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ORIGINAL RESEARCH

Efficacy and tolerability of naproxen/esomeprazole magnesium tablets compared with non-specific NSAIDs and COX-2 inhibitors: a systematic review and network analyses

This article was published in the following Dove Press journal:
Open Access Rheumatology: Research and Reviews
26 February 2013
Number of times this article has been viewed

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Abstract: Non-steroidal anti-inflammatory drugs (NSAIDs), such as non-selective NSAIDs (nsNSAIDs) or selective cyclooxygenase-2 (COX-2) inhibitors, are commonly prescribed for arthritic pain relief in patients with osteoarthritis (OA), rheumatoid arthritis (RA), or ankylosing spondylitis (AS). Treatment guidelines for chronic NSAID therapy include the consideration for gastroprotection for those at risk of gastric ulcers (GUs) associated with the chronic NSAID therapy. The United States Food and Drug Administration has approved naproxen/esomeprazole magnesium tablets for the relief of signs and symptoms of OA, RA, and AS, and to decrease the risk of developing GUs in patients at risk of developing NSAID-associated GUs. The European Medical Association has approved this therapy for the symptomatic treatment of OA, RA, and AS in patients who are at risk of developing NSAID-associated GUs and/or duodenal ulcers, for whom treatment with lower doses of naproxen or other NSAIDs is not considered sufficient. Naproxen/esomeprazole magnesium tablets have been compared with naproxen and celecoxib for these indications in head-to-head trials. This systematic literature review and network meta-analyses of data from randomized controlled trials was performed to compare naproxen/esomeprazole magnesium tablets with a number of additional relevant comparators. For this study, an original review examined MEDLINE®, Embase®, and the Cochrane Controlled Trials Register from database start to April 14, 2009. Using the same methodology, a review update was conducted to December 21, 2009. The systematic review and network analyses showed naproxen/esomeprazole magnesium tablets have an improved upper gastrointestinal tolerability profile (dyspepsia and gastric or gastroduodenal ulcers) over several active comparators (naproxen, ibuprofen, diclofenac, ketoprofen, etoricoxib, and fixed-dose diclofenac sodium plus misoprostol), and are equally effective as all active comparators in treating arthritic symptoms in patients with OA, RA, and AS. Naproxen/esomeprazole magnesium tablets are therefore a valuable option for treating arthritic symptoms in eligible patients with OA, RA, and AS.

Keywords: non-steroidal anti-inflammatory drug, proton pump inhibitor, upper gastrointestinal tolerability, arthritis

Introduction

Patients with chronic rheumatic musculoskeletal conditions such as osteoarthritis (OA), rheumatoid arthritis (RA), and ankylosing spondylitis (AS) experience increased morbidity due to joint pain and stiffness.[1] Analgesics commonly used to treat pain caused by OA, RA, and AS are either non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs), such as naproxen, ibuprofen, diclofenac, or ketoprofen, or cyclooxygenase-2 (COX-2)-selective NSAIDs (COX-2 inhibitors), such as celecoxib

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or etoricoxib.[2–6] nsNSAIDs and COX-2 inhibitors are both associated with adverse upper gastrointestinal (GI) tolerability, due to gastric or gastroduodenal ulcers, dyspepsia, and upper GI bleeding.[7,8] While COX-2 inhibitors can be associated with a lower rate of upper GI ulcers and the associated events, when compared with nsNSAIDs, concomitant use of medications such as low-dose aspirin (LDA) may limit some of this benefit.[9] Treatment guidelines to address the upper GI risk associated with NSAID (both selective and non-selective) therapies have been developed and include the recommendation for use of gastric acid lowering agents such as proton pump inhibitors (PPIs).[7,10,11] Concerns have also been raised about the cardiovascular (CV) safety of nsNSAIDs and COX-2 inhibitors.[12] In the United States, the Food and Drug Administration (FDA) has issued a boxed warning on nsNSAIDs and COX-2 inhibitors highlighting that the use of these agents may cause an increased risk of CV events.[13]

Naproxen/esomeprazole magnesium delayed-release tablets contain enteric-coated naproxen and immediate-release esomeprazole (naproxen/esomeprazole magnesium tablets), combining an NSAID and a PPI in one tablet. This treatment has been approved by the US FDA for the relief of signs and symptoms of OA, RA, and AS, and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers.[14] In Europe, the European Medical Association (EMA) has approved naproxen/esomeprazole magnesium tablets for the symptomatic treatment of OA, RA, and AS in patients who are at risk of developing NSAID-associated gastric and/or duodenal ulcers, for whom treatment with lower doses of naproxen or other NSAIDs is not considered sufficient.[15]

The efficacy and upper GI tolerability of naproxen/esomeprazole magnesium tablets have been compared with the nsNSAID naproxen and the COX-2 inhibitor celecoxib in head-to-head trials (PN400-301 [NCT01129011], PN400-302 [NCT00527787], PN400-307 [NCT00664560], PN400-309 [NCT00665431] Clinical Study Reports; Pozen Inc, data on file, 2009). However, there is a lack of data comparing naproxen/esomeprazole magnesium tablets with other relevant comparators; for example, nsNSAIDs and COX-2 inhibitors, with and without PPIs, and a fixed-dose combination comprising diclofenac sodium and the GI mucosal protective prostaglandin E1 analog misoprostol. Salvo et al highlighted knowledge gaps relating to the systematic safety evaluation of individual NSAIDs, and stated that further systematic pooled analyses of randomized controlled trials (RCTs) should be conducted.[16]

The objective of this study was to further explore the relative efficacy in the treatment of arthritic symptoms, upper GI tolerability, and CV safety of naproxen/esomeprazole magnesium tablets with relevant comparators in addition to (and including) the comparators used in its head-to-head trials for the treatment of arthritic symptoms in patients with OA, RA, and AS, utilizing a systematic literature review and network meta-analyses.

Methods

A systematic review was conducted to identify all RCTs examining the efficacy in the treatment of arthritic symptoms, upper GI tolerability, and/or CV safety of specified nsNSAIDs and COX-2 inhibitors used for the relief of arthritic symptoms in patients diagnosed with OA, RA, or AS. Network meta-analyses of the data were performed to indirectly compare treatments across studies, utilizing meta-analysis for direct head-to-head data, indirect comparison via a common comparator, and mixed-treatment comparison (MTC) where both direct and indirect methods were possible. The review was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines.[17,18]

Data sources

The systematic review was conducted in two parts: (1) an original review and (2) an update to the original review to expand the scope of the searches to include trials of a single nsNSAID or COX-2 inhibitor versus placebo, and trials of an nsNSAID or COX-2 inhibitor versus the same nsNSAID/COX-2 inhibitor plus PPI or other gastroprotective agent. In the original review, MEDLINE®, Embase®, and the Cochrane Controlled Trials Register (CCTR) were examined from database start to April 14, 2009 using the Ovid interface. Using the same methodology, the review update was conducted on December 21, 2009.

Standard filters developed by the Scottish Intercollegiate Guidance Network (SIGN), and based on the methodology of the Cochrane group[19] were used to identify RCTs in MEDLINE® and Embase®. The CCTR does not require use of a study design filter as this is specifically a controlled trial database. Clinical keywords and medical subject headings were used to search for disease (for example, rheumatoid arthritis, arthritis pain, arthritis, osteoarthritis, and ankylosing spondylitis) and intervention (for example, naproxen, arthroxen, naprosyn, synflex, napratec, anaprox, aleve, and naprelan). An example search strategy is provided in Table S1.

In addition, four unpublished clinical study reports of naproxen/esomeprazole magnesium tablets were included in

the review and network analyses (PN400-301, PN400-302, PN400-307, PN400-309 Clinical Study Reports; Pozen Inc, data on file, 2009). Data from these unpublished clinical study reports have been published following completion of the review and network analyses; however, these publications were not identified or included in the review and network analyses as they were published after these were conducted.[20–22]

The proceedings from meetings held between 2004 and 2009 for eight relevant annual symposia were also hand-searched (European League against Rheumatism [EULAR], American College of Gastroenterology [ACG], United European Gastroenterology Week [UEGW], Digestive Diseases Week [DDW], American College of Rheumatology [ACR], European Society of Cardiology [ESC], American Heart Association [AHA], American College of Cardiology [ACC]).

No efforts were made to contact authors, as this did not form part of the study protocol.

Study eligibility

English language publications of RCTs comparing at least two of the specified interventions for efficacy in the treatment of arthritic symptoms, upper GI tolerability, and/or CV safety within an adult population experiencing arthritic pain due to OA, RA, or AS were included in the systematic review. The specified nsNSAIDs were: naproxen, diclofenac, ibuprofen, and ketoprofen; the specified COX-2 inhibitors were celecoxib and etoricoxib. All interventions could be administered alone or in combination with a PPI (for example, omeprazole, lansoprazole, or esomeprazole) or other gastroprotective agent (misoprostol). In addition, a fixed-dose combination comprising diclofenac sodium and misoprostol was also included as a comparator of interest. Non-English language publications with English language abstracts were included if relevant data were reported in the abstract, and there was no restriction on blinding.

The systematic review update expanded the scope to include trials of a single nsNSAID or COX-2 inhibitor versus placebo and trials of an nsNSAID/COX-2 inhibitor versus the same nsNSAID/COX-2 inhibitor plus a PPI or other gastroprotective agent.

Study selection

Bibliographic details and abstracts of all citations detected by the search were downloaded into the HERON Systematic Review Database, a bespoke SQL-based internet database. A team of reviewers, information scientists specializing in evidence-based medicine, independently determined the eligibility of each publication. Citations were first screened based on the title/abstract supplied with each citation by applying the defined set of eligibility criteria described above. Two different reviewers considered each citation, with discrepancies resolved by a third reviewer. Duplicates of citations (due to overlap in the coverage of the databases) were excluded at this first pass of the citations.

Full-text copies were ordered for studies that potentially met the eligibility criteria. The eligibility criteria were then applied to the full-text publications in a second pass of the citations, with each publication reviewed by two independent reviewers and reconciliation of any discrepancies by a third independent reviewer.

Data extraction

All studies included after this second pass of the citations underwent data extraction using a specifically designed data extraction grid. Data were extracted by two independent reviewers in parallel, with a third independent reviewer comparing the extractions and resolving any differences through team discussion. Only one dataset per study was compiled from all publications relating to that study so as to avoid double-counting patients.

Data extracted included study design, patient population characteristics, efficacy in treatment of arthritic symptoms (Western Ontario and McMaster Osteoarthritis Index [WOMAC] to assess stiffness, pain, and function,[21,23] American College of Rheumatology Criteria [ACR20],[24] Global Assessment of Disease Activity,[21] Pain Visual Analogue Scale [Pain (VAS)],[21] and Health Assessment Questionnaire Disease Index),[25] upper GI tolerability (dyspepsia, gastric ulcers, gastroduodenal ulcers, GI bleed/hemorrhage, upper GI event, and any GI event), and CV safety (myocardial infarction [MI], fatal MI, CV death, stroke, nonfatal stroke, angina, congestive heart failure, and any CV event). It was assumed that similarly named outcomes reported by different studies could be judged to be the same. For example, studies may use different means of identifying upper GI ulcers, such as through scheduled endoscopies or through clinical judgment. Trials reporting outcomes at different time points were pooled together to maximize the comparisons available. For composite outcomes such as "any GI event," "upper GI event," or "any CV event," data were extracted only if a study reported such a composite outcome. For example, data reported by studies as composite outcomes such as "GI-related adverse event," "GI adverse event," or "GI tract adverse event" were extracted for the outcome

of "any GI event" in the systematic review; GI outcomes reported individually in studies such as "dyspepsia" and "gastric ulcers" were not included in the outcome of "any GI event" to avoid double counting of events

The quality of each study was appraised through use of the Jadad score[26] and evaluation of the adequacy of concealment (adequate, inadequate, unclear, and not used) assessed; however, this assessment was not used to exclude studies.

Quantitative data synthesis

Trial networks were created and examined to identify the most relevant method of analysis to be performed with the data available (meta-analysis, indirect comparison, or MTC). Any networks that were connected such that multiple direct and indirect comparisons could be made were analyzed using MTCs. A nominal significance level of 5% was taken in all analyses.

Data relating to OA, RA, and AS were pooled, as were trials reporting outcomes at different time points. This pooling was conducted to maximize the possibility of comparison across treatments for the outcomes of interest.

Only doses licensed by the FDA and EMA were included in the analyses. Within the licensed range, data relating to different doses of the same drug were pooled. Similarly, different formulations of the same therapy were deemed sufficiently similar to be grouped together. Where studies included more than one treatment arm with the same intervention, such as two different doses of the same drug (within the licensed range), data for the two arms were pooled. As it has been demonstrated previously that high-dose naproxen (1000 mg/day) and naproxen/esomeprazole magnesium tablets are bioequivalent,[15] high-dose naproxen was used as a surrogate for naproxen/esomeprazole magnesium in analyses of efficacy and tolerability outcomes where no naproxen/esomeprazole magnesium tablets data were available. The exception was for analyses of upper GI outcomes, as naproxen/esomeprazole magnesium tablets comprise a PPI, which is likely to affect the upper GI tolerability profile demonstrated by the high-dose naproxen.

In addition to the quality assessments described above, a critical appraisal of studies included in the quantitative analyses was performed in accordance with NICE guidelines[27] to identify studies with a high risk of bias. Any studies identified as biased based on this assessment were excluded from the subsequent data analyses. Statistical heterogeneity was assessed using the I-squared test of statistical heterogeneity[28] values, which were calculated using the Stata® (StataCorp LP, College Station, TX, USA) statistical software, version 9.0, and are presented alongside effect size results.

Where possible, subgroup analyses were performed for patients administered concomitant LDA and naproxen/esomeprazole magnesium tablets compared with high-dose nsNSAIDs, as defined by Garcia-Rodriguez and Barreales.[29]

Direct meta-analysis

Pooled comparisons were performed using conventional meta-analysis techniques according to a predetermined statistical analysis plan (details available upon request). When conducting the meta-analysis, Stata (version 9.0) statistical software was used to run the metan meta-analysis command. Both fixed and random effects were used in all analyses, with the appropriate result selected based upon the statistical heterogeneity observed; the Mantel-Haenszel method[30] for fixed effects and DerSimonian and Laird[31] for random effects were used to weight the studies. Meta-analyses were conducted to assess the direct evidence comparing naproxen/esomeprazole magnesium tablets with naproxen, celecoxib, and placebo for efficacy in the treatment of arthritic symptoms outcomes, and upper GI tolerability/CV safety outcomes where at least two studies reported sufficient data for the outcome of interest.

For dichotomous outcomes, the intention-to-treat (ITT) population number (N) and the number of events for each treatment arm (n) were used to produce an odds ratio and the absolute risk difference. Studies with zero events for both treatment arms were excluded.

For continuous data, the mean for each treatment arm was weighted according to the number of patients in the arm and used to calculate a weighted mean difference between the two groups in an individual study.

For continuous outcomes, the pooled weighted mean difference between treatments was calculated for each outcome. First, the mean difference in outcome between the treatments was calculated for each individual study. The results from each study were then pooled, with each study given a weighting based on the number of patients included in the study. For CV events, the effect of varying study durations was incorporated into the analysis by approximating the distribution of events over the total number of patient weeks to a Poisson distribution. The meta-analysis was then constructed on the incident rate ratios produced.

MTC

The approach used for the MTCs was based on published methodologies to combine direct and indirect evidence for

any given pair of treatments.[32–34] Analyses were performed using a random effects model within a Bayesian framework, applying Markov chain Monte Carlo methods in WinBUGS® (The BUGS Project, Cambridge, UK), version 14, using vague priors for model estimation. The prior distributions for the study effect sizes and the underlying true intervention effect sizes were normal distributions with a mean of 0 and a precision of 0.001. The presented credible intervals (CrIs) from the MTC analyses were taken from the median of the posterior distributions.

All analyses were performed at 70,000 iterations after a burn-in of 10,000 iterations, and demonstrated satisfactory convergence to their supporting posterior distributions.

For dichotomous outcomes, a model built around an extension to a logistic regression was used. For continuous outcomes, a normal likelihood function was used to fit the data to a generalized linear regression.

Residual deviance values were utilized to determine whether random effects analysis or fixed effects analysis was appropriate for MTC analyses, with a lower residual deviance value indicating a better fit.[35]

Indirect comparison

Indirect comparisons were conducted for outcomes where the network contained a limited number of studies and there was no closed loop within the network (for example, the comparison of two treatments that have not been compared in head-to-head trials but which have both been compared against a third common treatment). Indirect comparisons were made according to the method of Bucher et al[36] using random effects analyses to account for the heterogeneity between studies.

Results

Included studies

Literature searching for the original review and review update yielded 3477 and 1898 references, respectively, 228 and 217 of which were identified as being potentially relevant studies that were retrieved for detailed evaluation (Figure 1). In total, 167 studies were included in the systematic review, with 109 studies (see listings in Table S2) suitable for inclusion in the reported network meta-analyses (Figure 1).

Assessment of RCT quality by the Jadad score found that the majority of trials were reasonably well conducted, with 79% of trials scoring 3 or higher on the Jadad score, and none were excluded from the analyses as a result of this assessment. Appraisal of studies included in MTC analyses identified no studies of very poor quality, and no studies were excluded as a result of this appraisal. Quality grading data of the studies included in the network analyses are available on request. Of all the studies used in MTCs, 70.6% were 6 weeks or longer in duration, involving over 95,000 patients in total. An example network diagram of MTC analysis for the outcome of dyspepsia is provided in Figure 2.

Study heterogeneity

Direct meta-analyses were performed to assess the direct evidence comparing the efficacy in the treatment of arthritic symptoms, upper GI tolerability, and/or CV safety of naproxen/esomeprazole magnesium tablets with naproxen, celecoxib, and placebo, pooling data from the naproxen/esomeprazole magnesium tablets clinical trials (PN400-301, PN400-302, PN400-307, and PN400-309, Pozen Inc, data on file, 2009). For the majority of outcomes, the direct meta-analyses involved pooling of data from the PN400-307 and PN400-309 studies only. It was judged that for the majority of direct meta-analyses, fixed effects results are more suitable than random effects results. This is because results represent pooled data from very similar trials, namely the two trials of naproxen/esomeprazole magnesium versus naproxen, and the two trials of naproxen/esomeprazole magnesium versus celecoxib, in which there is not a substantial degree of between-study heterogeneity. In all but three cases (out of 38; naproxen/esomeprazole magnesium tablets versus naproxen and placebo for the outcome of dyspepsia, and naproxen/esomeprazole magnesium tablets versus naproxen for the outcome of gastroduodenal ulcers), this is borne out by the low value in the I-squared test of statistical heterogeneity[28] ($<30\%$). For such cases where there is more than a low degree of between-study heterogeneity (value in the I-squared test of statistical heterogeneity[28] of $>30\%$), it was judged that random effects results are more suitable.

In cases where high-dose naproxen was used as a surrogate for naproxen/esomeprazole magnesium tablets in efficacy in the treatment of arthritic symptoms and CV safety outcomes, heterogeneity was also low, as Pain (VAS) change from baseline (high-dose naproxen versus placebo and etoricoxib) and ACR20 response (high-dose naproxen versus placebo) were the only outcomes (out of 16 analyses) with a value in the I-squared test of statistical heterogeneity greater than 30%.

Random effect results are presented for indirect analyses and MTCs due to the additional heterogeneity that exists in such analyses, which renders the assumptions underlying a fixed effects model less reasonable. This is borne out by residual deviance values which favored random effects analysis for the majority of outcomes (14 out of 23). For outcomes where

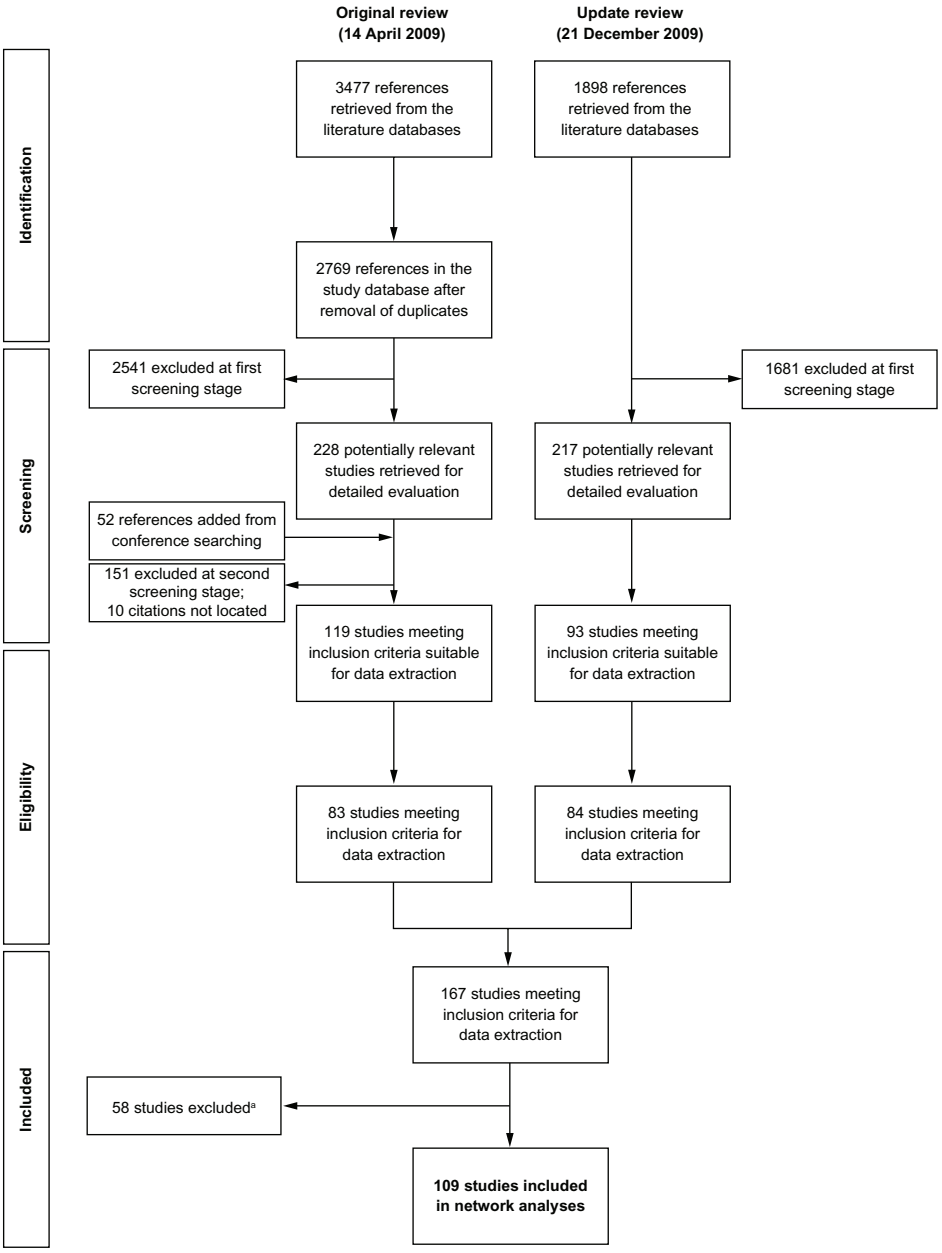


Figure 1 Study flow diagram.
Note: [a]studies excluded due to a lack of relevant data for analyses performed, dosing outside of a legal range, or data reported for the whole population rather than by treatment arms.
Abbreviation: RCT, randomized controlled trial.

fixed effects analysis was favored, differences between the residual deviance values for the fixed effects analysis and random effects analysis were minimal (difference in residual deviance values of <1) (see Table S3).

Efficacy in the treatment of arthritic symptoms

The direct meta-analyses and MTCs found no significant difference in efficacy between naproxen/esomeprazole magnesium tablets and the active comparators in all but one of the efficacy outcomes (Pain [VAS] change from baseline; Tables 1 and 2).

Direct meta-analyses indicated that, where data were available, there was no significant difference between naproxen/esomeprazole magnesium tablets and any nsNSAID or COX-2 inhibitor with respect to any of the reported efficacy outcomes apart from Pain (VAS) change from baseline. Etoricoxib was superior for this outcome as compared with naproxen/esomeprazole magnesium tablets (using high-dose naproxen as a surrogate) (Table 1).

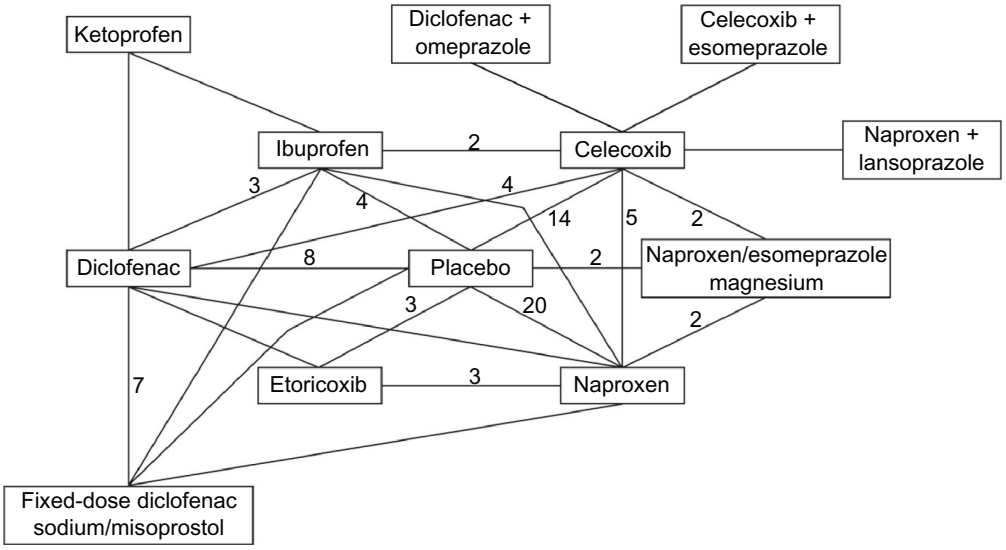


Figure 2 Network diagram for mixed treatment comparison analysis of dyspepsia.[37,44–47,49,50,53,58,60–62,64,69–78,80,81,83,84,86,88–119]

Similarly, MTCs indicated no significant difference between naproxen/esomeprazole magnesium tablets and celecoxib with respect to any of the reported efficacy outcomes (Table 2, Figure 3A and B), such as total WOMAC score change from baseline and WOMAC pain subscale change from baseline (Figure 3A and B). The only significant difference between naproxen/esomeprazole magnesium and an active comparator was for Pain (VAS) change from baseline, in which etoricoxib was superior, as also observed in direct meta-analysis (Table 2).

Safety and tolerability

Upper GI tolerability

Gastric ulcers

Direct meta-analyses showed that naproxen/esomeprazole magnesium was significantly better than naproxen for incidence of gastric ulcers. When compared with celecoxib, there was no significant difference (Figure 4A). MTCs showed that the odds of developing gastric ulcers were significantly lower with naproxen/esomeprazole magnesium tablets than with naproxen (odds ratio [OR] 0.19; 95% CrI 0.07–0.49) or ibuprofen (OR 0.16; 95% CrI 0.03–0.69). No other significant differences were seen between naproxen/esomeprazole magnesium tablets and other nsNSAIDs or COX-2 inhibitors (diclofenac, celecoxib, diclofenac plus omeprazole, or fixed-dose diclofenac sodium plus misoprostol) (Figure 4A).

Gastroduodenal ulcers

Direct meta-analyses showed that use of naproxen/esomeprazole magnesium tablets was significantly better than naproxen for gastroduodenal ulcers, where the odds of an ulcer with naproxen/esomeprazole magnesium tablets was reduced by 83% from that of naproxen (OR 0.17; 95% confidence interval [CI] 0.10–0.31). MTCs showed that naproxen/esomeprazole magnesium tablets were associated with significantly lower odds of gastroduodenal ulcers compared with naproxen (OR 0.17; 95% CrI 0.09–0.31), ibuprofen (OR 0.25; 95% CrI 0.10–0.56), and diclofenac (OR 0.43; 95% CrI 0.18–0.90). There were no significant differences between naproxen/esomeprazole magnesium tablets and ketoprofen, etoricoxib, celecoxib, and fixed-dose diclofenac sodium plus misoprostol (Figure 4B).

Dyspepsia

Direct meta-analyses showed that there were no significant differences when comparing naproxen/esomeprazole magnesium tablets with naproxen or celecoxib (Figure 5A). MTCs showed the odds of dyspepsia with naproxen/esomeprazole magnesium tablets were approximately half that of the NSAIDs naproxen (OR 0.57; 95% CrI 0.40–0.80), diclofenac (OR 0.63; 95% CrI 0.42–0.95), ibuprofen (OR 0.58; 95% CrI 0.38–0.89), fixed-dose diclofenac sodium plus misoprostol (OR 0.52; 95% CrI 0.33–0.82), or etoricoxib (OR 0.57; 95% CrI 0.32–0.96). No significant differences were found for dyspepsia when comparing naproxen/esomeprazole tablets and other interventions concomitant with PPI (Figure 5A).

Any GI event

Direct meta-analyses showed that naproxen/esomeprazole magnesium tablets were significantly better than naproxen for the outcome of any GI event (OR 0.56; 95% CI 0.42–0.75) (Figure 5B). MTCs showed that the odds of any GI event

Table 1 Summary of the direct meta-analysis results for efficacy in the treatment of arthritic symptoms outcomes, naproxen/esomeprazole magnesium tablets versus comparators

Outcome[a]	Comparator	No of studies	N	Effect measure	Statistical heterogeneity (I^2)[a,b]	ES (95% CI)	
						Fixed effects	Random effects
Total WOMAC score endpoint	Celecoxib	2	978	WMD	10	−0.60 (−3.85 to 2.65)	−0.60 (−4.02 to 2.83)
	Placebo	2	736	WMD	0	−5.06 (−9.10 to −1.02)	−5.06 (−9.10 to −1.02)
WOMAC pain subscale endpoint	Placebo	2	736	WMD	0	−4.51 (−8.88 to −0.15)	−4.51 (−8.88 to −0.15)
	Celecoxib	2	978	WMD	0	−0.22 (−3.56 to 3.13)	−0.22 (−3.56 to 3.13)
WOMAC function subscale endpoint	Placebo	2	736	WMD	0	−4.54 (−8.93 to −0.16)	−4.54 (−8.93 to −0.16)
	Celecoxib	2	978	WMD	29	−0.84 (−4.22 to 2.54)	−0.87 (−4.88 to 3.15)
WOMAC function subscale change from baseline	Placebo	2	736	WMD	0	−8.24 (−12.59 to −3.89)	−8.24 (−12.59 to −3.89)
	Celecoxib	2	978	WMD	0	−1.26 (−4.83 to 2.31)	−1.26 (−4.83 to 2.31)
WOMAC stiffness subscale endpoint	Celecoxib	2	978	WMD	0	−0.42 (−3.69 to 2.86)	−0.42 (−3.69 to 2.86)
	Placebo	2	736	WMD	0	−6.10 (−10.36 to −1.84)	−6.10 (−10.36 to −1.84)
WOMAC stiffness subscale change from baseline	Celecoxib	2	978	WMD	0	−2.05 (−5.73 to 1.63)	−2.05 (−5.73 to 1.63)
	Placebo	2	736	WMD	9	−10.30 (−14.79 to −5.81)	−10.29 (−14.99 to −5.59)
Patient's GADA change from baseline (0–100 VAS scale)	Celecoxib	2	978	WMD	0	0.14 (−3.92 to 4.21)	0.14 (−3.92 to 4.21)
	Placebo	2	736	WMD	0	−7.35 (−12.27 to −2.44)	−7.35 (−12.27 to −2.44)
Patient's GADA endpoint (0–100 VAS scale)	Placebo	2	736	WMD	0	6.62 (1.37 to 11.89)	6.63 (1.37 to 11.89)
ACR20 response[c]	Placebo[d]	5[43–47]	2388	OR	36	1.84 (1.55 to 2.18)	1.85 (1.50 to 2.30)
	Celecoxib	1[47]	700	OR	–	0.79 (0.57 to 1.09)	0.79 (0.57 to 1.09)
	Etoricoxib[d]	2[43,44]	1027	OR	45	0.78 (0.60 to 1.01)	0.78 (0.55 to 1.10)
Pain (VAS) change from baseline[c]	Placebo[d]	3[37,45,47]	1211	WMD	89	−9.14 (−11.99 to −6.29)	−11.05 (−19.82 to −2.29)
	Celecoxib	2[47,58]	966	WMD	0	2.39 (−1.30 to 6.08)	2.39 (−1.30 to 6.08)
	Etoricoxib	1[37]	202	WMD	–	7.80 (1.56 to 14.04)	7.80 (1.56 to 14.04)
Physician's GADA change from baseline (0–100 VAS scale)[c]	Placebo	1[45]	563	WMD	–	−6.50 (−9.97 to −3.03)	−6.50 (−9.97 to −3.03)
Physician's GADA change from baseline (0–4 Likert scale)[c]	Placebo	1[49]	277	WMD	–	−0.51 (−0.74 to −0.28)	−0.51 (−0.74 to −0.28)
	Etoricoxib	1[49]	445	WMD	–	0.03 (−0.13 to 0.19)	0.03 (−0.13 to 0.19)
HAQ-DI change from baseline[c]	Placebo	1[45]	563	WMD	–	−0.10 (−0.19 to −0.01)	−0.10 (−0.19 to −0.01)

Notes: [a]See Figure 3A and B for total WOMAC score change from baseline and WOMAC pain subscale change from baseline, respectively; [b]a value of 0 indicates no heterogeneity, and larger values to a maximum of 100 show increasing heterogeneity;[28] it was judged that for analyses with an I^2 value of <30, fixed effects results are more appropriate, and for analyses with an I^2 value of >30, random effects results are more appropriate; "–" indicates insufficient data for analysis; [c]high-dose naproxen used as a surrogate for naproxen/esomeprazole magnesium tablets for this comparison; [d]comparisons for which random effects results are more appropriate than fixed effects results.

Abbreviations: ACR20, American College of Rheumatology Criteria; CI, confidence interval; GADA, Global Assessment of Disease Activity; ES, effect size; HAQ-DI, Health Assessment Questionnaire Disease Index; MTC, mixed treatment comparison; OR, odds ratio; VAS, Visual Analogue Scale; WMD, weighted mean difference; WOMAC, Western Ontario and McMaster Osteoarthritis Index.

Table 2 Summary of the MTC results for efficacy in the treatment of arthritic symptoms outcomes, naproxen/esomeprazole magnesium tablets versus comparators[a]

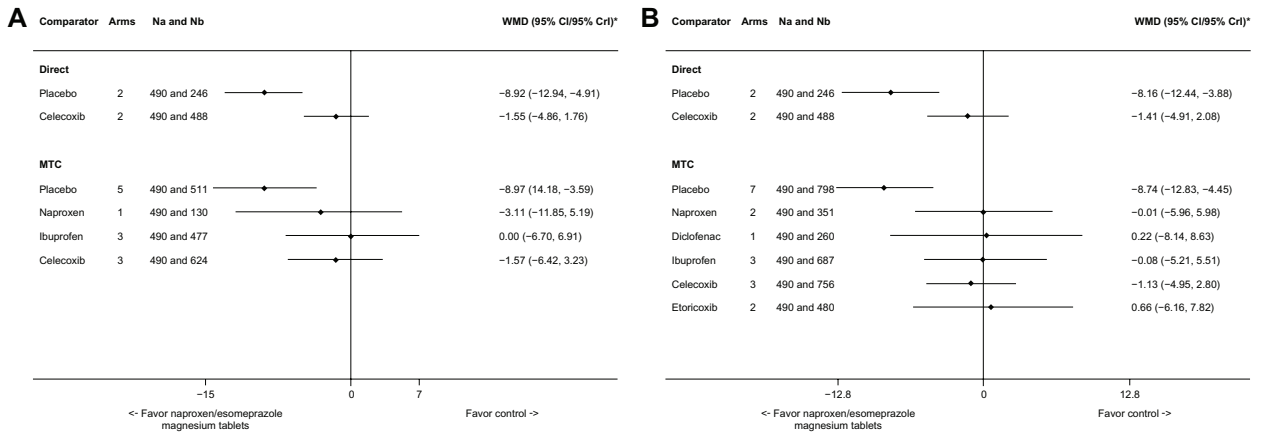
Outcome[b]	Comparator	Naproxen/esomeprazole magnesium study data		Comparator study data		Effect measure	ES (95% CrI)
		Number of arms	N (n/N)	Number of arms	N (n/N)		
WOMAC stiffness subscale change from baseline (0–100 VAS scale)	Placebo[c]	2	490	6[49–51,53]	644	WMD	−10.46 (−15.83, −4.93)
	Naproxen	2	490	2[48,49]	351	WMD	−4.39 (−11.99, 3.25)
	Diclofenac	2	490	1[54]	260	WMD	−3.19 (−13.94, 8.43)
	Ibuprofen	2	490	2[50,51]	423	WMD	−1.49 (−9.20, 6.19)
	Celecoxib	2	490	4[48,53]	756	WMD	−1.97 (−7.17, 3.17)
	Etoricoxib	2	490	2[49,54]	480	WMD	−2.69 (−11.76, 6.50)
WOMAC function subscale change from baseline (0–100 VAS scale)	Placebo[c]	2	490	7[49,50,52–54]	822	WMD	−7.34 (−11.37, −3.29)
	Naproxen	2	490	2[48,49]	351	WMD	−0.79 (−6.73, 5.09)
	Diclofenac	2	490	1[54]	260	WMD	−0.61 (−8.81, 7.91)
	Ibuprofen	2	490	2[49,52]	267	WMD	−0.01 (−6.07, 5.94)
	Celecoxib	2	490	5[48,53,55]	1202	WMD	−1.64 (−5.31, 2.15)
	Etoricoxib	2	490	2[49,54]	480	WMD	−0.19 (−6.92, 7.18)
Patient's GADA change from baseline (0–100 VAS scale)	Placebo	2	490	10[37,45,49,50,55–58]	1835	WMD	−7.09 (−14.93, 0.61)
	Naproxen	2	490	3[37,45,49]	599	WMD	3.68 (−6.67, 14.02)
	Diclofenac	2	490	1[59]	155	WMD	1.53 (−12.27, 15.56)
	Ibuprofen	2	490	1[50]	213	WMD	1.02 (−13.32, 15.12)
	Ketoprofen	2	490	1[56]	90	WMD	−3.32 (−17.32, 10.57)
	Celecoxib	2	490	7[55–59]	2055	WMD	−0.49 (−8.00, 7.25)
	Etoricoxib	2	490	2[37,49]	327	WMD	8.79 (−2.54, 20.25)
ACR20 response[d]	Placebo[c]	5[43–47]	(478/1022)	5[43–47]	(450/1366)	OR	1.86 (1.30, 2.69)
	Diclofenac	5[43–45,47]	(478/1022)	1[60]	(73/329)	OR	1.02 (0.36, 3.07)
	Celecoxib	5[43–45,47]	(478/1022)	2[47,60]	(278/801)	OR	0.90 (0.45, 1.82)
	Etoricoxib	5[43–45,47]	(478/1022)	2[43,44]	(389/676)	OR	0.71 (0.43, 1.20)
Pain (VAS) change from baseline[d]	Placebo[c]	4[37,45,47,48]	733	9[45,47,55,56,58,61–63]	1639	WMD	−9.25 (−15.77, −2.75)
	Diclofenac	4[37,45,47,48]	733	4[59,61,62,64]	631	WMD	5.80 (−3.06, 14.70)
	Ketoprofen	4[37,45,47,48]	733	1[56]	90	WMD	−3.68 (−17.50, 9.89)
	Fixed-dose diclofenac sodium plus misoprostol	4[37,45,47,48]	733	1[62]	327	WMD	6.31 (−6.90, 19.62)
	Celecoxib	4[37,45,47,48]	733	9[47,48,55,56,58,59,61,63,64]	2195	WMD	−0.50 (−7.53, 6.36)
	Etoricoxib[c]	4[37,45,47,48]	733	1[37]	1	WMD	13.64 (1.80, 25.21)
Physician's GADA change from baseline (0–4 Likert scale)[d]	Placebo[c]	1[53]	221	6[49–51,61,62,65]	590	WMD	−0.44 (−0.86, −0.05)
	Diclofenac	1[49]	221	6[61,62,64–66]	10 056	WMD	−0.07 (−0.52, 0.32)
	Ibuprofen	1[49]	221	2[50,51]	423	WMD	−0.07 (−0.59, 0.43)
	Fixed dose diclofenac sodium plus misoprostol	1[49]	221	1[62]	327	WMD	0.02 (−0.55, 0.55)
	Celecoxib	1[49]	221	2[61,64]	327	WMD	−0.12 (−0.63, 0.35)
	Etoricoxib	1[49]	221	3[49,66]	9834	WMD	−0.01 (−0.41, 0.38)
HAQ-DI change from baseline[d]	Placebo	1[49]	279	2[45]	597	WMD	−0.10 (−12.73, 12.10)
	Celecoxib	1[49]	279	1[57]	318	WMD	−0.05 (−17.52, 17.24)

Notes: [a]Random effects have been presented for MTCs to account for any between-study heterogeneity; [b]see Figure 3A and B for total WOMAC score change from baseline and WOMAC pain subscale change from baseline, respectively; [c]statistically significant results; [d]high-dose naproxen used as a surrogate for naproxen/esomeprazole magnesium.
Abbreviations: ACR20, American College of Rheumatology Criteria; CrI, credible interval; ES, effect size; GADA, Global Assessment of Disease Activity; HAQ-DI, Health Assessment Questionnaire Disease Index; MTC, mixed-treatment comparison; n/N, number of patients with event out of total number of patients; OR, odds ratio; VAS, Visual Analogue Scale; WMD, weighted mean difference; WOMAC, Western Ontario and McMaster Osteoarthritis Index.

were approximately 35% less with naproxen/esomeprazole magnesium tablets than with naproxen (OR 0.64; 95% CrI 0.49–0.84) or diclofenac (OR 0.67; 95% CrI 0.50–0.91), and were 83% less than with ketoprofen (OR 0.17; 95% CrI 0.02–0.96) (Figure 5B).

Other GI outcomes

RCTs included in the review were not designed to measure the outcome of any GI bleed/hemorrhage. Results for the outcome of any GI bleed/hemorrhage outcome were inconclusive due to the rarity of any GI bleed/hemorrhage

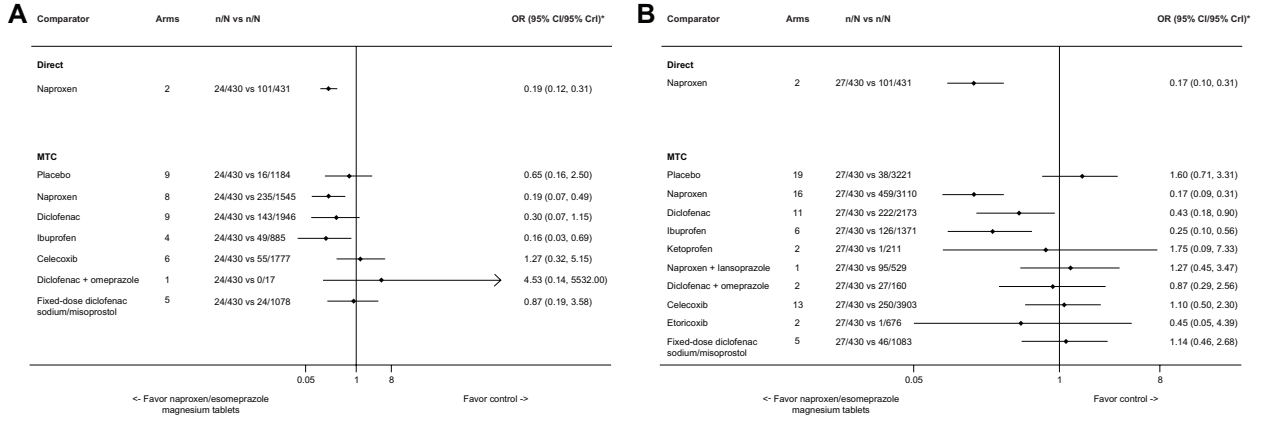


in the studies included in the review, and the corresponding lack of statistical power to detect a significant difference in GI bleeding events between treatments (Table 3).

Direct meta-analysis showed that naproxen/esomeprazole magnesium tablets were associated with significantly less odds of upper GI event than naproxen (OR 0.51; 95% CI 0.38–0.67) (Table 4). This is in contrast with MTCs, which showed no significant differences between comparators (including naproxen/esomeprazole magnesium tablets) for the outcome of upper GI event, except celecoxib + esomeprazole, which had significantly lower odds of upper GI event compared with all other nsNSAIDs and COX-2 inhibitors analyzed (Table 4). There was considerable heterogeneity in this network, with different trials reporting strikingly different proportions of patients experiencing upper GI events, and these MTC results should be interpreted with caution.

CV safety

RCTs included in the review were not designed to measure CV safety. Results for CV safety outcomes were inconclusive



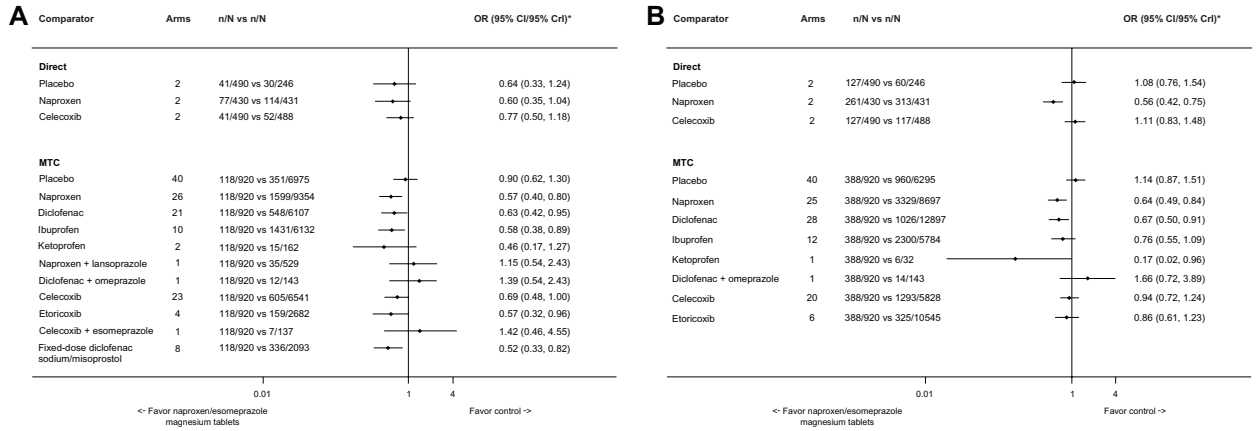


Figure 5 Summary plot of naproxen/esomeprazole magnesium versus comparators for the outcomes of (**A**) dyspepsia[37,44-47,49,50,53,58,60–62,64,69–78,80,81,83,84,86,88–119] and (**B**) any gastrointestinal event.[43,45,47,49,53–55,58–60,64,66,68,71–74,77,81,82,86,87,89,91,93,95–99,102,103,105–110,112,119–137]

Notes: The results of the direct meta-analyses (Direct) and mixed-treatment comparisons (MTC) are displayed within this figure as "forest plot" diagrams. These diagrams display the results from analysis of naproxen/esomeprazole magnesium versus different comparators on separate rows. The graphical display plots the ES on the outcome of naproxen/esomeprazole magnesium versus comparator as a dot, with its CIs marked as a line extending either side of the dot. Fixed-effect results are presented for direct meta-analysis results of naproxen/esomeprazole magnesium tablets with celecoxib in A due to low between-study heterogeneity (value in the I-squared test of statistical heterogeneity of 41) and for all meta-analysis results in B due to no between-study heterogeneity (value in the I-squared test of statistical heterogeneity of 0). Random effects results are presented for all other analyses in A and B to account for any heterogeneity between studies. *95% CIs used for direct meta-analyses, 95% CrIs used for MTCs.

due to the rarity of CV events in the studies included in the review, and the corresponding lack of statistical power to detect a significant difference in CV events between treatments.

Data for naproxen/esomeprazole magnesium tablets were available for the outcomes of any CV event, stroke, MI, and angina, with high-dose naproxen used as a surrogate for all other outcomes. There were no identified significant differences between comparators (including naproxen/esomeprazole magnesium) for any CV event, any MI, fatal MI, CV death, stroke, nonfatal stroke, angina, or congestive heart failure in either direct meta-analyses or MTCs. Due to the aforementioned rarity of these events and inconclusiveness of results, these findings should be interpreted with caution since there is insufficient statistical power to detect underlying differences between treatments.

Subgroup analysis

Concomitant LDA

There were no data for efficacy in the treatment of arthritic symptoms for subgroups of patients taking an nsNSAID plus LDA. Meta-analysis and indirect analysis of the available upper GI tolerability data demonstrated that naproxen/esomeprazole magnesium tablets plus LDA were significantly less likely to cause gastroduodenal ulcers compared with naproxen plus LDA (direct meta-analysis OR 0.09; 95% CI 0.03–0.26), naproxen plus PPI and LDA (indirect analysis OR 0.25; 95% CI 0.06–0.95), and celecoxib plus LDA (indirect analysis OR 0.22; 95% CI 0.06–0.78).

High-dose nsNSAIDs

Subgroup analysis was conducted using studies presenting data on a high-dose nsNSAID or high-dose nsNSAID plus PPI. In MTCs, naproxen/esomeprazole magnesium tablets

Table 3 Summary of direct meta-analyses results for upper GI event outcomes, naproxen/esomeprazole magnesium tablets versus comparators

Outcome[a]	Comparator	No of studies	N	Effect measure	Statistical heterogeneity (I^2)[b]	ES (95% CI)	
						Fixed effects	Random effects
Any GI bleed/ hemorrhage	Celecoxib	2	978	OR	–	1.00 (0.06–15.88)	1.00 (0.06–15.88)
	Naproxen	2	861	OR	17%	0.39 (0.15–1.01)	0.41 (0.14–1.21)
	Placebo	2	736	OR	–	1.51 (0.06–36.91)	1.51 (0.06–36.91)
Upper GI event	**Naproxen**	**2**	**861**	**OR**	**0%**	**0.51 (0.38–0.67)**	**0.51 (0.38–0.67)**

Notes: [a]See Figure 4A and B for gastric ulcers and gastroduodenal ulcers, respectively; see Figure 5A and B for dyspepsia and any GI event, respectively; [b]a value of 0 indicates no heterogeneity, and larger values to a maximum of 100 show increasing heterogeneity;[28] it was judged that for analyses with an I^2 value of <30%, fixed effects results are more appropriate, and for analyses with an I^2 value of >30%, random effects results are more appropriate. Boldface represents statistical significance.
Abbreviations: CI, confidence interval; ES, effect size; GI, gastrointestinal; N, number of patients with event out of total number of patients; OR, odds ratio.

Table 4 Summary of the MTC results for upper GI event outcomes, naproxen/esomeprazole magnesium tablets versus comparators[a]

Outcome[b]	Comparator	Naproxen/esomeprazole magnesium study data		Comparator study data		Effect measure	ES (95% CrI)
		Number of arms	n/N	Number of arms	n/N		
Any GI bleed/hemorrhage	Placebo	4	7/920	14[44,69,71,73,82,83,86,96,97,104,105,138]	6/2382	OR	0.87 (0.26–2.99)
	Naproxen	4	7/920	14[44,71,73,74,83,86,96,104,119,139–141]	43/6933	OR	0.38 (0.14–1.00)
	Diclofenac	4	7/920	7[77,78,97,105,111,114,142]	11/1406	OR	0.25 (0.04–1.28)
	Ibuprofen	4	7/920	5[82,114,119,138,141]	17/5286	OR	0.36 (0.09–1.40)
	Naproxen + lansoprazole	4	7/920	1[90]	1/529	OR	0.17 (0.00–7.95)
	Diclofenac + omeprazole	4	7/920	1[89]	9/143	OR	0.78 (0.11–5.32)
	Fixed-dose diclofenac sodium + esomeprazole	4	7/920	1[78]	0/193	OR	3.08 (0.10–5878.00)
	Celecoxib	4	7/920	10[71,73,74,77,86,89,90]	11/2719	OR	1.00 (0.26–3.87)
	Etoricoxib	4	7/920	2[44,142]	0/425	OR	1.64 (0.10–76.10)
	Celecoxib + esomeprazole	4	7/920	1[92]	4/137	OR	4.16 (0.61–31.07)
Upper GI event	Placebo	2	226/430	7[56,102,103,143–146]	25/393	OR	1.10 (0.32–5.22)
	Naproxen	2	226/430	6[74,144–146]	304/849	OR	0.52 (0.26–1.06)
	Diclofenac	2	226/430	5[54,59,64,103,143]	59/672	OR	0.34 (0.08–2.19)
	Ibuprofen	2	226/430	1[91]	75/260	OR	0.37 (0.07–2.56)
	Ketoprofen	2	226/430	1[56]	23/90	OR	0.75 (0.16–4.52)
	Celecoxib	2	226/430	7[56,59,64,74,91,92,102]	100/1236	OR	0.79 (0.20–4.30)
	Etoricoxib	2	226/430	1[54]	8/256	OR	0.57 (0.09–5.66)
	Celecoxib + esomeprazole[c]	2	226/430	1[92]	0/137	OR	57.27 (2.15–31,809.99)

Notes: [a]Random effects have been presented for MTCs to account for any between study heterogeneity; [b]see Figure 4A and B for gastric ulcers and gastroduodenal ulcers, respectively; see Figure 5A and B for dyspepsia and any GI event, respectively; [c]statistically significant results.
Abbreviations: CrI, credible interval; ES, effect size; GI, gastrointestinal; MTC, mixed-treatment comparison; n/N, number of patients with event out of total number of patients; OR, odds ratio.

were found to have significantly lower odds of dyspepsia when compared with high-dose naproxen (OR 0.58; 95% CrI 0.42–0.78), diclofenac (OR 0.61; 95% CrI 0.42–0.93), and ibuprofen (OR 0.52; 95% CrI 0.36–0.77). Similarly, the odds of gastric ulcers (OR 0.19; 95% CrI 0.05–0.62), gastroduodenal ulcers (OR 0.17; 95% CrI 0.08–0.37), and any GI event (OR 0.64; 95% CrI 0.47–0.85) were significantly lower with naproxen/esomeprazole magnesium tablets than with high-dose naproxen. Further, the odds of gastroduodenal ulcers were significantly lower with naproxen/esomeprazole magnesium tablets than high-dose ibuprofen (OR 0.24; 95% CrI 0.07–0.66), and naproxen/esomeprazole magnesium tablets were associated with lower odds of any GI event than high-dose ketoprofen (OR 0.12; 95% CrI 0.01–0.96).

Discussion

The purpose of this systematic review and network meta-analyses was to compare the efficacy in the treatment of arthritic symptoms, upper GI tolerability, and/or CV safety of naproxen/esomeprazole magnesium tablets with a range of nsNSAIDs and COX-2 inhibitors, with and without concomitant gastroprotective agents in patients with RA, OA, and AS. In general, naproxen/esomeprazole magnesium tablets were shown to provide potential benefits in upper GI tolerability profile compared with naproxen, ibuprofen, diclofenac, etoricoxib, and ketoprofen dosed without a PPI, and fixed-dose diclofenac sodium plus misoprostol. Naproxen/esomeprazole magnesium tablets were equally effective in the treatment of arthritic symptoms in patients with RA, OA, and AS compared with nsNSAIDs and COX-2 inhibitors, and no conclusions could be made regarding differences in CV safety due to low study numbers.

These results confirm the conclusion drawn by the authors of a PN400-301/PN400-302 clinical trial publication that found naproxen/esomeprazole magnesium tablets to be superior to naproxen with respect to incidence of gastric

and duodenal ulcers,[20] and provides additional insights into the relative upper GI tolerability of naproxen/esomeprazole magnesium tablets across a range of different comparators and outcomes. For example, naproxen/esomeprazole magnesium tablets were also found to be associated with significantly lower odds of gastric ulcers when compared with ibuprofen; gastroduodenal ulcers when compared with ibuprofen or diclofenac; dyspepsia when compared with naproxen, ibuprofen, diclofenac, etoricoxib, or fixed-dose diclofenac sodium plus misoprostol; and any GI event when compared with naproxen, diclofenac, and ketoprofen. Results were directionally consistent when comparing naproxen/esomeprazole magnesium tablets and naproxen for the outcome of dyspepsia between direct meta-analysis (directionally favoring naproxen/esomeprazole magnesium tablets with no statistical significance) and MTC analysis (significant difference favoring naproxen/esomeprazole magnesium tablets). That statistical significance was observed in the MTC analysis (but not in the direct meta-analysis) can be attributed to the increased statistical power of the MTC analysis due to its bigger sample size. This bigger sample size resulted in narrower 95% CrIs (difference in point estimates of 0.40) compared with the 95% CIs in the direct meta-analysis (difference in point estimates of 0.69), suggesting that the results from the MTC analysis are more reliable. Aside from the outcomes of dyspepsia and upper GI event (results from the latter were previously stated to be inconclusive due to substantial heterogeneity), results for all other GI outcomes were consistent when comparing direct meta-analysis results and MTC analysis results with respect to identifying either no significant difference between comparators or a significant difference favoring one comparator over another.

The results also demonstrate that naproxen/esomeprazole magnesium tablets are as effective in the treatment of arthritic symptoms as other nsNSAIDs (naproxen, diclofenac, ibuprofen, ketoprofen, and fixed dose diclofenac sodium plus misoprostol) and COX-2 inhibitors (celecoxib [consistent with conclusions drawn by authors of PN-400-307/PN400-309 clinical trial publications][21,22] and etoricoxib) as assessed by a variety of efficacy outcomes. The only outcome that appeared to differ was Pain (VAS) change from baseline, in which etoricoxib was superior to naproxen/esomeprazole magnesium tablets (using high-dose naproxen as a surrogate). However, the etoricoxib data, which fed into the network analysis comparing naproxen/esomeprazole magnesium tablets with etoricoxib was derived from only one study in a population of patients with AS only (in which naproxen also showed a clinically meaningful benefit).[37] Therefore, this individual result should be interpreted with caution, and it may not be appropriate to generalize it to a wider population of patients with OA or RA. Results were consistent for all other efficacy outcomes when comparing direct meta-analysis results and MTC analysis results with respect to identifying either no significant difference between comparators or a significant difference favoring one comparator over another. These results are also consistent with previously published systematic reviews. A comparative effectiveness review for OA conducted by AHRQ (Agency for Healthcare Research and Quality) in 2006 and updated in 2011 which included all of the nsNSAIDs and COX-2 inhibitors considered within the current review concluded that evidence regarding the benefits of oral NSAIDs is abundant and demonstrates no clear, consistent differences for relieving pain or other OA-related symptoms between individual nsNSAIDs, individual COX-2 inhibitors, or when comparing nsNSAIDs and COX-2 inhibitors.[38,39] Likewise, systematic reviews in populations with AS and OA/RA have concluded that there is no clear indication that one NSAID treatment is more efficacious than another.[40,41] As the addition of a PPI or other gastroprotective agent such as misoprostol is unlikely to have an effect on the efficacy of an NSAID in treating arthritic symptoms, it can be concluded that the results from the current analyses showing that naproxen/esomeprazole magnesium tablets and active comparators were equally effective in the treatment of arthritic symptoms are consistent with previously published analyses.

RCT studies identified in the systematic review and utilized within the network meta-analyses were not designed to measure CV safety outcomes. No statistically significant differences were found between naproxen/esomeprazole magnesium tablets and comparators for any of the assessed CV safety outcomes, which is potentially due to the rarity of such events. These findings should be interpreted with caution since there is insufficient statistical power to detect underlying differences between treatments. Recently, a systematic review was performed by Salvo et al on meta-analyses of RCTs that assessed CV and GI outcomes for patients on NSAID treatment for 15 indications, including OA, RA, and AS.[16] The authors speculated as to whether their discovered knowledge gap of systematic CV safety evaluation for nsNSAIDs was due to a lack of interest in evaluating these outcomes for nsNSAIDs or a lack of relevant RCTs.[16] The current analyses suggest the latter is the case, and that the rarity of CV events in identified RCTs of patients with

OA, RA, and AS treated with nsNSAIDs indicate meaningful comparisons between naproxen/esomeprazole tablets and nsNSAIDs for CV outcomes cannot be made.

One limitation of the current study is that limited RCT data is available for comparison of efficacy in the treatment of arthritic symptoms between naproxen/esomeprazole magnesium and nsNSAIDs or COX-2 inhibitors concomitant with a PPI. However, as the PPI mechanism causes a reduction in gastric acid, PPIs are unlikely to have an effect on arthritic pain efficacy from concomitant NSAID therapy.

A second limitation is that potential additional real-world benefits of a fixed-dose NSAID plus PPI treatment (such as naproxen/esomeprazole magnesium tablets) compared with NSAID plus PPI dosed as individual monocomponents may not be appreciated in the setting of RCTs, which were the basis of the systematic review and network analyses. This is because RCTs are more regimented than clinical practice, and so do not completely reflect how a patient will use the treatment in the real-world setting. It has been demonstrated that 44%–50% of patients at risk of NSAID-induced GI toxicity are nonadherent to NSAID and PPI co-prescribed therapy.[3,42] In patients with high GI risk (for whom concomitant gastroprotection would be particularly important), adherence was low for co-therapy, even when a PPI was provided at no cost and written guidance was made available.[42] It has been proposed in the literature that a fixed-dose NSAID plus PPI regimen may improve patient adherence compared with a regimen in which an NSAID and PPI are dosed as individual monocomponents.[3,42]

A final limitation of the review relates to the included source publications from which the data were extracted. The quality of the study reporting necessarily influenced the information that could be extracted for each study. Further, there were differences between studies in relation to study design, methods of analysis, and patient population. Any uncertainty resulting from the quality of the reporting or any differences in design, analysis, or population between studies could have introduced heterogeneity, and therefore greater uncertainty, into the review. For example, the definition of endpoints was not always clearly reported, meaning that there is some uncertainty as to whether the same definition was used in each case where it is reported. Any such heterogeneity does not introduce systematic bias into the analyses, but it may increase the variability of effect estimates between the studies, which in turn means that effect estimates in the current analyses may have been less likely to reach statistical significance than would be the case in the absence of such heterogeneity.

Conclusion

In the treatment of arthritic symptoms in patients with OA, RA, and AS, network meta-analyses have demonstrated that naproxen/esomeprazole magnesium tablets have superior upper GI tolerability (dyspepsia and gastric or gastroduodenal ulcers) to the majority of NSAIDs and fixed-dose diclofenac sodium plus misoprostol. In the setting of concomitant LDA administration, the upper GI tolerability profile of naproxen/esomeprazole magnesium tablets plus LDA relative to other nsNSAIDs plus LDA and COX-2 inhibitors plus LDA remains unabated. No significant difference was shown when comparing the upper GI tolerability of naproxen/esomeprazole magnesium tablets with nsNSAIDs combined with PPIs (although naproxen/esomeprazole magnesium does show superiority over fixed-dose diclofenac sodium plus misoprostol for the outcome of dyspepsia). However, any potential real-world benefits (such as compliance or adherence benefits) of fixed-dose NSAID plus PPI combinations such as naproxen/esomeprazole magnesium tablets relative to regimens in which an NSAID and PPI are dosed as individual monocomponents were not captured in the setting of RCTs, and were therefore not identified in this study.

The network meta-analyses showed naproxen/esomeprazole magnesium tablets to be equally effective in treating arthritic symptoms as active comparators. CV safety conclusions could not be drawn from the network meta-analyses of identified RCTs.

Naproxen/esomeprazole magnesium tablets are therefore concluded to be a valuable treatment option for treating arthritic symptoms in eligible patients with OA, RA, and AS.

Acknowledgments

With thanks to James Cann, Jessica May, and Ebony Samuels at HERON Evidence Development for contributing to the preparation of the draft manuscript.

Author contributions

Mohd Siddiqui was responsible for study design, data extraction, and statistical analysis; Catherine Datto and Richard Hellmund contributed to study concept, design, and data interpretation. All authors contributed to the development of and review of the draft manuscript and approved the final submitted version.

Disclosure

Catherine Datto and Richard Hellmund are employees of AstraZeneca Pharmaceuticals LP. The study was funded

by AstraZeneca Pharmaceuticals LP. Mohd Siddiqui is an employee of HERON Pvt India, which was commissioned to undertake the research for this study by AstraZeneca Pharmaceuticals LP.

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Supplementary material

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