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Systematic review: the lower gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs

L. LAINE*, R. SMITH†, K. MIN†, C. CHEN‡ & R. W. DUBOIS†

*Division of Gastrointestinal and Liver Diseases, University of Southern California, Los Angeles, CA, USA; †Cerner LifeSciences, Beverly Hills, CA, USA; ‡Pfizer Inc., New York, NY, USA

Correspondence to:
Dr L. Laine, Division of Gastrointestinal and Liver Diseases, 1200 North State Street, Room 12-137, University of Southern California, Los Angeles, CA 90033, USA.
E-mail: llaine@usc.edu

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SUMMARY

Background
Lower gastrointestinal effects of non-steroidal anti-inflammatory drugs (NSAIDs) are much more poorly characterized than upper gastrointestinal effects.

Aim
To determine if NSAIDs increase lower gastrointestinal adverse effects and if the risk with non-selective NSAIDs is greater than with cyclooxygenase-2-selective inhibitors (coxibs).

Methods
Computerized databases were searched to identify studies of NSAID use reporting on lower gastrointestinal integrity (e.g. permeability), visualization (e.g. erosions, ulcers) and clinical events.

Results
Designs in 47 studies were randomized (18), case–control (14), cohort (eight) and before-after (seven). Non-selective-NSAIDs had significantly more adverse effects vs. no NSAIDs in 20 of 22 lower gastrointestinal integrity studies, five of seven visualization studies, seven of 11 bleeding studies (OR: 1.9–18.4 in case–control studies), two of two perforation studies (OR: 2.5–8.1) and five of seven diverticular disease studies (OR: 1.5–11.2). Coxibs had significantly less effect vs. non-selective-NSAIDs in three of four integrity studies, one endoscopic study (RR mucosal breaks: 0.3), and two randomized studies (RR lower gastrointestinal clinical events: 0.5; haematochezia: 0.4).

Conclusions
An increase in lower gastrointestinal injury and clinical events with non-selective-NSAIDs appears relatively consistent across the heterogeneous collection of trials. Coxibs are associated with lower rates of lower gastrointestinal injury than non-selective-NSAIDs. More high-quality trials are warranted to more precisely estimate the effects of non-selective-NSAIDs and coxibs on the lower gastrointestinal tract.

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) have been widely used for decades to relieve pain, inflammation and fever. An estimated 60 million Americans use NSAIDs regularly.[1] In the United States, approximately $5 billion are spent annually on prescription NSAIDs and an additional $2 billion are spent on over-the-counter NSAIDs.[2] The main factor that limits use of NSAIDs is concern over the development of gastrointestinal (GI) side effects. NSAIDs cause GI tract mucosal injury (e.g. erosions, ulcers) and GI complications (e.g. bleeding, perforation, obstruction). The incidence and risks of NSAID-associated upper GI tract injury and complications are well described, with a large number of randomized-controlled trials and observational studies providing information on the upper GI adverse effects of NSAIDs.[2] A number of reports have been published suggesting that traditional non-selective NSAIDs (NS-NSAIDs) also may cause lower GI tract injury and complications, but the lower GI effects of NS-NSAIDs are still uncertain and much more poorly characterized than the upper GI tract effects.

NSAID use by arthritis patients is estimated to cause over 100 000 hospitalizations annually for GI complications in the US.[3] In the general population, lower GI tract complications such as bleeding occur at a rate equaling approximately one-fifth the rate of upper GI tract complications.[4, 5] If NSAIDs increase the risk of lower GI tract complications to the same degree that they increase the risk of upper GI complications, then NSAID-associated lower GI complications would account for approximately one-fifth of all NSAID GI complications – or over 20 000 hospitalizations annually among arthritis patients.

The cyclooxygenase (COX)-2 selective inhibitors (coxibs) were developed to provide analgesic and anti-inflammatory activity comparable with traditional NS-NSAIDs, but with a lower risk of GI tract injury. Double-blind randomized endoscopic trials document that these agents decrease the risk of developing gastroduodenal ulcers;[6, 7] and double-blind randomized outcome studies have shown a decrease in upper GI complications and clinical events.[8, 9] The relative risk of coxibs when compared with NS-NSAIDs for lower GI tract injury and clinical events, however, also is much less well characterized than is the risk in the upper GI tract.

In order to develop an understanding of the current state of knowledge regarding NSAID effects on the lower GI tract and to determine potential areas for further investigation, we systematically reviewed the published literature to assess the effect of traditional NS-NSAIDs and coxibs on lower GI mucosal injury and on clinical events such as lower GI bleeding. We sought to determine if there was an increased risk of mucosal injury or clinical events with NS-NSAIDs or coxibs when compared with no therapy, and if the risk of adverse effects was lower with coxibs than with NS-NSAIDs.

METHODS

Literature search

We performed a systematic review of the published medical literature using the computerized bibliographic databases PubMed and Cochrane Reviews for English language articles published between 1950 and November 2005. The strategy consisted of multiple separate searches, each combining medical subject headings (MeSH) and/or text words from three categories: drugs (e.g. non-steroidal anti-inflammatory agents, cyclooxygenase inhibitors), location (e.g. lower gastrointestinal tract, small bowel) and measurement (e.g. clinical outcomes, endoscopy, GI integrity). Specific terms are displayed in Table 1. The drug search and the location search were combined in turn with the clinical outcome, endoscopy and GI integrity searches. We pooled the results of the three searches, excluding duplicate articles. Hand searches of bibliographies from relevant articles yielded additional references.

Inclusion and exclusion criteria

To be included in the review, studies had to meet the following criteria: (i) the population consisted of human subjects taking NSAIDs; (ii) the interventions included coxibs and/or NS-NSAIDs; (iii) the study compared subjects taking NS-NSAIDs vs. no treatment/placebo or subjects taking coxibs vs. NS-NSAIDs; (iv) the outcomes included lower GI integrity, visualization of lower GI tract lesions, or lower GI clinical events. Lower GI tract was defined as small intestine (beyond the duodenum) and/or colon. Studies were excluded if they contained the keywords neoplasms, inflammatory bowel disease, or warfarin, or if they included only paediatric subjects. Excluded study designs were reviews, meta-analyses, letters, case reports, case series and editorials.

Table 1. Search terms by category

Drugs	MeSH terms: Non-steroidal anti-inflammatory agents; NSAIDs; cyclo-oxygenase inhibitors; aspirin-like agents; anti-inflammatory agents; non-steroidal Non-MeSH terms: Generic names of specific NSAID
Location	MeSH terms: Lower gastrointestinal tract; intestine, large; intestine, small; colon; rectum; ileum; jejunum Non-MeSH terms: Lower gastrointestin*; large bowel; small bowel; rectal
Clinical outcomes	MeSH terms: Anti-inflammatory agents, non-steroidal/adverse effects; diverticulum; diverticulosis; diverticula; intestinal mucosa/drug effects; intestine, small/drug effects; naproxen/adverse effects; intestinal diseases/chemically induced; ulcer/chemically induced; gastrointestinal hemorrhage; gastrointestinal hemorrhage/chemically induced Non-MeSH terms: Lower gastrointestinal events; ulcer*; ulceration; injury; bleed*; hemorrhage; perforation; obstruction; stricture; haematochezia; melena; colitis; occult blood; fecal blood loss; anemia
Endoscopy	MeSH terms: Endoscopy; colonoscopy; gastroenterology/instrumentation; endoscopy, gastrointestinal/methods; intestinal mucosa/drug effects; intestinal mucosa/pathology; intestine, small/pathology; video recording; intestinal diseases/pathology; ulcer/pathology; capsules Non-MeSH term: Video capsule
GI integrity	MeSH terms: Erythrocytes/radionuclide imaging; gastrointestinal hemorrhage/radionuclide imaging; feces/chemistry; feces/analysis; permeability; mucosa; histology Non-MeSH term: Enteropathy

MeSH, medical subject heading; NSAID, non-steroidal anti-inflammatory drug.

Article review and data abstraction

Based on these explicit criteria, two reviewers trained in health services research and the principles of critical appraisal independently reviewed a 10% sample of abstracts identified by the search strategy. Inter-rater agreement was assessed using the κ-statistic, and the remaining abstracts were split between reviewers once a sufficient level of agreement was achieved (κ: ≥0.8). We obtained the full-text publication for each accepted abstract and repeated this review process, including a 10% sample and inter-rater reliability assessment, for all full-text articles. If the abstract was ambiguous, the full-text article was reviewed.

Data from accepted articles were abstracted into a predefined review spreadsheet and included study design, study duration, patient population, number of subjects, treatment arms, outcome measures, results and measures of association. We abstracted all relevant treatment arms and outcomes from each article, so a single study could contribute several observations.

Data synthesis

We performed a qualitative data synthesis with the aim of summarizing the results of the studies. We first classified the studies into two groups by type of NSAID used as the intervention: (i) NS-NSAIDs vs. no NS-NSAID/placebo and (ii) coxibs vs. NS-NSAIDs or no NS-NSAID/placebo. We further segmented each group of studies by three general investigative approaches: (a) examinations of GI integrity (permeability, inflammation and microscopic lesions), (b) visualization of the intestine (by endoscopy or postmortem examination) and (c) clinical outcome (lower GI bleeding, lower GI perforation and diverticular disease). Studies with multiple interventions or with multiple outcome measures could be placed in more than one category.

Numerical results and calculations

We recorded measures of association [odds ratio (OR), relative risk (RR)] and *P*-values where given by the authors of the study. If no such measures were reported, we calculated the appropriate effect measures and the *P*-value from available data if possible. Studies were categorized as significant [increased adverse outcomes with NS-NSAIDs, coxibs, or control/placebo with $P < 0.05$ or upper and lower bounds of 95% confidence interval (CI) both <1 or >1] or non-significant ($P > 0.05$ or 95% CI including 1). For studies with multiple treatment arms or outcomes (e.g. separate analyses for aspirin and non-aspirin medications, multiple aspects of GI permeability), we categorized the study by its 'significant' outcome and noted any discrepancies or differences in the Results section.

RESULTS

Literature review

The initial search strategy identified a total of 930 references. We accepted 179 titles and abstracts for article retrieval and further screening; of these, 46 papers met our explicit inclusion and exclusion criteria.[10–55] Figure 1 depicts the results of the screening process. The majority of the rejected full-text articles failed to address outcomes of interest; for example, only upper GI events were evaluated, upper GI and lower GI event results were not differentiated, or the focus of the study was economic outcomes. To calculate inter-rater agreement, the titles and abstracts of 90 articles were reviewed by two investigators and the resulting κ-value was 0.84. At the paper review stage, 21 full-text articles were co-reviewed; the κ-value was 0.80.

Characteristics of studies

The 46 accepted articles yielded 47 studies, as one article reported on two separate case–control studies.[37] Of 47 studies, 18 were randomized-controlled trials, and seven were non-randomized before-after trials. Ten of the 18 randomized trials used a crossover design. Twenty-two studies were observational (eight cohort and 14 case–control). The number of subjects included in each study ranged from 6 to 35 615.

Twenty-two studies[10, 14, 16, 20–23, 26, 33, 35, 39–42, 44, 45, 47–50, 52, 55] investigated lower GI integrity, the largest single category. Seven studies[10–12, 27, 38, 45, 51] used visualization approaches. Twenty studies looked at clinical outcomes: 11 lower GI bleeding,[19, 24, 30, 31, 34, 36, 37, 51, 53, 54] two lower GI perforation[32, 54] and seven diverticular disease.[13, 15, 18, 28, 29, 43, 46] Seven articles[11, 14, 17, 20, 23, 25, 52] compared coxibs with NS-NSAIDs or placebo. Studies using multiple approaches were counted more than once.

Studies comparing NS-NSAIDs vs. control

Lower GI integrity

Lower GI integrity was measured by small intestinal permeability ($n = 16$[14, 16, 20–23, 26, 35, 39–42, 44, 48, 49, 52]), large intestinal permeability ($n = 4$[14, 16, 20, 40]), intestinal permeability (both large and small intestine,

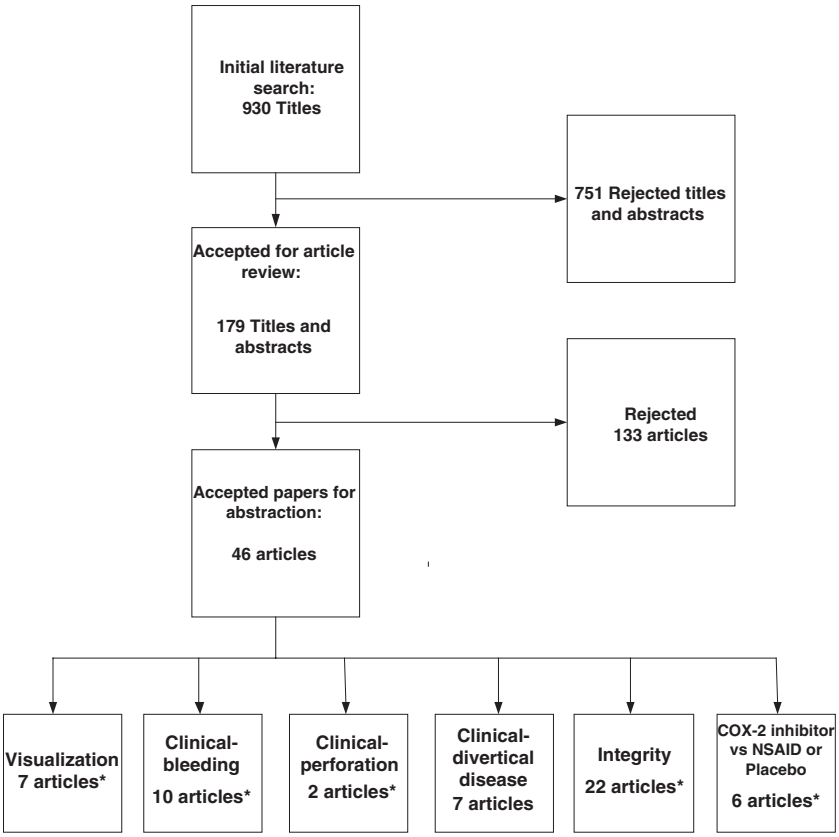

Figure 1. Flow of citations through the review process (* Articles were counted in more than one category).

$n = 6$[16, 33, 44, 47, 50, 55]), intestinal inflammation ($n = 2$[10, 23]) and histological examination for lower GI microscopic lesions ($n = 1$[45]) (data not shown). The concept of intestinal permeability refers to the passive movement of low-molecular weight molecules across the intestinal mucosa.[40] It occurs with injury and is measured by the ability of test substances, such as labelled ethylenediaminetetraacetic acid (EDTA) or lactulose to cross the intestinal mucosa. The substance is transported to the bloodstream and excreted in the urine, where it can be quantified as an indication of non-specific intestinal wall injury. Increased urinary excretion implies increased intestinal permeability.

Most studies used a before-after design; in eight studies this was in the setting of a randomized trial.[20, 23, 33, 39, 41, 42, 47, 48] Sample sizes ranged from 6 to 164 subjects. Permeability was measured in healthy volunteers before and after administration of NS-NSAID and/or placebo. In several studies, subjects took a series of different NS-NSAIDs over several weeks with intervening washout periods. Investigators used various methods to measure permeability, sometimes using multiple approaches in a single study including ^{51}Cr-EDTA/L-rhamnose urinary excretion ratio, ^{51}Cr-EDTA excretion, lactulose/rhamnose urinary excretion ratio and sucralose excretion. Five studies used a cohort design.[26, 40, 44, 45, 55]

All 22 studies reported a greater negative effect on lower GI integrity with NS-NSAID treatment when compared with placebo or the before-treatment state. Twenty of these studies found statistically significant differences with an NS-NSAID group, although eight of the 20 studies reported additional results using another type of NS-NSAID or integrity measurement that did not show statistical significance. Two of the 22 studies showed a trend towards an adverse effect of NS-NSAIDs on lower GI integrity that did not reach statistical significance.

Small intestinal permeability

Urinary excretion of ^{51}Cr-EDTA$_{0\text{-}5 \text{ or } 0\text{-}6h}$ and lactulose and urinary excretion ratios of ^{51}Cr-EDTA/L-rhamnose and lactulose/mannitol were used to assess small intestinal permeability. Small intestinal permeability was significantly higher with indomethacin,[52] naproxen[14] and aspirin[21] vs. placebo. It was also significantly higher with indomethacin vs. no treatment.[49] Indomethacin significantly increased small intestinal permeability from baseline in seven studies.[16, 20, 35, 39, 41, 42, 48] Naproxen,[20] meloxicam[20] and sustained-release diclofenac[35] also significantly increased small intestinal permeability from baseline. In three studies, small intestinal permeability was significantly higher with NS-NSAID use[40, 44] or ibuprofen use[26] vs. no NS-NSAID use.

In three before-after studies, there was no significant difference in small intestinal permeability with nabumetone,[42] diclofenac[35] and tenoxicam.[35] Naproxen[23] and aspirin[22] increased small intestinal permeability from baseline without statistical significance. A retrospective cohort study found no significant differences in permeability between self-reported aspirin users (dose not specified) and subjects not using NS-NSAIDs.[26]

Large intestinal permeability

Urinary excretion of ^{51}Cr-EDTA$_{5\text{-}24 \text{ or } 6\text{-}24h}$ and sucralose were used to assess large intestinal permeability in four studies. Large intestinal permeability was significantly higher with naproxen vs. placebo[14] and with indomethacin vs. baseline.[16] One study found no significant change in large intestinal permeability from baseline to after ingestion of meloxicam, sustained-released indomethacin or naproxen.[20] No significant difference was observed between NS-NSAID and no NS-NSAID use in a retrospective cohort study.[40]

Intestinal permeability

Urinary excretion of ^{51}Cr-EDTA$_{0\text{-}24h}$ was used to assess both large and small intestinal permeability in six studies. In four before-after studies, intestinal permeability was significantly greater after ingestion of indomethacin,[16, 33, 50] naproxen,[47] aspirin[50] and ibuprofen,[50] compared with the before-treatment state. A prospective cohort study of nine arthritis patients found that intestinal permeability with NS-NSAID use was significantly greater vs. no NS-NSAID use.[44] A cohort study found significantly elevated permeability in NSAID-using subjects without inflammatory joint disease compared with non-users; no such difference was seen in patients with spondyloarthropathy and rheumatoid arthritis.[55]

Intestinal inflammation

Intestinal inflammation was measured in two studies by faecal calprotectin levels. Calprotectin is a neutrophil cytosolic protein that resists bacterial degradation; its

presence in stool relates quantitatively to acute intestinal inflammatory activity.[10] A before-after study found that diclofenac (given in combination with omeprazole) significantly increased faecal calprotectin from baseline.[10] Faecal calprotectin was also significantly increased in a randomized-controlled crossover study evaluating the before-after effects of naproxen.[23]

Lower GI microscopic lesions

Simenon *et al.*[45] evaluated the incidence of lower GI microscopic lesions in patients using NS-NSAIDs vs. patients not using NS-NSAIDs. Microscopic lesions were identified as focal inflammation of chorion and lymphoid hyperplasia, multiple inflammatory lesions with villi involvement, or aphthoid ulcers and granulomas. No significant differences were observed between groups.

Lower GI visualization

Lower GI lesions (i.e. ulcers, mucosal breaks) were visualized using the following methods: flexible sigmoidoscopy (examination of distal colon), colonoscopy (examination of entire colon), video capsule endoscopy (examination of entire small intestine) and postmortem examination (examination of entire small intestine) (Table 2). Seven studies[10–12, 27, 38, 45, 51] assessed lower GI outcomes with visualization methods. Study designs included one randomized-controlled trial,[11] three before-after studies[10, 27, 51] and three retrospective cohort studies.[12, 38, 45] One before-after trial[27] used low-dose aspirin (10–325 mg) as the intervention; the remainder of the studies used non-aspirin NS-NSAIDs.

Five studies[10–12, 38, 51] reported significantly increased intestinal injury in patients treated with NS-NSAIDs in an experimental[10, 11] or therapeutic[12, 38, 51] setting. Findings included small intestinal red spots, mucosal breaks, erosions and ulcers. Goldstein *et al.*[11] and Graham *et al.*[12] demonstrated that NS-NSAID use was associated with a significantly increased risk of small intestinal injury compared with control (RR: 6.8; 95% CI: 2.9–14.5 and OR: 22.5; 95% CI: 3.9–128, respectively). An autopsy cohort study[38] demonstrated that a significantly greater proportion of subjects with NS-NSAID use vs. controls had evidence of small intestinal ulcers (8% vs. 0.6%; OR: 14.2; 95% CI: 4.2–47.9).

Two studies did not show an effect of NS-NSAIDs on intestinal damage. Cryer and Feldman[27] found no change in rectal mucosa appearance by flexible sigmoidoscopy after 3 months of aspirin therapy in 29 healthy volunteers. Simenon *et al.*[45] found no significant difference in the percentage of patients with macroscopic ileocolonic lesions related to NS-NSAID use in a retrospective cohort study of 96 patients who underwent colonoscopy. No study found control or placebo to be associated with increased lower GI injury.

Clinical outcomes

Lower GI bleeding

Eleven studies examined the association between NS-NSAID use and lower GI bleeding (Table 3). Definitions of lower GI bleeding varied across studies, from doctor-reported fresh blood per rectum[36] to lesions confirmed by colonoscopy or other procedures.[24, 30, 31, 34] Two randomized-controlled trials reported the incidence of lower GI bleeding.[24, 36] Slattery *et al.*[36] performed a large-scale, 48-month trial of aspirin vs. placebo that included the incidence of haematochezia. No significant difference was found between patients who received aspirin 300 mg/day vs. placebo (RR: 1.8; 95% CI: 0.5–6.0) or aspirin 1200 mg/day vs. placebo (RR: 1.5; 95% CI: 0.4–5.3). In a 3-month randomized trial of 313 osteoarthritis patients, one patient treated with meloxicam experienced lower GI bleeding while none did with placebo (RR: 3.0; 95% CI: 0.1–73.6).[24] One 8-patient 2-week before-after study[51] investigated the withdrawal of indomethacin suppositories as the intervention and found no significant effect on the degree of patient-reported rectal bleeding.

Of the eight case–control studies[19, 30, 31, 34, 37, 53, 54] (one article[37] included two separate studies), all but one reported significantly increased aspirin or NS-NSAID use in cases of lower GI bleeding vs. controls, with ORs ranging from 1.9 to 18.4. One study examining aspirin, ibuprofen and naproxen use in cases with lower GI bleeding found significantly higher rates of aspirin use relative to controls (OR: 1.9; 95% CI: 1.2–3.2), but the increased rates of use of other NS-NSAIDs did not reach statistical significance.[30] Three studies[37, 54] included cases with lower GI bleeding and age- and sex-matched controls. Four studies[30, 31, 34, 53] included cases of both lower GI bleeding and upper GI bleeding compared with controls.

In most studies, the risk of NS-NSAID use in lower and upper GI bleeding cases was similar. Day *et al.*

Table 2. Non-selective NSAIDs vs. control: lower GI visualization

Author	Study design	Study duration	Comparison	Effective sample size (Tx/control)	Outcomes	Measured by	Case/Tx /before	Control /follow-up	Measure of association, OR (95% CI)
Goldstein *et al.*[11]	RCT	2 weeks	Naproxen + omeprazole vs. placebo	111/113	Small intestinal mucosal breaks	Percentage of subjects with erosions or ulcers by video capsule endoscopy	55%	7%	RR: 6.8 (2.9–14.5)*
					Small intestinal mucosal breaks	Number of erosions or ulcers per subject by video capsule endoscopy; MN ± S.E.M.	2.9 ± 0.51	0.11 ± 0.04	$P < 0.001$
Cryer and Feldman[27]	Before-after	3 months	Aspirin 10, 81, or 325 mg	29	Rectal mucosal injury	Flexible sigmoidoscopy; mucosal injury score	0	0	$P =$ N.S.
Maiden *et al.*[10]	Before-after	2 weeks	Diclofenac + omeprazole	40	Small intestinal mucosal breaks	Percentage of subjects with erosive-ulcerative damage by video capsule endoscopy	0%	40%	$P < 0.001$*
Rampton and Barton[51]	Before-after	2 weeks	Indomethacin suppository†	8	Rectal mucosal injury	Sigmoidoscopic score; MN	1.1	0.2	$P = 0.05$
Allison *et al.*[38]	Retrospective cohort	NA	NSAID vs. no NSAID	249/464	Small intestinal ulcers	Percentage of subjects with ulcers found at autopsy	8%	0.6%	14.2 (4.2–47.9)*
Simenon *et al.*[45]	Retrospective cohort	NA	NSAID vs. no NSAID	74/22	LGI macroscopic lesions	Percentage of subjects with lesions found by ileocolonoscopy	38%	36%	1.1 (0.4–2.9)*
Graham *et al.*[12]	Retrospective cohort	NA	NSAID vs. no NSAID	21/20	Small intestinal injury	Percentage of subjects with red spots, erosions, or large erosions/ulcers by video capsule endoscopy	71%	10%	22.5 (3.9–128)*

Tx, treatment; RCT, randomized-controlled trial; RR, relative risk; MN, mean; S.E.M., standard error of the mean; N.S., non-significant; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio; 95% CI, 95% confidence interval; LGI, lower gastrointestinal.

* Calculated value.

† The intervention was discontinuation of the indomethacin suppository; the comparison was bleeding before discontinuation vs. after discontinuation of indomethacin.

Table 3. Non-selective NSAIDs vs. control: clinical outcome – lower GI bleeding

Author	Study design	Study duration	Comparison	Effective sample size [Tx(case) /control]	Outcomes	Case/Tx /before	Control /follow-up	Measure of association, OR (95% CI)
Slattery *et al.*[36]	RCT	48 months	Aspirin 300 mg vs. placebo	806/814	Haematochezia	0.9%	0.5%	RR: 1.8 (0.5–6.0)
			Aspirin 1200 mg vs. placebo	815/814	Haematochezia	0.7%	0.5%	RR: 1.5 (0.4–5.3)
Yocum *et al.*[24]	RCT	3 months	Meloxicam vs. placebo	156/157	LGIB (from acute diverticulosis)	0.6%	0%	RR: 3.0 (0.12–73.6)*
Rampton and Barton[51]	Before-after	2 weeks	Indomethacin suppository†	8	Rectal bleeding (patient-reported rectal bleeding score); MN	0.2	0	P = N.S.
Day *et al.*[34]	Case–control	NA	LGIB vs. no LGIB	8/29	NSAID use	88%	41%	9.9 (1.1–91.5)*
Holt *et al.*[37]‡	Case–control	NA	LGIB vs. no LGIB	98/95	NSAID use	35%	19%	2.3 (1.2–4.4)
Holt *et al.*[37]‡	Case–control	NA	LGIB vs. no LGIB	90/90	NSAID use	29%	18%	1.9 (1.2–3.1)
Kaplan *et al.*[19]	Case–control	NA	LGIB vs. no LGIB	43/821	Aspirin use	NR	42%	Adjusted RR 0.79 (0.41–1.5)
			LGIB vs. no LGIB	43/821	Ibuprofen use	NR	20%	Adjusted RR 0.97 (0.45–2.1)
			LGIB vs. no LGIB	43/821	NSAID use (other than aspirin and ibuprofen)	NR	14%	Adjusted RR 1.1 (0.47–2.5)
Lanas *et al.*[53]	Case–control	NA	LGIB vs. no LGIB	21/138	NSAID use	86%	25%	18.4 (5.1–66.2)*
Langman *et al.*[54]	Case–control	NA	LGIB vs. no LGIB	161/161	NSAID use	20%	6%	3.8 (1.8–7.9)*
Peura *et al.*[30]	Case–control	NA	LGIB vs. no LGIB	125/600	Aspirin use	22%	12%	1.9 (1.2–3.2)*
			LGIB vs. no LGIB	125/600	Ibuprofen use	10%	6%	1.8 (0.9–3.4)*
			LGIB vs. no LGIB	125/600	Naproxen use	2%	0.7%	3.7 (0.8–16.6)*
Wilcox *et al.*[31]	Case–control	NA	LGIB vs. no LGIB	105/1895	NSAID use	60%	34%	Adjusted OR 2.6 (1.7–3.9)

Tx, treatment; RCT, randomized-controlled trial; RR, relative risk; 95% CI, 95% confidence interval; LGIB, lower gastrointestinal bleeding; MN, mean; N.S., non-significant; NA, not applicable; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio; NR, not reported.

* Calculated value.

† The intervention was removal of the indomethacin suppository; the comparison was bleeding before removal vs. after removal of the NSAID.

‡ Holt *et al.* textsuperscript37 included two separate studies, which are counted individually here.

Table 4. Non-selective NSAIDs vs. control: clinical outcome – lower GI perforation

Author	Study design	Study duration	Comparison	Effective ample size case/control)	Outcomes	Case (%)	Control %)	Measure of association, OR (95% CI)
Lanas *et al.*[32]	Case–control	NA	LGI perforation vs. no LGI perforation	16/152	NSAID use	75	27	8.1 (2.5–26.6)
Langman *et al.*[54]	Case–control	NA	LGI perforation vs. no LGI perforation	107/107	NSAID use	22	10	2.5 (1.2–5.5)*

NA, not applicable; LGI, lower gastrointestinal; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio; 95% CI, 95% confidence interval.
* Calculated value.

found ORs for NS-NSAID use of 9.9 (95% CI: 1.1–91.5) in lower GI bleeding and 10.9 (95% CI: 2.6–44.6) in upper GI bleeding cases.[34] Another study found adjusted ORs of NS-NSAID use of 2.6 (95% CI: 1.7–3.9) and 3.2 (95% CI: 2.6–4.0) in lower and upper GI bleeding cases respectively.[31] Other reports of ORs of NS-NSAID use in lower and upper GI bleeding cases included: 18.4 (95% CI: 5.1–66.2; lower GI) vs. 10.7 (95% CI: 4.8–23.9; upper GI)[53] and 1.9 (95% CI: 1.2–3.2; lower GI) vs. 2.8 (95% CI: 2.1–3.9; upper GI); both studies investigated aspirin use.[30] Peura *et al.* found that the risks of ibuprofen (OR: 1.7; 95% CI: 1.1–2.6) and naproxen use (OR: 4.8; 95% CI: 1.6–14.5) in upper GI bleeding cases were significantly higher but the risks of use of ibuprofen (OR: 1.8; 95% CI: 0.9–3.4) and naproxen (OR: 3.7; 95% CI: 0.8–16.6) in lower GI bleeding cases were not significantly higher.[30] Kaplan *et al.* found that NS-NSAID use other than aspirin and ibuprofen was significantly higher in upper GI bleeding cases (adjusted RR: 2.3; 95% CI: 1.4–3.7) but not in lower GI bleeding cases (adjusted RR: 1.1; 95% CI: 0.5–2.5).[19] Ibuprofen use was not significantly increased in upper or lower GI bleeding cases in this study: adjusted RRs were 1.3 (95% CI: 0.8–2.0; upper GI) vs. 0.97 (95% CI: 0.4–2.1; lower GI).[19]

Lower GI perforation

Two case–control studies[32, 54] examined rates of NS-NSAID use in patients with and without lower GI perforation (Table 4). Lanas *et al.*[32] and Langman *et al.*[54] found significantly increased odds of NS-NSAID use in lower GI perforation cases vs. control patients (OR: 8.1; 95% CI: 2.5–26.6 and OR: 2.5; 95% CI: 1.2–5.5, respectively). Lanas *et al.* also found similarly increased odds of NS-NSAID use in cases with upper GI perforation (OR: 6.3; 95% CI: 3.3–12.2).[32]

Diverticular disease

Seven studies[13, 15, 18, 28, 29, 43, 46] examined the association between NS-NSAID use and clinical manifestations of diverticular disease (Table 5). One randomized-controlled 10-day trial[28] reported acute diverticulitis in one subject taking ibuprofen vs. none in the placebo group. A large prospective cohort study[29] found that NS-NSAID users were significantly more likely than non-users to develop symptomatic diverticular disease (RR: 1.5; 95% CI: 1.1–2.1).

Five case–control studies[13, 15, 18, 43, 46] evaluated the association between NS-NSAID use and complicated diverticular disease (i.e. perforation, fistula formation, pericolic abscess, peritonitis). Four[15, 18, 43, 46] of these studies found significantly higher NS-NSAID use in cases with complicated diverticular disease vs. controls with no disease, with ORs ranging from 1.8 to 11.2, and the fifth had a strong trend towards an association (adjusted OR: 1.8; 95% CI: 0.96–3.4). One study included two different control groups.[15] With dermatology patients as controls, both aspirin and non-aspirin NS-NSAID use were greater in cases, significantly so only for non-aspirin NS-NSAID use. A cataract surgery control group had a non-significantly higher increase of aspirin use vs. cases (data not reported in table).

Studies comparing coxibs vs. NS-NSAIDs or placebo

Lower GI integrity

Lower GI integrity in subjects taking coxibs vs. NS-NSAIDs or placebo was measured by small intesti-

Table 5. Non-selective NSAIDs vs. control: clinical outcome – diverticular disease

Author	Study design	Study duration	Comparison	Effective sample size [Tx(case)/control]	Outcomes	Tx (case; %)	Control (%)	Measure of association, OR (95% CI)
Doyle *et al.*[28]	RCT	10 days	Ibuprofen vs. placebo	833/413	Diverticulitis (acute)	0.1	0	RR: 1.5 (0.06–36.5)*
Aldoori *et al.*[29]	Prospective cohort	48 months	NSAID use vs. no NSAID use	3605/32 010	Symptomatic diverticular disease	1	0.83	Adjusted RR 1.5 (1.1–2.1)
Campbell and Steele[43]	Case–control	NA	Severe complications of diverticular disease vs. no disease	50/50	NSAID use	48	18	4.0 (1.5–13.6)
Goh and Bourne[18]	Case–control	NA	Perforated diverticular disease vs. no disease	20/600	NSAID use	45	10	7.1 (2.8–17.8)*
Morris *et al.*[15]	Case–control	NA	Perforated colonic diverticular disease vs. no disease	120/240	NANSAID use	28	10	Adjusted OR 4.4 (2.2–8.8)
			Perforated colonic diverticular disease vs. no disease	120/240	Aspirin use	14	10	1.4 (0.8–2.7)
Mpofu *et al.*[13]	Case–control	NA	Sigmoid diverticular abscess perforation vs. no disease	64/320	NSAID use	42	26	Adjusted OR 1.8 (0.96–3.4)
Wilson *et al.*[46]	Case–control	NA	Complicated diverticular disease vs. no disease	92/92	NSAID use	34	4	11.2 (3.8–33.3)*

Tx, treatment; RCT, randomized-controlled trial; RR, relative risk; 95% CI, 95% confidence interval; NSAID, non-steroidal anti-inflammatory drug; NA, not applicable; OR, odds ratio; NANSAID, non-aspirin non-steroidal anti-inflammatory drug.
* Calculated value.

nal permeability, large intestinal permeability and intestinal inflammation (data not shown). All studies were randomized-controlled crossover trials.[14, 20, 23, 52]

Small intestinal permeability

Four studies evaluated small intestinal permeability coxibs, NS-NSAIDs and/or placebo.[14, 20, 23, 52] Sigthorsson *et al.*[52] demonstrated significantly higher small intestinal permeability with indomethacin vs. rofecoxib 25 and 50 mg. Atherton *et al.*[14] found that naproxen significantly increased small intestinal permeability vs. lumiracoxib. Two studies showed a small, non-significantly greater increase with naproxen vs. nimesulide[23] and naproxen vs. celecoxib.[20] Small intestinal permeability was not significantly different when comparing coxibs and placebo in two studies.[14, 52]

Large intestinal permeability

Two studies evaluated large intestinal permeability.[14, 20] Large intestinal permeability was significantly higher with naproxen compared with lumiracoxib.[14] There was no significant difference between naproxen and celecoxib[20] or between lumiracoxib and placebo.[14]

Intestinal inflammation

Shah *et al.*[23] found that intestinal inflammation, as measured by faecal calprotectin, was significantly higher with naproxen vs. nimesulide.

Lower GI visualization

Our review yielded one randomized-controlled trial in which healthy subjects receiving celecoxib, naproxen (given with omeprazole), or placebo underwent video capsule endoscopy (Table 6).[11] The percentage of subjects with small intestinal mucosal breaks (RR: 0.3; 95% CI: 0.2–0.5) and the number of mucosal breaks per patient ($P < 0.001$) were significantly lower in the celecoxib vs. the naproxen group. Compared with placebo, celecoxib was associated with a borderline significantly greater percentage of subjects with small intestinal mucosal breaks (RR: 2.2; 95% CI: 1.002–4.9) and a significantly greater number of mucosal breaks per subject ($P = 0.04$, data not shown).

Clinical outcomes

Lower GI events

Two randomized-controlled trials[17, 25] compared the risk of lower GI events between coxibs and NS-NSAIDs (Table 6). Laine *et al.*[17] showed a significantly lower risk of serious lower GI clinical events (defined as gross rectal bleeding, other than melena, associated with a haemoglobin level decrease of >2 g/dL or hospitalization; positive test for faecal occult blood associated with a haemoglobin level decrease of >2 g/dL and negative upper endoscopy; or hospitalization for intestinal perforation, obstruction, diverticulitis, or ulcers) with rofecoxib vs. naproxen (RR: 0.5; 95% CI: 0.2–0.9; $P = 0.03$). Another trial[25] found a significantly lower incidence of haematochezia in arthritis patients treated with celecoxib vs. NS-NSAIDs, regardless of low-dose aspirin use for cardiovascular prophylaxis.

DISCUSSION

We systematically searched the available literature investigating the relationship between NSAID use and lower GI outcomes and found an increased likelihood of adverse events with NS-NSAIDs. This increased risk was observed across study methods. Table 7 provides an overview of the results across all study categories comparing NS-NSAIDs with controls (placebo or no treatment).

First, we assessed GI integrity, which may provide insight into primary physiological processes and effects on intestinal mucosa and may serve as a foundation for the endoscopic, autopsy and clinical outcomes observed in other studies. Twenty of 22 articles using GI integrity as an outcome reported significantly increased adverse outcomes (i.e. permeability, inflammation and microscopic lesions) with NS-NSAIDs. No study found significantly worse outcomes in the control group than in the NS-NSAID-treated group.

Further, we examined publications that reported on visualization of the intestinal mucosa. These studies offer a more concrete description of the effect of NS-NSAIDs, such as erosions or ulcers. Again, the majority of the seven studies found significantly increased injury associated with NS-NSAIDs. NS-NSAIDs significantly increased small intestinal injury even in the two studies in which proton-pump inhibitors (PPI) were combined with the NS-NSAID.[10, 11] Antisecretory

Table 6. COX-2 inhibitors vs. non-selective NSAIDs/placebo: lower GI visualization and lower GI clinical events

Author	Study design	Study duration	Comparison	Effective sample size (Tx/control)	Outcomes	Measured by	Tx	Control	Measure of association
Goldstein *et al.*[11]	RCT	2 weeks	Celecoxib vs. naproxen + omeprazole	115/111	Small intestinal mucosal breaks	Percentage of subjects with erosions or ulcers by video capsule endoscopy	16%	55%	0.29 (0.18–0.45)*
			Celecoxib vs. naproxen + omeprazole	115/111	Small intestinal mucosal breaks	Number of erosions or ulcers per subject by video capsule endoscopy; MN ± S.E.M.	0.32 ± 0.10	2.9 ± 0.51	$P < 0.001$
			Celecoxib vs. placebo	115/113	Small intestinal mucosal breaks	Percentage of subjects with erosions or ulcers by video capsule endoscopy	16%	7%	2.2 (1.002–4.9)*
			Celecoxib vs. placebo	115/113	Small intestinal mucosal breaks	Number of erosions or ulcers per subject by video capsule endoscopy; MN ± S.E.M.	0.32 ± 0.10	0.11 ± 0.04	$P = 0.04$
Laine *et al.*[17]	RCT	13 months	Rofecoxib vs. naproxen	4029/4047	Serious LGI events	Percentage of subjects with bleeding, perforation, diverticulitis, obstruction or ulcers	0.3%	0.6%	0.46 (0.22–0.93)
Silverstein *et al.*[25]	RCT	6 months	Celecoxib vs. (ibuprofen or diclofenac)	3987/3981	Haematochezia	Percentage of subjects with haematochezia	0.4%	1%	0.42 (0.24–0.75)*

NSAIDs, non-steroidal anti-inflammatory drugs; Tx, treatment; RCT, randomized-controlled trial; RR, relative risk; 95% CI, 95% confidence interval; MN, mean; S.E.M., standard error of mean; LGI, lower gastrointestinal.
* Calculated value.

Table 7. Non-selective NSAIDs vs. control: summary of studies

Study category	Total number of studies	Results		
		Significantly increased adverse outcomes with NS-NSAIDs	Significantly increased adverse outcomes with control	Non-significant
Integrity	22	20	0	2 (8*)
Visualization	7	5	0	2
Clinical				
Bleeding	11	7	0	4 (1*)
Perforation	2	2	0	0
Diverticular disease	7	5	0	2 (1*)

NS-NSAIDs, non-selective non-steroidal anti-inflammatory drugs.
* Numbers in parentheses denotes the number of significant studies that reported additional non-significant results for a different intervention, outcome measure, or control group.

Table 8. COX-2 inhibitors vs. non-selective NSAIDs or placebo: summary of studies

Study category	Total number of studies	Results				
		Significantly increased adverse outcomes with NS-NSAIDs vs. coxibs	Significantly increased adverse outcomes with coxibs vs. NS-NSAIDs	Non-significant (NS-NSAIDs vs. coxibs)	Significantly increased adverse outcomes with coxibs vs. placebo	Non-significant (coxibs vs. placebo)
Integrity	4	3	0	1 (1*)	0	2†
Visualization	1	1	0	0	1†	0
Clinical-lower GI events	2	2	0	0	NA	NA

NS-NSAID, non-selective non-steroidal anti-inflammatory drug; coxibs, COX-2 inhibitors; GI, gastrointestinal.
* Shah *et al.*[23] reported a significant and non-significant result for intestinal inflammation and small intestinal permeability respectively.
† In addition to evaluating coxibs vs. NS-NSAIDs, these studies evaluated coxibs vs. placebo.

therapy would not be expected to decrease injury beyond the duodenum, but no trial compared a PPI with placebo in NS-NSAID users to directly address this question.

Finally, the most important and clinically relevant end points are lower GI events, such as bleeding, perforation and complicated diverticular disease. Our results show that across all clinical categories, the majority of studies observed statistically significant increases in adverse outcome rates associated with NS-NSAIDs: seven of 11 lower GI bleeding studies, two of two lower GI perforation studies and five of seven diverticular disease studies.

We also compared the effects of coxibs vs. NS-NSAIDs on lower GI outcomes. Table 8 shows that of the seven studies, six found significantly increased adverse effects with NS-NSAID treatment compared with coxibs. This finding was consistent across multiple domains including lower GI integrity, lower GI visualization and lower GI clinical events. The study showing no significant difference was a GI integrity study with a small sample size ($n = 9$).[20] No study found significantly worse outcomes in the coxib group.

The studies we reviewed were markedly heterogeneous, which precluded our performing a quantitative synthesis of the data in a meta-analysis. In order to

provide a simplified overview of the results, we have presented a 'scorecard' listing the number of significant and non-significant studies. However, this form of summary has the shortcoming of appearing to treat all studies equally. The quality and primary aims of the studies in our review vary markedly: results coming from a study of higher methodological quality designed to assess lower GI effects are likely to be more meaningful than results coming from a low-quality study or a study in which lower GI effects were not a predefined end point.

One of the two visualization studies failing to identify a risk of NS-NSAID use for mucosal lesions was a small retrospective endoscopic study of patients who underwent colonoscopy without a specific aim of identifying NS-NSAID-associated GI lesions; the analysis was a *post hoc* comparison of two small unmatched cohorts based only on the use of NS-NSAIDs.[45] The other negative study assessed sigmoidoscopic findings in 29 healthy volunteers given low-dose aspirin (10–325 mg).[27] Low-dose aspirin is known to cause relatively limited mucosal injury, even in the upper GI tract[56] and also causes fewer GI complications than standard doses of NS-NSAIDs (including high-dose aspirin).[57] Thus, a larger trial assessing a greater portion of the lower GI tract with higher doses of aspirin would be better suited to assess the lower GI effects of NS-NSAIDs.

Four studies evaluating lower GI bleeding found that NS-NSAIDs did not have a significant effect.[19, 24, 36, 51] However, the two randomized-controlled trials were not specifically designed to detect lower GI bleeding; therefore, ascertainment of cases may be incomplete and of uncertain validity.[24, 36] Furthermore, the sample sizes and/or durations were far too small to identify events that would be expected to occur at rates below 1% a year.[24, 36] The third study was a 2-week uncontrolled trial in eight patients, relying on patient-reported rectal bleeding as an outcome measure.[51] None of these three trials would be expected to identify a significant association of NS-NSAIDs with lower GI bleeding. The one study of diverticular disease with no suggestion of an association with NS-NSAIDs was a randomized-controlled trial of 10 days duration.[28] No trial of this duration could be expected to identify a sufficient number of cases of diverticulitis to appropriately assess the risk of this disease with NS-NSAID use.

In the general population, lower GI tract complications such as bleeding occur at a rate of approximately one-fifth the rate of upper GI tract complications.[4, 5] Longstreth reported an incidence of hospitalization for lower GI bleeding of 20.5/100 000 person-years compared with 102/100 000 person-years for upper GI bleeding in a San Diego health maintenance organization.[4, 58] Similar results were reported in a Spanish study in which hospitalizations for combined upper and lower GI complications were estimated to occur at a rate of 120/100 000 person-years, with lower GI events accounting for at least 15% of the total.[5] Mortality because of lower GI complications such as bleeding has also been reported to be comparable with the mortality because of upper GI complications.[4, 5, 58] Observational studies have shown that the relative risk increase of lower GI tract complications with NS-NSAIDs is comparable with the relative risk increase of upper GI events.[31, 32, 53] Therefore, if 20% of GI complications occur in the lower GI tract in the general population, one would expect that the same proportion would be seen among NS-NSAID users. Consistent with this estimate are reports indicating that among NS-NSAID users who develop GI clinical adverse events, the proportion with lower GI events is in the range of 13–40%.[5, 17, 59] While upper GI clinical events are more common with NS-NSAID use, the available literature suggests that a substantial minority of NS-NSAID-associated GI complications do occur in the lower GI tract.

Our review has some limitations. The studies we identified in our literature search were not uniform in design, patient population, intervention, or outcome measure. Patient populations ranged from healthy subjects to patients with chronic disease (arthritis) to patients with acute lower GI bleeding or perforation. Articles often included multiple comparator groups within the same study, and different control groups sometimes gave different results with significance reached using one control group but not the other. In five of the eight lower GI bleeding case–control studies, patients with upper GI bleeding were also included in the study.[19, 30, 31, 34, 53] While the cases were distinguished by the site of bleeding (lower GI vs. upper GI), the control patients were not separated. ORs therefore compared the rate of NS-NSAID use in lower GI bleeding patients with the rate in all control patients, not just the control patients matched to the lower GI patients. If a systematic difference existed between controls matched to upper GI bleeding vs. controls for lower GI bleeding patients, this could have introduced bias into the study results.

The methodology of the intestinal integrity studies was not standardized; several different test substances, osmotic fillers and times of urine collection were employed across the included studies. Therefore, the sensitivity and specificity of the tests may vary such that studies must be grouped and compared with caution. Some studies[14, 16, 40] used a single marker (^{51}Cr-EDTA) with two timed urine collections (0–5 and 6–24 h) to assess small and large intestinal permeability respectively. However, this method does not allow for the definitive conclusion that the later collection time demonstrates increased large intestinal rather than small intestinal permeability.

Some studies included aspirin within the NSAID interventions; other studies kept aspirin separate in the analysis or limited the scope of the intervention to a single NSAID. Most studies of clinical events were observational rather than high-quality prospective randomized trials. Some studies – in particular the randomized trials – were not specifically designed or powered to capture relatively infrequent outcomes such as lower GI bleeding. Although NSAID-associated intestinal obstruction and stricture are reported in case reports and case series,[60, 61] no studies addressing these outcomes met our study inclusion criteria. Our systematic review focuses on the clinical outcomes of lower GI bleeding, perforation and diverticular disease because these were the clinical end points assessed in the available clinical studies comparing NSAID use and no NSAID use. Additionally, our aim was to examine the influence of NSAIDs on patients without underlying clinical GI disease. Therefore, we did not include studies assessing the effects of NSAIDs in patients with inflammatory bowel disease.

We believe that the message obtained from this systematic review is clear despite its limitations, even more strongly because it persists across the heterogeneous nature of the available data. NS-NSAIDs are associated with increased lower GI injury compared with controls and coxibs across healthy subjects and ill patients, from the microscopic level of mucosal integrity to the most relevant scale of clinical outcomes. Therefore, we believe that our results are quite broadly generalizable. Clinicians and patients can use this information in treatment planning for conditions requiring chronic medication for pain and/or inflammation. Further high-quality research is warranted to examine and precisely quantify the risk of and risk factors for lower GI tract effects with NS-NSAIDs, NS-NSAIDs plus PPI or misoprostol co-therapy, and COX-2 selective inhibitors.

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