Prevention of NSAID-induced gastroduodenal ulcers (Review)

Rostom A, Dube C, Wells GA, Tugwell P, Welch V, Jolicoeur E, McGowan J, Lanas A

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[Intervention Review]

Prevention of NSAID-induced gastroduodenal ulcers

Alaa Rostom[1], Catherine Dube[1], George A Wells[2], Peter Tugwell[3], Vivian Welch[4], Emilie Jolicoeur[5], Jessie McGowan[6], Angel Lanas[7]

[1]University of Calgary Department of Medicine / Gastroenterology, Foothills Medical Centre, Calgary, Canada. [2]Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Canada. [3]Centre for Global Health, Institute of Population Health, Faculty of Medicine, University of Ottawa, Ottawa, Canada. [4]Centre for Global Health, Institute of Population Health, University of Ottawa, Ottawa, Canada. [5]Division of Gastroenterology, A-1 Endoscopy Unit, Ottawa, Canada. [6]Institute of Population Health/Ottawa Health Research Institute, University of Ottawa, Ottawa, Canada. [7]University of Zaragoza, Zaragoza, Spain

Contact address: Alaa Rostom, University of Calgary Department of Medicine / Gastroenterology, Foothills Medical Centre, 1403 - 29 St. N.W, Calgary, Alberta, T2N 2T9, Canada. arostom@ucalgary.ca.

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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-2's 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-Haenzel 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.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded 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. Similary, out of 41 articles identified in the EBMR 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.

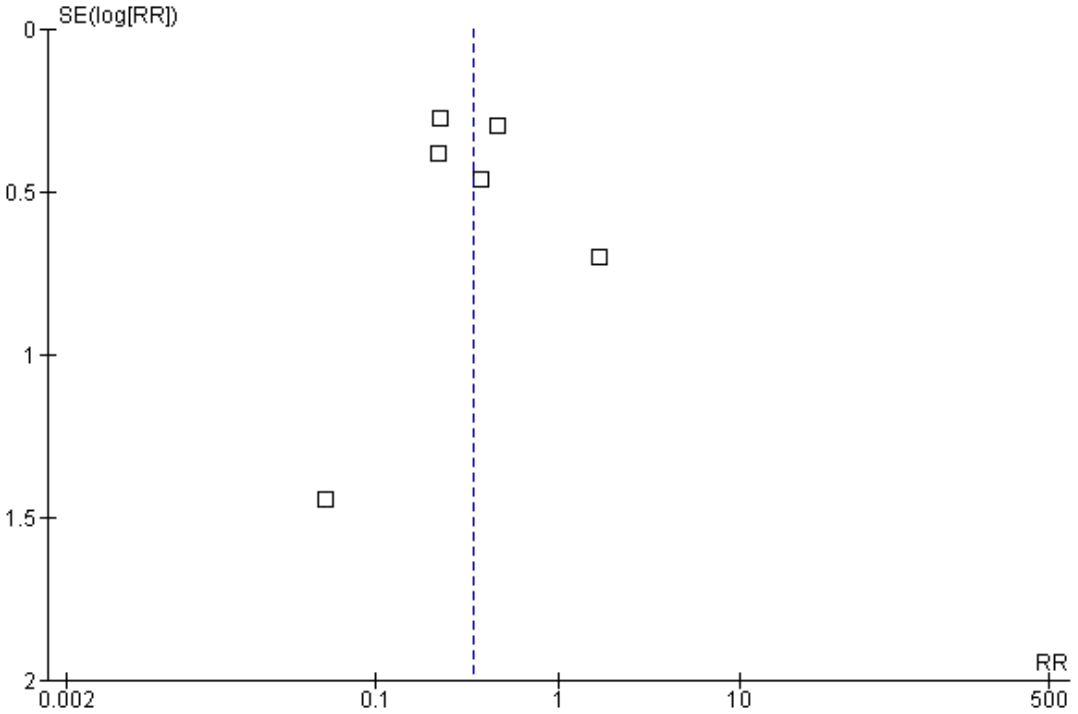
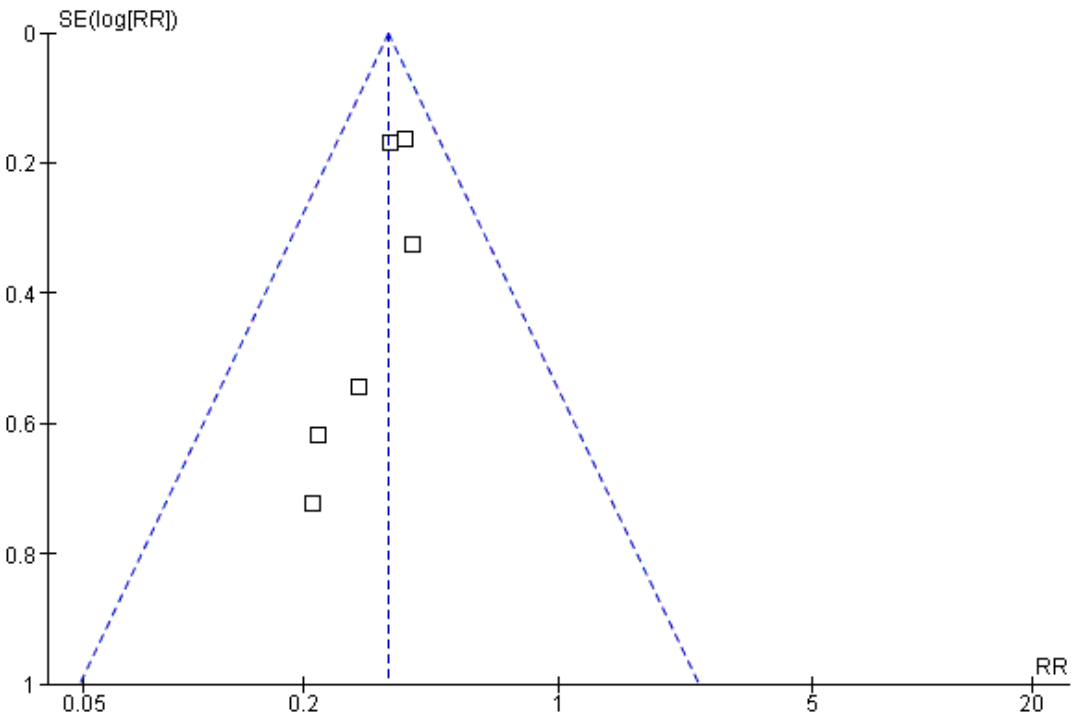


Figure 2. Funnel plot of comparison: 11 PPI vs placebo - 8 weeks or longer studies, outcome: 11.3 Total endoscopic ulcers.



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; Saggioro 1991; Graham 1988; Jensen 2000; Silverstein 1995; Stupnicki 2003). Some of these were head to head studies.

Endoscopic ulcers

Eleven studies with 3,641participants 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 demon-

strated 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; Chandresekaran 1991; Saggioro 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 trade-off. 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 tNSIADs 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 my be small. Misoprostol use is associated with greater adverse effects then 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.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Agrawal 1991

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

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: Misoprostrol: 66; placebo: 70 Type of NSAID: diclofenac

Agrawal 1995 (*Continued*)

	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

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 aspiring qid
Outcomes	Endoscopic gastric ulcer (>3 mm) Endoscopic duodenal ulcer (>3 mm) Withdrawals overall Withdrawals due to side effects
Notes	Quality = 3

Berkowitz 1987 (*Continued*)

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

Bianchi Porro 2000

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

Methods	Randomized controlled trial Double-blind 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	Patient: osteoarthritis 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

Bocanegra 1998 (*Continued*)

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

Risk of bias

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

Bolten 1992

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

Bolten 1992 (*Continued*)

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

Chan 2001a

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

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

Chan 2001b (*Continued*)

	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

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

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 Sex % F: 47% Type of NSAID:ASA, ibuprofen, diclofenac, indomethacin Previous peptic ulcers (%): n/a - but no history of gastroduodenal surgery

Chandresekaran 1991 (*Continued*)

	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

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

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

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

Ehsanullah 1988 (*Continued*)

Outcomes	Endoscopic ulcers 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

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

Methods	Randomized controlled trial Double-blind Sample size at entry: misoprostol: 40: placebo: 43 Study duration: 12 months
Participants	Patient: rheumatic arthritis, osteoarthritis Mean age (yrs): misoprostol: 65; placebo: 65 Sex % F: misoprostol: 37.5, placebo: 51.2 Type of NSAID: pisoxica, 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 Endosopic 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

Methods	Randomized controlled trial Double-blind Sample size at entry: isosprotol 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; piroxen; 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

Graham 1988 (*Continued*)

	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	Qualtiy=3	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	D - Not used

Graham 1993

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 Diarhea drop out Nausea drop out Abdominal pain drop out	
Notes	Qualtiy=3	
Risk of bias		

Graham 1993 (*Continued*)

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

Graham 2002

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

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

Hawkey 1998 (*Continued*)

	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
Notes	Quality = 3

Risk of bias

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

Henriksson 1993

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

Henriksson 1993 (*Continued*)

Notes	Quality = 4	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	D - Not used

Hudson 1997

Methods	Randomized controlled trial Double-blind Sample size at entry: famotidine: 39; placebo: 39 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

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	

Jensen 2000 (*Continued*)

	Type of NSAID:ASA >=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**
Allocation concealment (selection bias)	Unclear risk	D - Not used

Lai 2003

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

Methods	Randomized controlled trial Double-blind Sample size at entry: niztidine: 248; placebo: 248 Study duration: 3 months
Participants	Patient:osteoarthritis Mean age (yrs): niztidine: 56.9; placebo: 51.5 Sex % F: niztidine: 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
Notes	Quality =3

Risk of bias

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

Melo Gomes 1993

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

Melo Gomes 1993 (*Continued*)

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

Methods	Randomized controlled trial Double-blind Sample size at entry: misoprostol 400: 462; misoprostol 600: 474; misoprostol 800: 228; placebo: 454 Study duration: 3 months
Participants	Patient: rheumatoid arthritis, osteoarthritis, psoriatic arthritis, ankylosing spondylitis, Reiter syndrome Median age (yrs): misoprostol 400: 58; misoprostol 600: 58; misoprostol 800: 58; placebo: 58 Sex % F: misoprostol 400: 56; misoprostol 600: 60; misoprostol 800: 60; placebo: 59 Type of NSAID: diclofenac, ketoprofen; naproxen Previous peptic ulcers (%): 0 Primary vs secondary prophylaxis: primary H pylori positive (%): not mentioned
Interventions	1) placebo: 4 x day 2) misoprostol 200 μg x 2 = 400 μg 3) misoprostol 200 μg x 3 = 600 μg 4) misoprostol 200 μg x 4 = 800 μg
Outcomes	Endoscopic gastric ulcers (>3 mm) Endoscopic duodenal ulcers (>3 mm) Clinical ulcers: not mentioned Withdrawals overall Withdrawals due to side effects All adverse events
Notes	Quality = 5

Raskin 1995 (*Continued*)

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

Raskin 1996

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

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

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

Robinson 1991 (*Continued*)

Notes	Qualtiy=2	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	D - Not used

Roth 1987

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

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	

Roth 1993 (*Continued*)

	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	Endosopic 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

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 2) placebo
Outcomes	Endoscopic ulcers Symptoms
Notes	Quality = 3

Risk of bias

Saggioro 1991 (*Continued*)

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

Silverstein 1995

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

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

Simon 1994 (*Continued*)

	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

Risk of bias

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

Stupnicki 2003

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

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

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

Taha 1996 (*Continued*)

	3) placebo	
Outcomes	Endoscopic ulcers 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

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

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

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

van Groenendaci 1996 (*Continued*)

Outcomes	Endoscopic ulcers and erosions GI symptoms	
Notes	Quality = 1	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	D - Not used

Verdickt 1992

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

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 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

(*Continued*)

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
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 Gastric ulcers - 4 - 11 week studies	8	2033	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.09, 0.31]
2 Duodenal ulcers - 4 - 11 week studies	6	1546	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.14, 0.62]
3 Total ulcers - 4 - 11 week studies	4	1323	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.14, 0.42]
4 Gastric ulcers - 12 weeks or longer studies	11	3641	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.17, 0.39]
5 Duodenal ulcers - 12 weeks or longer studies	8	2785	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.22, 0.81]
6 Total endoscopic ulcers - 12 weeks or longer studies	6	1791	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.20, 0.59]
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]
8 Clinical ulcers - 12 weeks or longer studies	2	9276	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.27, 0.87]

Comparison 2. Misoprostol vs placebo - toxicity causing withdrawal

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea	6	11021	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.07, 1.48]
2 Dyspepsia	7	10634	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.95, 1.36]
3 Constipation	2	9199	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.38, 1.06]
4 Diarrhea	10	11793	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [2.01, 2.77]
5 Abdominal pain	6	11098	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.20, 1.55]
6 Flatulence	3	9638	Risk Ratio (M-H, Random, 95% CI)	2.46 [0.91, 6.65]
7 Vomiting	2	9525	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.36, 7.31]
8 Drop-outs due to side-effects	12	12146	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.31, 1.51]
9 Drop-outs overall	15	13239	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.11, 1.86]

Comparison 3. Misoprostol vs placebo - toxicity symptoms only

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

Comparison 4. Misoprostol vs placebo - efficacy by dosage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gastric ulcers - 1 month	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Low dose (400-600 ug)	5	1555	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.11, 0.41]
1.2 Mid-range dose (600 ug)	2	370	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.07, 0.69]
1.3 High dose (800 ug)	4	710	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.03, 0.32]
2 Duodenal ulcers - 1 month	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Low dose (400-600 ug)	4	1274	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.08, 0.56]
2.2 Mid-range dose (600 ug)	3	410	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.25, 1.58]
2.3 High dose (800 ug)	1	183	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.06, 6.97]
3 Total ulcers - 1 month	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Low dose (400-600 ug)	3	1091	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.11, 0.43]
3.2 Mid-range dose (600 ug)	2	370	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.17, 0.79]
3.3 High dose (800 ug)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Gastric ulcers - 3-24 months	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Low dose (400-600 ug)	6	2461	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.28, 0.67]
4.2 Mid-range dose (600 ug)	1	928	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.13, 0.44]
4.3 High dose (800 ug)	7	2377	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.12, 0.27]
5 Gastric ulcers - 3-24 months (sensitivity analysis excluding Chan 2001)	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Low dose (400-600 ug)	5	2371	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.30, 0.51]
5.2 Mid-range dose (600 ug)	1	928	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.13, 0.44]
5.3 High dose (800 ug)	7	2377	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.11, 0.24]
6 Duodenal ulcers - 3-24 months	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Low dose (400-600 ug)	5	2180	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.39, 0.81]
6.2 Mid-range dose (600 ug)	1	928	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.23, 0.93]
6.3 High dose (800 ug)	4	1521	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.09, 0.49]
7 Total endoscopic ulcers 3-24 months	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Low dose (400-600 ug)	3	813	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.27, 1.31]
7.2 Mid-range dose (600 ug)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 High dose (800 ug)	3	978	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.14, 0.34]
8 Clinical ulcers - 3-24 months	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

8.1 Low dose (400-600 ug)	1	433	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.17]
8.2 Mid-range dose (600 ug)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 High dose (800 ug)	1	8843	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.27, 0.89]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Misoprostol 400 ug/day	3	1629	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.44, 1.74]
1.2 Misoprostol 600 ug/day	2	1234	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.06, 2.93]
1.3 Misoprostol 800 ug/day	4	10281	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.00, 1.48]
2 Dyspepsia	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Misoprostol 400 ug/day	3	1629	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.20, 1.11]
2.2 Misoprostol 600 ug/day	2	1214	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.32, 1.47]
2.3 Misoprostol 800 ug/day	5	10157	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.96, 1.39]
3 Constipation	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Misoprostol 400 ug/day	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Misoprostol 600 ug/day	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Misoprostol 800 ug/day	2	9199	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.38, 1.06]
4 Diarrhea	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Misoprostol 400 ug/day	4	2062	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.78, 2.90]
4.2 Misoprostol 600 ug/day	2	1234	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [1.20, 5.95]
4.3 Misoprostol 800 ug/day	7	10886	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [2.09, 2.88]
5 Abdominal pain	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Misoprostol 400 ug/day	3	1733	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.90, 2.59]
5.2 Misoprostol 600 ug/day	1	928	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.04, 3.51]
5.3 Misoprostol 800 ug/day	4	10291	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.17, 1.63]
6 Flatulence	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Misoprostol 400 ug/day	1	916	Risk Ratio (M-H, Random, 95% CI)	1.97 [0.60, 6.48]
6.2 Misoprostol 600 ug/day	1	928	Risk Ratio (M-H, Random, 95% CI)	4.31 [1.47, 12.64]
6.3 Misoprostol 800 ug/day	3	9638	Risk Ratio (M-H, Random, 95% CI)	2.46 [0.91, 6.65]
7 Vomiting	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Misoprostol 400 ug/day	1	916	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.04, 5.40]
7.2 Misoprostol 600 ug/day	1	928	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.24, 8.56]
7.3 Misoprostol 800 ug/day	2	9525	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.34, 6.25]
8 Dropouts due to side effects	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Misoprostol 400 ug/day	5	2176	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.88, 1.51]
8.2 Misoprostol 600 ug/day	1	928	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.76, 1.57]
8.3 Misoprostol 800 ug/day	9	11521	Risk Ratio (M-H, Random, 95% CI)	1.68 [1.31, 2.17]
9 Dropouts overall	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Misoprostol 400 ug/day	5	2073	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.82, 1.14]
9.2 Misoprostol 600 ug/day	2	968	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.88, 1.36]
9.3 Misoprostol 800 ug/day	8	10703	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.10, 1.65]

Comparison 6. Misoprostol vs placebo - symptoms - by dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Misoprostol 400 ug/day	7	3043	Risk Ratio (M-H, Random, 95% CI)	1.46 [1.13, 1.89]
1.2 Misoprostol 600 ug/day	2	1234	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.01, 1.60]
1.3 Misoprostol 800 ug/day	5	1576	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.54, 1.75]
2 Dyspepsia	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Misoprostol 400 ug/day	8	3219	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.80, 1.23]
2.2 Misoprostol 600 ug/day	5	1539	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.70, 0.97]
2.3 Misoprostol 800 ug/day	6	1849	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.83, 1.82]
3 Constipation	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Misoprostol 400 ug/day	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Misoprostol 600 ug/day	2	469	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.22, 1.57]
3.3 Misoprostol 800 ug/day	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Diarrhea	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Misoprostol 400 ug/day	8	3219	Risk Ratio (M-H, Random, 95% CI)	1.76 [1.37, 2.26]
4.2 Misoprostol 600 ug/day	4	1363	Risk Ratio (M-H, Random, 95% CI)	2.13 [1.28, 3.55]
4.3 Misoprostol 800 ug/day	9	2580	Risk Ratio (M-H, Random, 95% CI)	3.16 [2.33, 4.29]
5 Abdominal pain	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Misoprostol 400 ug/day	7	2943	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.07, 1.60]
5.2 Misoprostol 600 ug/day	3	1273	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.85, 1.60]
5.3 Misoprostol 800 ug/day	5	1845	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.57, 1.64]
6 Flatulence	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Misoprostol 400 ug/day	4	1897	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.06, 2.52]
6.2 Misoprostol 600 ug/day	1	928	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.06, 1.71]
6.3 Misoprostol 800 ug/day	3	1411	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.24, 1.96]
7 Vomiting	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Misoprostol 400 ug/day	1	916	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.04, 5.40]
7.2 Misoprostol 600 ug/day	1	928	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.24, 8.56]
7.3 Misoprostol 800 ug/day	2	9525	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.34, 6.25]
8 Dropouts due to side effects	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Misoprostol 400 ug/day	5	2176	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.88, 1.51]
8.2 Misoprostol 600 ug/day	1	928	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.76, 1.57]
8.3 Misoprostol 800 ug/day	9	11521	Risk Ratio (M-H, Random, 95% CI)	1.68 [1.31, 2.17]
9 Dropouts overall	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Misoprostol 400 ug/day	5	2073	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.82, 1.14]
9.2 Misoprostol 600 ug/day	2	968	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.88, 1.36]
9.3 Misoprostol 800 ug/day	8	10703	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.10, 1.65]
10 Headache	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Misoprostol 400 ug/day	2	700	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.38, 1.06]
10.2 Misoprostol 600 ug/day	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Misoprostol 800 ug/day	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

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
1 Gastric ulcer	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 High dose	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.04, 0.85]
1.2 Low dose	5	715	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.31, 1.13]
2 Duodenal ulcer	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 High dose	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.30]
2.2 Low dose	6	942	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.10, 0.57]
3 Total endoscopic ulcers	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 High dose	2	268	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.11, 0.53]
3.2 Low dose	5	597	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.23, 0.71]

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
1 Gastric ulcer	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 High dose	3	298	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.26, 0.74]
1.2 Low dose	4	1005	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.50, 1.08]
2 Duodenal ulcer	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 High dose	3	298	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.11, 0.65]
2.2 Low dose	3	981	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.18, 0.74]
3 Total endoscopic ulcers	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 High dose	3	298	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.26, 0.63]
3.2 Low dose	3	981	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.45, 0.88]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total drop-outs	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 High dose	3	292	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.41, 1.70]
1.2 Low dose	6	1199	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.66, 1.01]
2 Drop-outs due to side effects	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 High dose	2	102	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.65]
2.2 Low dose	5	1011	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.58, 1.28]
3 Dropouts due to GI symptoms	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 High dose	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Low dose	2	793	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.41, 1.23]
4 Dropouts due to abdominal pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 High dose	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

4.2 Low dose	1	188	Risk Ratio (M-H, Fixed, 95% CI)	2.94 [0.12, 71.20]
5 Dropouts due to diarrhea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 High dose	1	190	Risk Ratio (M-H, Fixed, 95% CI)	2.88 [0.12, 69.76]
5.2 Low dose	1	188	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Diarrhea	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 High dose	1	190	Risk Ratio (M-H, Fixed, 95% CI)	2.88 [0.12, 69.76]
6.2 Low dose	1	188	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Abdominal pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 High dose	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.33, 0.98]
7.2 Low dose	1	188	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.39, 1.10]
8 GI symptoms	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 High dose	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Low dose	2	520	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.29, 1.19]
9 Flatulence	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 High dose	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Low dose	1	496	Risk Ratio (M-H, Fixed, 95% CI)	2.43 [1.03, 5.75]
10 Dyspepsia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 High dose	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Low dose	2	520	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.29, 1.19]
11 Rash	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 High dose	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Low dose	2	684	Risk Ratio (M-H, Fixed, 95% CI)	3.85 [1.20, 12.33]

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

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

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

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

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

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

Comparison 13. PPI vs placebo - toxicity

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

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
1 Endoscopic gastric ulcers	1	425	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.17, 0.62]
2 Endoscopic duodenal ulcers	1	425	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 0.89]
3 Total endoscopic ulcers	1	425	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.15, 0.51]
4 Total clinical ulcers	1	425	Risk Ratio (M-H, Fixed, 95% CI)	3.07 [0.13, 74.96]
5 Toxicity- dropouts due to side effects	1	425	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [0.77, 4.67]
6 Vomiting	1	2	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Abdominal pain	1	2	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Diarrhea	1	2	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

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
1 Endoscopic gastric ulcer	2	917	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.33, 1.18]
2 Endoscopic duodenal ulcer	1	570	Risk Ratio (M-H, Fixed, 95% CI)	3.97 [1.77, 8.88]
3 Total endoscopic ulcers	4	1478	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.58, 2.13]

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
1 Endoscopic gastric ulcer	2	917	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.85, 3.06]
2 Endoscopic duodenal ulcer	1	570	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.11, 0.56]
3 Total endoscopic ulcers	4	1478	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.47, 1.72]

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
1 Dropouts overall	2	974	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.52, 0.97]
2 Dropouts due to side effects	3	1019	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.29, 0.78]

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
1 Endoscopic gastric ulcers	2	599	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.03, 0.51]
2 Endoscopic duodenal ulcers	2	599	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.14, 7.05]
3 Dropouts due to side effects	2	599	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [1.16, 3.37]
4 Total endoscopic ulcers	1	538	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.07, 0.80]
5 Dropouts overall	2	599	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.94, 1.54]
6 Dropouts due to abdominal pain	1	538	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [1.11, 8.14]
7 Dropouts due to nausea	1	538	Risk Ratio (M-H, Fixed, 95% CI)	3.67 [1.03, 13.00]
8 Dyspepsia	2	599	Risk Ratio (M-H, Random, 95% CI)	2.49 [0.39, 15.92]
9 Abdominal pain symptoms	1	538	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.01, 1.52]
10 Flatulence symptoms	1	538	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [1.10, 1.99]
11 Nausea symptoms	1	538	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.81, 1.50]
12 Diarrhea symptoms	1	538	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.38, 2.99]

Comparison 19. Nizatidine 150 mg vs 300 mg efficacy

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

Comparison 20. NSAID + PPI vs COX 2

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

FEEDBACK

Endoscopic ulcers are not the same as clinical ulcers, 14 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

Stephanie Halliday, BSc (Pharm)
Aaron Tejani, BSc (Pharm), PharmD, ACPR
Alaa Rostom MD MSc FRCPC

WHAT'S NEW

Last assessed as up-to-date: 11 May 2009.

Date	Event	Description
15 April 2011	Amended	Correction of typos

HISTORY

Review first published: Issue 3, 2000

Date	Event	Description
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.
16 July 2008	Amended	Converted to new review format.
25 July 2002	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

Screening for titles and abstracts

Alaa Rostom, Catherine Dube, Vivian Welch, Emily Jolicoeur.

Assessment for inclusion

Alaa Rostom, Catherine Dube, Vivian Welch, Emily Jolicoeur.

Quality assessment

Alaa Rostom, Catherine Dube, Vivian Welch.

Data extraction

Alaa Rostom, Catherine Dube, Vivian Welch.

Data entry into RevMan

Alaa Rostom, Vivian Welch.

Prepared the manuscript

Alaa Rostom, Catherine Dube.

Literature search

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

Review statistics / data and manuscript review

Peter Tugwel, George Wells, Angel Lanas.

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- Canadian Coordinating Office for Health Technology Assessment, Canada.

August 2002 search update

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

NOTES

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.

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 Pumps [*antagonists & inhibitors]; Randomized Controlled Trials as Topic; Stomach Ulcer [chemically induced; *prevention & control]

MeSH check words

Humans