62
DATABASES LIMITS KEY WORDS AND STRATEGY
133. Set 132 from Set 73
134. Set 131/1990:2002
135. cyclooxygenase 2 inhibitor! OR Set 106
136. Set 119 AND Set 135 AND (Set 130 OR Set 89 OR Set 90 OR Set 91 OR Set 92)
137. Set 136/1990:2002
138. Set 137 from 73
BIOSIS Previews®
(File 5, 1969-2002/Apr W4)
139. gastritis/de
140. gastrointestinal hemorrhage/de
141. gastrointestinal bleeding/de
142. gastric mucosal injury/de
143. gastric ulcer/de
144. gastroduodenal ulcer/de
145. duodenal ulcer/de
146. peptic ulcer/de

147. Set 139:Set 146
 148. Set 4:Set 11
 149. Set 13:16
 150. Set 18:Set 22
 151. Set 2 OR Set 24 OR Set 147 OR Set 148 OR
 Set 149 OR Set 150
 152. non-steroidal anti-inflammatory drugs/de
 153. nonsteroidal anti-inflammatory drugs/de
 154. Set 27:Set 59
 155. acetylsalicylic acid/de
 156. Set 152:Set 155
 157. Set 151 AND Set 156
 158. antiulcer-drug/de
 159. Set 158 OR sucralfate/de OR sucralfate/ti,ab
 OR rn=54182-58-0
 160. Set 158:Set 159
 161. Set 65 OR Set 66
 162. proton pump inhibitors/de
 163. Set 69 OR pantoprazole/de OR
 lansoprazole/de
 164. Set 70:Set 75
 165. Set 162 OR Set 163 OR S164
 166. histamine H2-receptor antagonist-drug/de
 167. Set 78:Set 82
 168. Set 166:Set 167
 169. Set 160 OR Set 161 OR Set 165 OR Set 168
 170. Set 157 AND Set 169
 171. (clinical trial OR randomized trial OR
 prospective study OR randomized controlled
 63
 DATABASES LIMITS KEY WORDS AND STRATEGY
 trial OR multicenter study OR randomized
 clinical trial)/de
 172. Set 171 OR Set 89 OR Set 90 OR Set 91 OR
 Set 92
 173. Set 170 AND Set 172
 174. Set 173/2000:2002
 175. Set 174 from 5
 176. Set 151 AND Set 106 AND Set 172
 177. Set 176/1990:2002
 178. Set 177 from 5
 Pharmaceutical News
 Index (PNI®)(File 42,
 1974-2002, Apr W4)
 Current Contents
 Search® (File 440,
 1990-2002, May W3)
 179. Set 4:Set 11
 180. Set 13:Set 16
 181. Set 18:Set 22
 182. Set 2 OR Set 179 OR Set 180 OR Set 181
 OR Set 24
 183. Set 27:Set 29
 184. [meclofenamic()acid OR
 acetylsalicylic()acid OR
 choline()magnesium()salicylate? OR
 choline()salicylate? OR tiaprofenic()acid?
 OR mefenamic()acid?]/ti,ab
 185. (sulindac OR tolmetin OR naproxen OR
 phenylbutazon OR oxyphenbutazone OR
 prenazone OR sulfipyrzazone OR
 ketoprofen OR indomethacin OR ketorolac

OR ibuprofen OR curcumin OR flurbiprofen
OR diclofenac OR clofazimine OR aspirin
OR antipyrene OR aminopyrine OR
dipyrene OR oxaprozin OR diflunisal
OR floctafenine OR piroxicam OR
tenoxicam OR nabumetone OR
fenoprofen)/ti,ab
186. Set 183:Set 185
187. Set 182 AND Set 186
188. [anti()ulcer()drug? OR antiulcer()drug? OR
sucralfate]/ti,ab
189. [prostaglandin()antagonist? OR
misoprostol]/ti,ab
190. [proton()pump?()inhibit? OR PPI? OR
omeprazole OR pantoprazole OR
lansoprazole OR timoprazole OR
rabeprazole OR esomeprazole OR
Nexium]/ti,ab
191. [histamine()H2()antagonist? OR H2RA OR
64
DATABASES LIMITS KEY WORDS AND STRATEGY
histamine()H2()receptor()antagonist? OR
histamine()type()2()receptor()antagonist?]/
ti,ab
192. [cimetidine OR famotidine OR
nizatidine]/ti,ab
193. Set 188:Set 192
194. Set 187 AND Set 193 AND (Set 89 OR Set
90 OR Set 91 OR Set 92)
195. Set 194/2000:2002
196. Set 195 from 42
197. Set 195 from 440
198. Set 195 from 173
199. [cyclo()oxygenase()2()inhibit? OR
cyclooxygenase()2()inhibit? OR
cox()2()inhibit?]/ti,ab
200. (celecoxib OR celebrex OR rofecoxib OR
vioxx OR meloxicam OR mobic OR
movalis OR mobec OR movicox OR
parocin OR uticox OR mobicox OR
etodolac)/ti,ab
201. Set 199:Set 200
202. Set 182 AND Set 201 AND (Set 89 OR Set
90 OR Set 91 OR Set 92)
203. Set 202/1990:2002
204. Set 203 from 42
205. Set 203 from 440
206. Set 203/from 173
207. Set 96 OR Set 97 OR Set 133 OR Set 175
OR Set 196 OR Set 197 OR Set 198
208. Reduce duplicates Set 207
209. type s208/4/all from
155,156,73,5,42,440,173 = CochraneUpdate
210. Set 109 OR Set 110 OR Set 138 OR Set 178
OR Set 204 OR Set 205 OR Set 206
211. Type S210/4/all from
155,156,73,5,42,440,173= Cox-2/GI safety
Cochrane Library on
CD-ROM (Cochrane
Collaboration and
Update Software);
Conference Papers

Index, CCOHTA HTA
Checklist; Google™
Dialog® OneSearch® Search Using the strategy above which was devised to
65
DATABASES LIMITS KEY WORDS AND STRATEGY
on MEDLINE® (File
155), ToxFile (File 156),
EMBASE® (File 73),
BIOSIS Previews®
(File 5), Pharmaceutical
News Index
(PNI®) (File
42), Current Contents
Search® (File 440)
performed
May 3, 2002
update the original Cochrane search, an additional
search on gastroprotective agents under
investigation, was performed. These were
bioprazol, rebamipide, polaprezinc, nocolprost,
lafutidine, dosmalfate, and osutidine. Titles and
abstracts of articles were searched, registry
numbers, and earlier names, such as FRG 8813, F
3616, T 593
Dialog® Adis Clinical
Trials Insight (File
173), Biobase (File 71),
Biosis Previews® (File
5), SciSearch® (File 34),
Pharmaceutical News
Index (File 42), Inside
Conferences (File 65),
EMBASE (File 72),
Pascal (File 144),
MEDLINE® (File 154),
F-D-C Reports (File
187), Current Contents
(File 440). PubMed
was also searched.
Search
performed
April 7, 2003
Re: COX-2/GI safety, an additional search was
conducted during the course of the review to
identify whether the results of the SUCCESS-1
trial had been published in full.

Appendix 3. Embase Search Strategy

- RCT filter updated by translating Medline terminology to Embase terms
- Line 31 amended to 'exp peptic ulcer bleeding/'
- Line 32 amended to 'exp ulcer perforation/'
- Lines 33 and 34 deleted: redundant (included in 'exp peptic ulcer/')
- Lines 44 and 45 deleted: redundant (see line 42)
- Line 53 amended to 'exp pylorus stenosis/'
- Line 54 amended to '(pylor\$ adj3 stenosis).tw'
- Line 59 amended to 'exp antiulcer agent/'
- Line 60 deleted: redundant (included in 'exp antiulcer agent/')
- Line 62 amended to 'lan?oprazole.tw'
- Lines 66, 67, 69, 71 and 73 deleted: redundant (included in 'exp antiulcer agent/')

- (After line 78) inserted 'exp proton pump inhibitor/'
- Lines 80 and 81 deleted: redundant (included in 'exp antiulcer agent/')
- Line 87 amended to 'nonsteroid\$ anti-inflammatory\$.tw'
- Line 88 amended to 'non-steroid\$ anti-inflammatory\$.tw'
- (After line 88) inserted 'nonsteroid\$ antiinflammator\$.tw' and 'non-steroid\$ antiinflammator\$.tw'
- Line 116 amended to 'exp phenazone/'
- (After line 116) inserted 'phenazone.tw'
- Line 120 amended to 'exp acetylsalicylic acid/'

Search as run 07/05/09

RCT filter updated 27/03/09

1. exp randomized controlled trial/
2. randomi?ed controlled trial\$.tw.
3. exp randomization/
4. exp single blind procedure/
5. exp double blind procedure/
6. or/1-5
7. animal.hw.
8. human.hw.
9. 7 not (7 and 8)
10. 6 not 9
11. exp clinical trial/
12. (clin\$ adj3 stud\$).ti,ab,tw.
13. (clin\$ adj3 trial\$).ti,ab,tw.
14. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab,tw.
15. exp placebo/
16. placebo\$.ti,ab,tw.
17. random.ti,ab,tw.
18. (crossover\$ or cross-over\$).ti,ab,tw.
19. or/11-18
20. 19 not 9
21. 20 not 10
22. exp comparative study/
23. exp evaluation/
24. exp prospective study/
25. exp controlled study/
26. (control\$ or prospective\$ or volunteer\$).ti,ab,tw.
27. or/22-26

28. 27 not 9
29. 10 or 21 or 28
30. exp peptic ulcer/
31. exp peptic ulcer bleeding/
32. exp ulcer perforation/
33. (pep\$ adj5 ulcer\$).tw.
34. (stomach adj5 ulcer\$).tw.
35. (duoden\$ adj5 ulcer\$).tw.
36. (gastr\$ adj5 ulcer\$).tw.
37. exp gastritis/
38. gastritis.tw.
39. gastropathy.tw.
40. (bleed\$ adj5 ulcer\$).tw.
41. (rebleed\$ adj5 ulcer\$).tw.
42. (gastrointestinal adj5 bleed\$).tw.
43. (gastrointestinal adj5 rebleed\$).tw.
44. (gastrointestinal adj5 hemorrhag\$).tw.
45. (gastrointestinal adj5 haemorrhag\$).tw.
46. (ulcer adj5 hemorrhag\$).tw.
47. (ulcer adj5 haemorrhag\$).tw.
48. (mucos\$ adj5 injur\$).tw.
49. exp pylorus stenosis/
50. (pylor\$ adj3 stenosis).tw.
51. (gastrointestinal adj3 perforat\$).tw.
52. (gi adj3 perforat\$).tw.
53. (ulcer\$ adj3 perforat\$).tw.
54. or/30-53
55. exp antiulcer agent/
56. omeprazole.tw.
57. lan?oprazole.tw.
58. pantoprazole.tw.
59. rabeprazole.tw.
60. esomeprazole.tw.
61. cimetidine.tw.
62. ranitidine.tw.

63. famotidine.tw.
64. nizatidine.tw.
65. (histamine adj3 H2 adj3 antagonist\$.tw.
66. (antiulcer adj5 agent\$.tw.
67. (anti\$ adj3 ulcer\$ adj3 agent\$.tw.
68. (H2 adj5 receptor adj5 antagonist\$.tw.
69. exp proton pump inhibitor/
70. (proton adj3 pump adj3 inhibitor\$.tw.
71. misoprostol.tw.
72. sucralfate.tw.
73. or/55-72
74. Anti-inflammatory agents, non-steroidal/
75. nsaid\$.tw.
76. nonsteroid\$ anti-inflammator\$.tw.
77. non-steroid\$ anti-inflammator\$.tw.
78. nonsteroid\$ antiinflammator\$.tw.
79. non-steroid\$ antiinflammator\$.tw.
80. exp ibuprofen/
81. ibuprofen\$.tw.
82. aceclofenac\$.tw.
83. acemetacin\$.tw.
84. dexketoprofen\$.tw.
85. exp diclofenac/
86. diclofenac\$.tw.
87. fenbufen\$.tw.
88. fenoprofen\$.tw.
89. flurbiprofen\$.tw.
90. exp indometacin/
91. indometacin\$.tw.
92. exp ketoprofen/
93. ketoprofen\$.tw.
94. exp mefenamic acid/
95. (mefenamic adj3 acid\$.tw.
96. nabumetone\$.tw.
97. exp naproxen/

98. naproxen\$.tw.
99. exp phenylbutazone/
100. phenylbutazone\$.tw.
101. exp piroxicam/
102. piroxicam\$.tw.
103. exp sulindac/
104. sulindac\$.tw.
105. exp tolmetin/
106. tolmetin.tw.
107. exp phenazone/
108. phenazone.tw.
109. antipyrine.tw.
110. tenoxicam\$.tw.
111. (tiaprofenic adj3 acid\$.tw.
112. exp acetylsalicylic acid/
113. aspirin\$.tw.
114. (acetylsalicylic adj3 acid\$.tw.
115. aminopyrine.tw.
116. curcumin.tw.
117. clofazimine.tw.
118. or/74-117
119. 54 and 73 and 118
120. 29 and 119
121. limit 120 to ("review" or short survey)
122. 120 not 121
123. limit 122 to yr="2004-2009"

Appendix 4. EBMR Search Strategy

1. exp peptic ulcer/
2. exp peptic ulcer hemorrhage/
3. (pep\$ adj5 ulcer\$.ti,ab.
4. (stomach adj5 ulcer\$.ti,ab.
5. (duoden\$ adj5 ulcer\$.ti,ab.
6. (gastr\$ adj5 ulcer\$.ti,ab.
7. exp gastritis/
8. gastritis.ti,ab.

9. gastropathy.ti,ab.
10. (bleed\$ adj5 ulcer\$).ti,ab.
11. (rebleed\$ adj5 ulcer\$).ti,ab.
12. (gastrointestinal adj5 bleed\$).ti,ab.
13. (gastrointestinal adj5 rebleed\$).ti,ab.
14. (gastrointestinal adj5 hemorrhag\$).ti,ab.
15. (gastrointestinal adj5 haemorrhag\$).ti,ab.
16. (ulcer adj5 hemorrhag\$).ti,ab.
17. (ulcer adj5 haemorrhag\$).ti,ab.
18. (mucos\$ adj5 injur\$).ti,ab.
19. exp pyloric stenosis/
20. (pylor\$ adj3 stenosis).ti,ab.
21. (gastrointestinal adj3 perforat\$).ti,ab.
22. (gi adj3 perforat\$).ti,ab.
23. (ulcer\$ adj3 perforat\$).ti,ab.
24. or/1-23
25. exp anti-ulcer agents/
26. exp omeprazole/
27. omeprazole.ti,ab.
28. lan?oprazole.ti,ab.
29. pantoprazole.ti,ab.
30. rabeprazole.ti,ab.
31. esomeprazole.ti,ab.
32. exp histamine H2 antagonists/
33. exp cimetidine/
34. cimetidine.ti,ab.
35. exp ranitidine/
36. ranitidine.ti,ab.
37. exp famotidine/
38. famotidine.ti,ab.
39. exp nizatidine/
40. nizatidine.ti,ab.
41. (histamine adj3 H2 adj3 antagonist\$).ti,ab.
42. (antiulcer adj5 agent\$).ti,ab.
43. (anti\$ adj3 ulcer\$ adj3 agent\$).ti,ab.

44. (H2 adj5 receptor adj5 antagonist\$.ti,ab.
45. exp proton pump inhibitors/
46. (proton adj3 pump adj3 inhibitor\$.ti,ab.
47. exp misoprostol/
48. exp sucralfate/
49. misoprostol.ti,ab.
50. sucralfate.ti,ab.
51. or/25-50
52. Anti-inflammatory agents, non-steroidal/
53. nsaid\$.ti,ab.
54. nonsteroid\$ anti-inflammator\$.ti,ab.
55. non-steroid\$ anti-inflammator\$.ti,ab.
56. nonsteroid\$ antiinflammator\$.ti,ab.
57. non-steroid\$ antiinflammator\$.ti,ab.
58. exp ibuprofen/
59. ibuprofen\$.ti,ab.
60. aceclofenac\$.ti,ab.
61. acetamin\$.ti,ab.
62. dexketoprofen\$.ti,ab.
63. exp diclofenac/
64. diclofenac\$.ti,ab.
65. fenbufen\$.ti,ab.
66. exp fenoprofen/
67. fenoprofen\$.ti,ab.
68. exp flurbiprofen/
69. flurbiprofen\$.ti,ab.
70. exp indomethacin/
71. indomet?acin\$.ti,ab.
72. exp ketoprofen/
73. ketoprofen\$.ti,ab.
74. exp mefenamic acid/
75. (mefenamic adj3 acid\$.ti,ab.
76. nabumetone\$.ti,ab.
77. exp naproxen/
78. naproxen\$.ti,ab.

79. exp phenylbutazone/
80. phenylbutazone\$.ti,ab.
81. exp piroxicam/
82. piroxicam\$.ti,ab.
83. exp sulindac/
84. sulindac\$.ti,ab.
85. exp tolmetin/
86. tolmetin.ti,ab.
87. exp antipyrine/
88. antipyrine.ti,ab.
89. phenazone.ti,ab.
90. tenoxicam\$.ti,ab.
91. (tiaprofenic adj3 acid\$).ti,ab.
92. exp aspirin/
93. aspirin\$.ti,ab.
94. (acetylsalicylic adj3 acid\$).ti,ab.
95. exp aminopyrine/
96. aminopyrine.ti,ab.
97. exp curcumin/
98. curcumin.ti,ab.
99. exp clofazimine/
100. clofazimine.ti,ab.
101. or/52-100
102. 24 and 51 and 101
103. limit 102 to yr="2004-2009"

Appendix 5. Search used for Canadian NSAID Consensus Conference

1. exp stomach/
2. stomach.tw.
3. gastr\$.tw.
4. exp duodenum/
5. duoden\$.tw.
6. antrum.tw.
7. pylor\$.tw.
8. gastroduoden\$.tw.
9. or/1-8

10. exp peptic ulcer/
11. exp peptic ulcer hemorrhage/
12. (peptic adj5 ulcer\$.tw.
13. (bleed\$ adj5 ulcer\$.tw.
14. (recurrent adj5 bleed\$ adj5 ulcer\$.tw.
15. (rebleed\$ adj5 ulcer\$.tw.
16. (ulcer\$ adj5 hemo\$.tw.
17. (ulcer\$ adj5 haemo\$.tw.
18. nonvaric\$.tw.
19. (gastrointestinal adj5 bleed\$.tw.
20. (gastrointestinal adj5 hemorrhag\$.tw.
21. (gastrointestinal adj5 haemorrhag\$.tw.
22. (GI adj5 bleed\$.tw.
23. (GI adj5 hemorrhag\$.tw.
24. (gi adj5 haemorrhag\$.tw.
25. UGIB.tw.
26. (gastritis or gastropathy).ti,ab.
27. peptic ulcer perforation/
28. (ulcer adj5 perforation).ti,ab.
29. pyloric stenosis/
30. (pyloric adj5 stenosis).ti,ab.
31. (pyloric adj5 obstruction).ti,ab.
32. (endoscop\$ adj5 ulcer).ti,ab.
33. (symptomatic adj5 ulcer).ti,ab.
34. nausea/
35. nausea.tw.
36. vomiting/
37. vomit\$.tw.
38. abdominal pain/
39. abdominal pain.tw.
40. dyspepsia/
41. dyspepsia.tw.
42. or/10-33
43. 9 and 42

NSAIDS section

1. exp anti inflammatory agents non steroidal/
2. nonsteroidal anti-inflammator\$.tw.
3. non-steroidal anti-inflammator\$.tw.
4. NSAIDs/
5. NSAID\$.tw.
6. diclofenac/ or diclofenac.ti,ab.
7. naproxen/ or naproxen.ti,ab.
8. ibuprofen/ or ibuprofen.ti,ab.
9. ketoprofen/ or ketoprofen.ti,ab.
- 10.indomethacin/ or indomethacin.ti,ab.
- 11.ketorolac/ or ketorolac.ti,ab.
- 12.flurbiprofen/ or flurbiprofen.ti,ab.
- 13.clofazimine/ or clofazimine.ti,ab.
- 14.piroxicam/ or piroxicam.ti,ab.
- 15.tenoxicam/ or tenoxicam.ti,ab.
- 16.nabumetone/ or nabumetone.ti,ab.
- 17.fenoprofen/ or fenoprofen.ti,ab.
- 18.or/1-17

misoprostol

1. prostaglandin antagonists/
2. (prostaglandin adj2 antagonist?).ti,ab.
3. misoprostol/ or misoprostol.ti,ab.
4. or/1-3

H2RAs

1. histamine H2 antagonists/
2. (histamine adj3 "2" adj3 antagonist?).ti,ab.
3. (histamine adj2 "2" adj2 receptor adj2 antagonist?).ti,ab.
4. H2RA?.ti,ab.
5. cimetidine/ or cimetidine.ti,ab.
6. famotidine/ or famotidine.ti,ab.
7. nizatidine/ or nizatidine.ti,ab.
8. ranitidine/ or ranitidine.ti,ab.
9. or/1-8

RCT filter

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized controlled trials/
4. random allocation/
5. double blind method/
6. single blind method/

7. or/1-6
8. (animals not human).sh.
9. 7 not 8
10. clinical trial.pt.
11. exp clinical trial/
12. (clin\$ adj25 trial\$).ti,ab.
13. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
14. placebos/
15. placebo\$.ti,ab.
16. Random\$.ti,ab.
17. research design/
18. or/10-17
19. 18 not 8
20. 19 not 9
21. comparative study/
22. exp evaluation studies/
23. follow-up studies/
24. prospective studies/
25. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
26. or/21-25
27. 26 not 8
28. 27 not (9 or 20)
29. 9 or 20 or 28

FEEDBACK

Endoscopic ulcers are not the same as clinical ulcers, October 2010

Summary

Original feedback

We were pleased to read the review article as it addresses an important clinical question ([Rostom 2002](#)). We did however identify some important issues that hinder our ability to apply the results in clinical practice.

Firstly, in the background, the authors noted that endoscopic ulcers can be found in approximately 40% of chronic NSAID users and up to 85% of documented endoscopic ulcers do not become clinically apparent ([Rostom 2002](#)). However, in the results, we have concerns about the lack of discussion regarding the use of surrogate endpoints, such as endoscopic ulcers, to predict meaningful endpoints such as clinical ulcers ([Moore 2009](#)). Evidence showing a direct relationship in the same trial between endoscopic gastroduodenal ulcers and clinically significant ulcer complications is lacking ([Moore 2009](#)). We would recommend including a discussion on the uncertain clinical relevance of endoscopic ulcers ([Graham 2009](#); [Moore 2009](#)).

Secondly, the overwhelming majority of trials included in the review (38/41) reported only on endoscopic ulcers; leaving a very small sample of only three trials that reported on clinical ulcers and the subsequent complications. It is believed that selective outcome reporting bias can have significant implications on the assessment of interventions ([McGauran 2010](#)). One way to address the issue of selective outcome reporting bias is through contacting the authors of the individual trials and requesting to see their clinical outcome data. In this

review article, there was no indication of an attempt to contact the authors of the individual trials for information on potential clinical events (i.e. symptomatic ulcers, bleeding, etc). The authors of the review discussed that the MUCOSA trial was the only true clinical outcome trial; however, no attempt was made to highlight the potential dangers of drawing conclusions from a single study without replication. In fact, the authors went on to summarize that “misoprostol at 800 ug daily reduces the occurrence of NSAID related clinical ulcer complications” (Rostom 2002). We do not feel that this statement is justified.

Ninety three percent of trials did not report on clinical ulcers and this should have been emphasized in the review. Our interpretation of the available literature is that there is insufficient evidence to determine if gastroprotection with any class of drugs reduces the incidence of clinical complications that are important to patients on long-term NSAID therapy.

Lastly, we would like to note a potential transcription error on page 40 (Rostom 2002). In the list of characteristics of included studies, the sample size described in the Silverstein 1995 trial appears to be missing the last numerical digit in the sample size at entry and should read 4404 and 4439 instead of 440 and 443. As a reader, it's helpful to understand all abbreviations used. In addition, the authors did not define the abbreviations POB and PUB used in reference to proton pump inhibitor clinical endpoint trials.

Stephanie Halliday, BSc (Pharm)

Aaron Tejani, BSc (Pharm), PharmD, ACPR

Reply

Thank you for your letter and comments.

Your major concerns revolve around the usage of the endoscopic endpoint in the majority of the trials included in this review, and you are also uncomfortable with the results of the mucosa study as it is a single clinical ulcer study.

Both these points were emphasised in our review including in the methods and discussion.

The feedback authors should be aware that the design and execution of a randomized controlled trial utilizing the endoscopic endpoint is very different than for a trial utilizing the clinical ulcer composite endpoints (which typically include bleeding, perforation, or obstruction). The common nature of endoscopic endpoints means that NSAID studies utilizing them can be small (few hundred patients), short (4 to 12 weeks), and relatively inexpensive despite all patients undergoing endoscopy. These studies can be high quality and powered to detect significant changes in this endpoint. For example, proton pump inhibitors reduce the relative risk of endoscopically detected duodenal ulcers by greater than 80% (Rostom 2009c; Rostom 2002). So it is no wonder that the vast majority of researchers conducting NSAID studies, particularly the early traditional NSAID (tNSAID) trials and cyclo-oxygenase 2 inhibitors (COX-2s) trials, utilized this endpoint.

NSAID trials that utilize clinical ulcer endpoints need to be very large (thousands of patients), quite long (6 months at least), and need formal adjudication of potential endpoint events as not every patient undergoes endoscopy. The complexity and expense of these studies limited their early usage until the COX-2 era arrived. Therefore, we feel the MUCOSA study (Silverstein 1995) can be considered landmark in that it was the first to exercise this more complex design and subsequently was used as a model for the clinical ulcer trials conducted for the COX-2s. Furthermore, the MUCOSA trial (Silverstein 1995) identified that clinical events occur at a rate of about 1.5% per 100 patient years amongst tNSAID users, a finding that was repeatedly identified in the COX-2 clinical ulcer studies (Rostom 2009c; Rostom 2002). MUCOSA was a high quality study and we have no reservation in the rating we gave it and as such in the believability of its results (Rostom 2009c; Rostom 2002).

There is no question that the clinical ulcer studies are the preferred source of evidence over endoscopic studies particularly for the evaluation of the safety of new agents as suggested by the FDA (FDA 2010). However at the same November 4th, 2010 FDA meeting, the Gastrointestinal Drugs Advisory Committee agreed that endoscopic ulcers are “an adequate primary efficacy endpoint for evaluating products intended to prevent NSAID-associated upper GI toxicity”. Therefore, it would be unwise to discount all the available data from endoscopic studies. These studies demonstrated remarkable consistency in placebo arms event rates across the tNSAID and COX-2 studies. Furthermore while there is not a one to one relationship between endoscopic ulcers and clinical ulcers, clearly there is a relationship and few experts in the field would discount that today. In our own work, we have found that misoprostol and COX-2 inhibitors reduce the risk of clinical ulcers by about 50%, while the same agents reduce the risk of endoscopic ulcers by close to 80% depending on whether one is speaking of endoscopic gastric or duodenal ulcers. Ironically, in previous versions of the review and in our book chapters we discussed at length the relationship between endoscopic ulcers and clinical ulcers, but this was removed recently as a relationship has become more accepted. So we feel that reporting on the endoscopic studies is valuable and appropriate (Rostom 2009c; Rostom 2002).

You also mention that one could contact authors for inclusion of unreported clinical events occurring within the endoscopic studies to avoid bias. However, we purposely did not include this type of data even when a clinical event was occasionally mentioned in a paper. The reason for this as detailed above is simply that these studies were not designed to look for these events in a systematic way, nor were adjudication of such events described a priori and consistently among the endoscopic ulcer studies. We strongly feel that inclusion of such reports would introduce multiple other sources of bias and would not improve our understanding in a tangible fashion. The Hong Kong studies included in our review are of course different in that they were designed to report on both types of endpoints by utilizing a very high risk NSAID population where clinical endpoints occur at a relatively high rate to allow for a relatively short, and small study (Chan 2002; FDA 2010).

Lastly thank you for identifying the typos related to the MUCOSA study table.

In summary, we respect your opinion that “that there is insufficient evidence to determine if gastroprotection with any class of drugs reduces the incidence of clinical complications that are important to patients on long-term NSAID therapy”, but we respectfully disagree.

Alaa Rostom MD MSc FRCPC

Contributors

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Aaron Tejani, BSc (Pharm), PharmD, ACPR

Alaa Rostom MD MSc FRCPC

WHAT'S NEW

Date	Event	Description
19 October 2021	Amended	Published note added

HISTORY

Review first published: Issue 3, 2000

Date	Event	Description
15 April 2011	Amended	Correction of typos
12 April 2011	Feedback has been incorporated	Endoscopic ulcers are not the same as clinical ulcers.
5 October 2010	Amended	Contact details updated.
11 May 2009	New search has been performed	5 new studies have been added since the last update. This is an updated version of the review first published in 2000. The changes include an updated search strategy, and new papers on PPIs. We have also updated the Background and Discussion to reflect the changes in NSAID field related to COX-2 inhibitor market withdrawals and new data on cardiovascular toxicity of COX-2s and NSAIDs.
16 July 2008	Amended	Converted to new review format.
25 July 2002	New citation required and conclusions have changed	Substantive amendment.

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Literature search

Jessie McGowen (original search) - subsequent searches performed by the Cochrane UGPD group.

Alaa Rostom.

Review statistics / data and manuscript review

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DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- Canadian Coordinating Office for Health Technology Assessment, Canada

August 2002 search update

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

NOTES

This review is no longer being updated. The review question will be addressed according to a new protocol (in progress).

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [*adverse effects]; Anti-Ulcer Agents [adverse effects] [*therapeutic use]; Chronic Disease; Duodenal Ulcer [chemically induced] [*prevention & control]; Histamine H2 Antagonists [*therapeutic use]; Misoprostol [adverse effects] [*therapeutic use]; *Proton Pump Inhibitors; Randomized Controlled Trials as Topic; Stomach Ulcer [chemically induced] [*prevention & control]

MeSH check words

Humans