REVIEW ARTICLE

# Nonsteroidal Anti-Inflammatory Drugs, Gastroprotection, and Benefit–Risk

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■ **Abstract**

*Background:* Gastroprotective agents (GPA) substantially reduce morbidity and mortality with long-term nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin.

*Objective:* To evaluate efficacy of NSAIDs, protection against NSAID-induced gastrointestinal harm, and balance of benefit and risk.

*Methods:* Free text searches of PubMed (December 2012) supplemented with "related citation" and "cited by" facilities on PubMed and Google Scholar for patient requirements, NSAID effectiveness, pain relief benefits, gastroprotective strategies, adherence to gastroprotection prescribing, and serious harm with NSAIDs and GPA.

*Results:* Patients want 50% reduction in pain intensity and improved fatigue, distress, and quality of life. Meta-analyses of NSAID trials in musculoskeletal conditions had bimodal responses with good pain relief or little. Number needed to treat (NNTs) for good pain relief were 3 to 9. Proton pump inhibitors (PPI) and high-dose histamine-2 receptor antagonists ($H_2$RA) provided similar gastroprotection, with no conclusive evidence of greater PPI efficacy compared with high-dose $H_2$RA. Prescriber adherence to guidance on use of GPA with NSAIDS was 49% in studies published since 2005; patient adherence was less than 100%. PPI use at higher doses over longer periods is associated with increased risk of serious adverse events, including fracture; no such evidence was found for $H_2$RA. Patients with chronic conditions are more willing to accept risk of harm for successful treatment than their physicians.

*Conclusion:* Guidance on NSAIDs use should ensure that patients have a good level of pain relief and that gastroprotection is guaranteed for the NSAID delivering good pain relief. Fixed-dose combinations of NSAID plus GPA offer one solution. ■

**Key Words:** pain, joint pain, nonsteroidal anti-inflammatory drugs, NSAID, gastroprotection, risk–benefit analysis, systematic review

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Disclosures: Horizon Pharma provided funding for this study but had no influence on its content; the company did have the right to see the finished manuscript before publication, but not to enforce changes or prevent publication. Andrew Moore, Lee Simon, and Paul Emery have had specified relationships with Horizon and have received financial reimbursement. Andrew Moore is an owner of Oxford Medical Knowledge, who was paid for the work on this study. Lee Simon and Paul Emery were paid consultants to Horizon Inc. RAM has provided expert advice for Menarinin, Pfizer, and MSD. PE has undertaken clinical trials and provided expert advice for Pfizer, MSD, Abbvie, UCB, BMS, Roche, Novartis. Sheena Derry has no disclosures.

Submitted: April 30, 2013; Revision accepted: June 03, 2013

DOI. 10.1111/papr.12100

## INTRODUCTION

Pain is one of the leading factors contributing to the global burden of disease as measured by years lived with disability.[1] Among the top 11 disorders contributing the greatest burden include low back pain, neck pain, other musculoskeletal disorders, migraine, and osteoarthritis. These patients want very considerable reductions in their pain,[2] and nonsteroidal anti-inflammatory drugs (NSAIDs) represent one major class of analgesic drugs used in these conditions.

There is a well-understood spectrum of gastrointestinal harm associated with use of NSAIDs, including gastrointestinal symptoms, increased incidence of endoscopic ulcers, bleeding, and death.[3,4] A number of different upper and lower gastrointestinal outcomes are now recognized together as clinically significant upper and lower GI events (CSULGIEs); incidence rates can vary between NSAIDs, and the background rate without NSAID in clinical trials is about 0.3%.[5] A history of prior gastrointestinal symptoms or bleeding, the presence of other risk factors like advancing age, higher doses of NSAID, and probably duration of NSAID use all increase the risk of upper gastrointestinal bleeding.[6] Individual NSAIDs come with different innate risks, most likely related to the half-life of the drug. Table 1 used information from 2 systematic reviews with different time periods[6,7] and some selected recent case–control studies that give results by individual drugs.[8–10] We have evidenced that the risk of upper gastrointestinal (GI) bleeding events with ibuprofen at doses up to 2,400 mg is equivalent to that for diclofenac at doses up to 100 mg daily. For naproxen doses up to 1,000 mg and piroxicam at doses up to 20 mg daily, risks are higher.

There is a significant increased risk of GI bleeding with use of NSAIDs, against a background that is not insignificant (even within the context of randomized trials, which frequently exclude patients at higher risk), where the annual rate of complicated upper gastrointestinal events with NSAIDs can be around 1%.[11,12] There is an appreciable mortality.[3,13]

Extensive use of gastroprotective agents (GPA) can substantially reduce the morbidity and mortality associated with long-term NSAID and aspirin use.[14] In the U.K., the National Institute for Health and Care Excellence (NICE) guidance on osteoarthritis suggests coprescription with a proton pump inhibitor (PPI) in every patient, irrespective of risk and whether the patient is prescribed an NSAID or a coxib.[15] Other guidance consistently advises the use of GPA with NSAIDs when there is any gastrointestinal risk factor, such as older age. Recent cohort studies in France and Japan demonstrate very significant population-based reductions in upper gastrointestinal bleeding through extensive and appropriate prescribing of PPI.[16,17]

This article brings together evidence about a number of different aspects of NSAIDs and protection against gastrointestinal harm induced by NSAIDs, and examines the balance of benefits and risks for their use. The manuscript will be informed by evidence compiled from systematic reviews and meta-analyses, paying particular regard to contemporary standards of evidence.

The main areas of interest for the review include evidence about the treatment outcome desired by patients with chronic pain, results obtained with NSA-

**Table 1. Meta-Analyses and Studies Indicating Increased Risk of Upper Gastrointestinal (GI) Bleeding**

| Study (number of participants) | Details | Relative Risk or Odds Ratio | | | | |
|---|---|---|---|---|---|---|
| | | Ibuprofen ≤ 2,400 mg | Diclofenac ≤ 100 mg | Naproxen ≤ 1,000 mg | Piroxicam ≤ 20 mg | Current NSAID use |
| Hernandez-Diaz and Rodríguez[6] (≥ 80,000) | Overview of epidemiology studies in 1990s | 2.1 (1.6 to 2.7) | 3.1 (2.0 to 4.7) | 3.5 (2.8 to 4.3) | 5.6 (4.7 to 6.7) | 4.2 (3.9 to 4.6) |
| Lewis et al., 2004 (*N* = 8,349)[8] | Individual patient meta-analysis of 3 retrospective case–control studies | 1.8 (0.8 to 3.7) | 3.2 (1.9 to 5.8) | 5.4 (2.9 to 9.9) | 12 (6.5 to 22) | 5.6 (4.6 to 7.0) |
| Lanas et al.[9] (*N* = 8,309) | Case–control study of national health system in Spain | 4.1 (3.1 to 5.3) | 3.1 (2.3 to 4.2) | 7.3 (4.7 to 11) | 13 (7.8 to 20) | 7.3 (4.0 to 13) |
| Garcia-Rodriguez and Barreales Tolosa[10] (*N* = 11,561) | Case–control study using U.K. database | 2.0 (1.4 to 2.9) | 3.7 (3.0 to 4.3) | 8.1 (4.7 to 12) | Not given | 2.6 (1.9 to 3.6) |
| Masso Gonzalez et al., 2010[7] (≥ 40,000) | Systematic review of epidemiological studies 2000 to 2008 | 2.7 (2.4 to 3.0) | 4.0 (3.5 to 4.4) | 5.2 (4.3 to 6.2) | 9.3 (7.5 to 11) | 4.6 (4.3 to 4.9) |

NSAID, nonsteroidal anti-inflammatory drugs.

IDs based on these expected outcomes, collateral benefits obtained, efficacy of PPI and histamine-2 receptor antagonist ($H_2$RA) gastroprotection, how well doctors and patients adhere to gastroprotection guidelines and therapy, other risks or rare but serious harm with NSAIDs and GPAs, and patient attitudes toward risk and benefit in chronic conditions.

## METHODS

We used several methodological techniques to maximize the relevance of the review. These involved systematic searching in a number of different areas, including using data from existing reviews of randomized double-blind trials for evidence of NSAID and gastroprotection efficacy, and broad acceptance of other study designs where appropriate. We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement guidelines where this guidance applied[18] and high standards for evidence for NSAID efficacy.[19,20]

### Literature Search

Searching for relevant studies was conducted with several different themes, namely for patient-level requirements for outcomes in chronic pain, individual patient data analysis of NSAID effectiveness in chronic pain conditions, benefits of pain relief, gastroprotective strategies used with NSAIDs, doctor and patient adherence to gastroprotection prescribing and use, and for rare, but serious adverse events associated with NSAIDs and GPA. These searches comprised different free text searches of PubMed (to December 2012), with follow-up on any potentially useful publication using the "related citation" and "cited by" facilities on PubMed. For those articles deemed useful, we also checked on citations of that publication using Google Scholar. In addition to electronic searches, retrieved articles were read for any other sources of data, as were general review articles and book chapters. Observational studies can be poorly elicited by electronic searching,[21,22] and our experience[22,23] is that this strategy captures a very high proportion of high quality, large studies.

### Study Selection

Publication in 1995 or later was required to accurately reflect evidence relevant to pain management in 2013. Where possible, extant systematic reviews and meta-analyses were sought, updated with any more recent information where available. Any study architecture was permitted, as appropriate for the subject. For example, when examining the effect of pain treatment on quality of life, the only architectures deemed appropriate were individual patient analysis of randomized trials or large comprehensive cohort studies with clear definition of inclusion criteria. For effect of NSAIDs or GPA, only data from randomized trials were deemed appropriate.

A single reviewer (RAM) was responsible for initial study selection and for data extraction, but other authors checked decisions over inclusion and accuracy of data extraction.

### Quality Assessment

The assessment of quality in observational studies is not straightforward, and no ideal universal quality scoring system exists.[24] We used study size in judging results because small size is associated with a large potential for random chance effects, whatever the study architecture.[24] We chose to concentrate on those aspects most likely to provide unbiased studies.

For comparative trials, we used only randomized, double-blind trials and had a description of withdrawals and dropouts, scoring at least 3/5 on the Oxford Quality Scale.[25]

### Data Analysis and Presentation

For NSAID effectiveness, we used responders defined as patients demonstrating a 50% reduction in pain intensity, as this has become a validated outcome important to patients.[19] However, "no worse than mild pain" may be a better outcome. In this definition, withdrawal from treatment for any reason is regarded as nonresponse and equivalent to baseline observation carried forward (BOCF), as imputation with the baseline level of pain intensity would exclude achievement of any of these levels of response. Responders were considered true responders if they experienced benefit and continued taking the drug. Imputation using last observation carried forward (LOCF), which the last nonmissing observation is carried forward from the time of withdrawal to the end of the trial, was not used because it has shown to introduce significant bias in some circumstances.[20]

Analysis of the effects of PPI and $H_2$RA in reducing NSAID-induced endoscopic ulcers used endoscopic

outcomes ideally measured at 12 weeks or later to capture appropriate beneficial effects of long-term therapy; studies or data before 6 weeks of NSAID and GPA treatment were not included. Any dose of any PPI was allowed, as long as it was equivalent to at least 20 mg omeprazole daily. For $H_2$RAs, only high doses were allowed in the analysis, equivalent to 80 mg of famotidine or 600 mg ranitidine daily.

When pooling data, clinical homogeneity was examined graphically.[26] Relative benefit (or risk) and number needed to treat to prevent one endoscopic ulcer (NNTp) were calculated with 95% confidence intervals. Relative benefit or risk was calculated using a fixed effects model,[27] with no statistically significant difference between treatments assumed when the 95% confidence intervals included unity. We added 0.5 to treatment and comparator arms of trials in which at least one arm had no events. Number needed to treat (or harm) was calculated by the method of Cook and Sackett,[28] using the pooled number of observations only when there was a statistically significant difference of relative benefit or risk (where the confidence interval did not include 1). Significance of differences between NNTs was calculated using the statistical *z*-test.[29]

## RESULTS

### Patient Desired Outcomes in Chronic Pain

A systematic review of studies on patient expectations indicates that large reductions in pain intensity, or being in a low pain state (no worse than mild pain), are consistently regarded as what chronic pain patients desire from treatment.[30] The ideal of being "good" rather than just "better" has been suggested previously in rheumatology.[31] Long-term reduction in pain intensity by 50% or more, together with concomitant reduction in fatigue, distress, and the loss of quality of life that accompanies chronic pain, is what patients want from treatment.[32–35]

Patients agree that a clinically important difference in pain outcomes would be at least a 33% level suggested in breakthrough pain,[36] or more than 40/100 mm (4/10 cm) reduction in pain, defined as much better in musculoskeletal pain.[37] In fibromyalgia, pain severity reductions of about 40% were regarded as clinically important.[38] For painful diabetic neuropathy and fibromyalgia, patients describing themselves as much or very much better typically had pain intensity reductions of 40% or more.[39] These are far greater than the minimally important difference of a 6% reduction in pain, suggested by patients with rheumatoid arthritis.[40]

The patient acceptable symptom state (PASS) is defined as the value beyond where patients consider themselves well. For osteoarthritis, the junction between satisfactory and unsatisfactory was about 32/100 mm (3.2/10 cm).[41] Similar results were obtained with numerical rating and function scales.[42]

In chronic pain, we define response as having both a large reduction in pain intensity of at least 50% (sometimes at least 30%) from baseline and either freedom from adverse events or—at worst—adverse events that are tolerable, allowing the patient to continue with therapy.[19,20] The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has defined ≥ 30% and ≥ 50% decrease in pain intensity, respectively, as "moderately important" and "substantial" improvements,[43] although more complex responder definitions have also been sought.[44]

When asked to rate how they imagine chronic pain might affect quality of life, members of the public without pain indicated that they considered pain scores greater or equal to 4 or 5 of 10 would have increasingly large detrimental effects.[45]

The consistent message from the literature is that a large reduction in pain intensity is an important and desired outcome for patients.

### Responder Analyses with NSAIDs

Several meta-analyses of individual patient data from several randomized trials have provided information on responder analyses with NSAIDs and cyclooxygenase-2 specific inhibitors (coxibs) in chronic pain conditions of osteoarthritis of the knee, hip,[46] hand,[47] chronic low back pain,[48] ankylosing spondylitis,[49] or antiepileptics in fibromyalgia.[50] These responder analyses provide 2 important insights:

1. Some people in trials get very large pain intensity benefits while others do not. Typically, there is no Gaussian frequency distribution of benefit. Figure 1 shows bimodal distributions of response in postoperative pain,[51] osteoarthritis,[46] chronic low back pain,[48] and ankylosing spondylitis.[49] This bimodal distribution is found in almost all acute and chronic pain conditions.
2. As a consequence of the bimodal distribution, only a few patients achieve a high level of response with any particular therapy. The drugs-specific (active minus placebo) proportion of

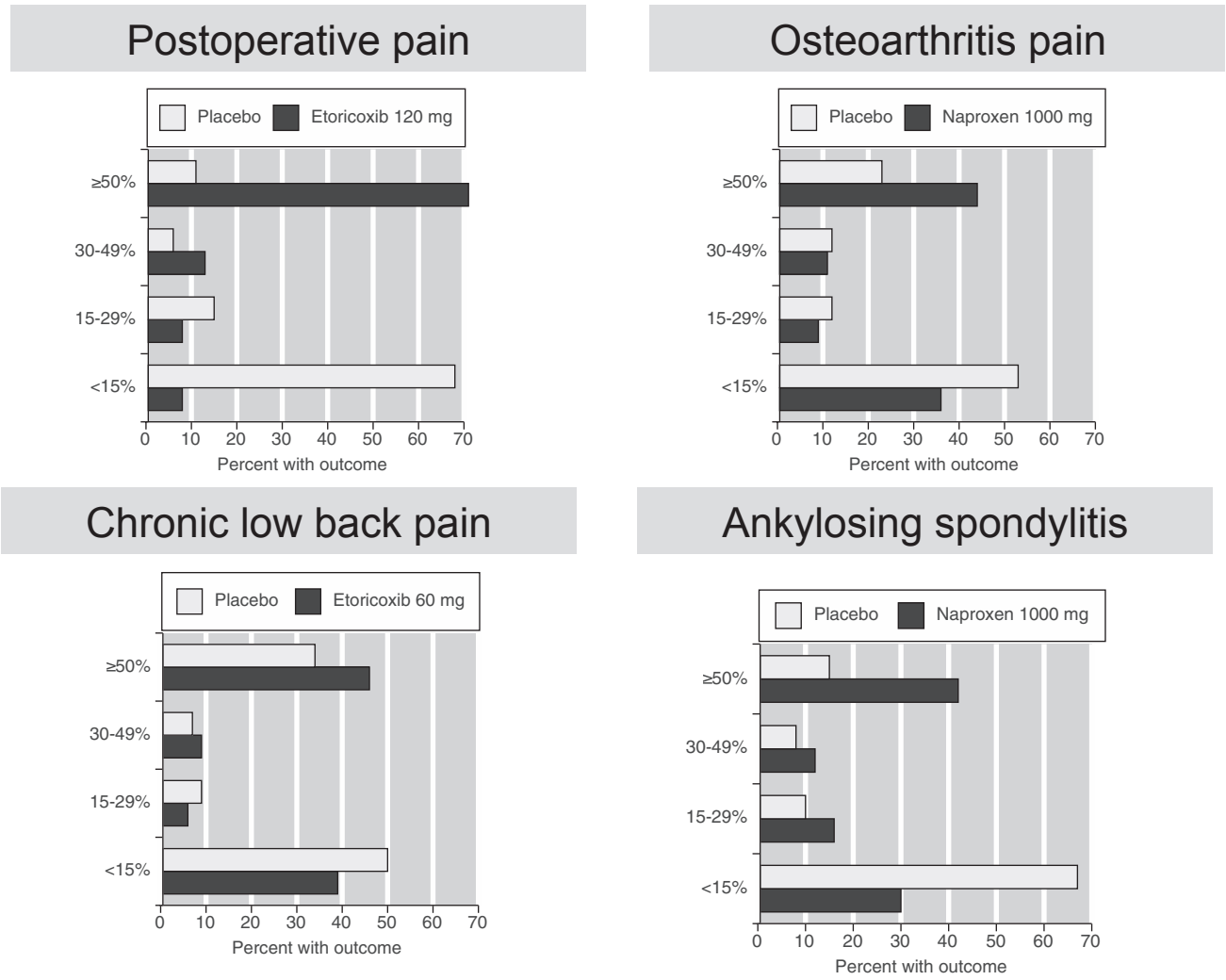


**Figure 1.** Bimodal distribution of pain intensity reduction (*Y*-axis) of patients in acute postoperative pain, or chronic musculoskeletal pain, with nonsteroidal anti-inflammatory drug or coxib.

patients achieving at least 50% pain intensity reduction with NSAIDs varies from about 30% in ankylosing spondylitis, 20% in osteoarthritis with NSAIDs, to 10% in chronic low back pain and fibromyalgia.[50]

Table 2 shows that because most treatment-specific responses are low, numbers needed to treat (NNTs) for effective treatment of chronic pain conditions with NSAIDs are in the range of about 3 to 9. Few are better; the exception may be NSAIDs in ankylosing spondylitis where the NNT is about 3 for at least 50% pain intensity reduction.[49]

There is a consistent bimodal pattern of response with NSAIDs in chronic musculoskeletal conditions. Some patients have very good pain relief with NSAIDs. The pattern that some patients respond to drug therapy, while others do not, is broadly recognized in pain and elsewhere.[52]

### Pain Relief and Other Benefits

Information was obtained from a comprehensive review of a series of linked systematic reviews examining chronic pain prevalence, impact, cost, and the benefits of successful treatment.[53] Information examining the beneficial effects of successful treatment derived from 13 studies with 7,586 patients with conditions including migraine, fibromyalgia, neuropathic pain, osteoarthritis, rheumatoid arthritis, chronic low back pain, and ankylosing spondylitis. There was a consistent link between good pain relief and some aspect of well-being, including activities of daily living or enjoyment of life,

**Table 2. Results from Meta-Analyses of Nonsteroidal Anti-Inflammatory Drugs in Chronic Musculoskeletal Conditions using Contemporary Evidence Standards and an Outcome Equivalent to at Least 50% Pain Intensity Reduction**

| Drug & Dose (mg) | Number of | | Percent with Outcome | | Number Needed to Treat (NNT) (95% CI) |
|---|---|---|---|---|---|
| | Trials | Patients | Active | Placebo | |
| Osteoarthritis—12 weeks of treatment | | | | | |
| Etoricoxib 60 | 3 | 711 | 44 | 23 | 4.7 (3.3 to 8.1) |
| Naproxen 1000 | 2 | 545 | 44 | 23 | 4.8 (3.3 to 8.5) |
| Etoricoxib 30 | 2 | 643 | 45 | 27 | 5.5 (3.9 to 9.3) |
| Celecoxib 200 | 2 | 722 | 39 | 22 | 5.8 (4.2 to 9.5) |
| Ibuprofen 2400 | 2 | 628 | 39 | 27 | 8.4 (5.1 to 24) |
| Ankylosing spondylitis—6 weeks of treatment | | | | | |
| Etoricoxib 120 | 2 | 185 | 55 | 15 | 2.5 (1.9 to 3.5) |
| Etoricoxib 90 | 2 | 196 | 55 | 15 | 2.5 (1.9 to 3.5) |
| Naproxen 1000 | 2 | 195 | 42 | 15 | 3.7 (2.5 to 6.6) |
| Chronic low back pain—12 weeks of treatment | | | | | |
| Etoricoxib 60 | 2 | 424 | 47 | 35 | 8.1 (4.6 to 33) |
| Etoricoxib 90 | 2 | 427 | 47 | 35 | 8.3 (4.7 to 33) |

Outcome of ≥ 50% pain intensity reduction (PIR) at 12 weeks, or ≥ 50% reduction in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at 6 weeks, and with withdrawal for any reason taken as non response

improved mood, sleep, functioning, quality of life, work, and less fatigue. All of the studies reported some link between pain relief and aspects of improved functioning or quality of life.

The magnitude of the improvements reported is not trivial and is perhaps best explained using the quality-adjusted life year (QALY), which has a scale from 1 (perfect health for 1 year) to 0 (death). Health status increases over 1 year were 0.22 with successful tumor necrosis factor (TNF) inhibitor in rheumatoid arthritis,[54] 0.35 for ≥ 50% pain intensity reduction in painful diabetic neuropathy,[55] and 0.11 for the same outcome in fibromyalgia.[56] In tapentadol trials in osteoarthritis or chronic low back pain, patients tolerating treatment with tapentadol or oxycodone and completing the trial were likely those with good pain benefit with increments of 0.31.[57] In hand osteoarthritis, there was a strong association between reduced pain and improved function.[58]

In comparison, a systematic review of quality-adjusted life years for estimating effectiveness of health care reported utility gains from healthcare interventions over 0.5–1.0 year.[58] Of 31 examples, only 9 (29%) had 1-year gains above 0.1, while 22 (71%) had gains well below 0.1. This makes the quality of life gains obtained with successful treatment of chronic pain very important, placing them among the highest in medicine.

There is consistent evidence across chronic pain that patients achieving good levels of pain relief, or achieving low pain states, have major improvements in quality of life.

Once it has been appropriately decided to significantly intervene and treat pain, choosing which intervention to employ becomes the issue. When using the most common chosen therapy, some form of NSAID, we must consider the inherent risks of using these drugs for their provided benefit. One of the major risks of these drugs, whether they are considered selective or nonselective cyclooxygenase inhibitors, is related to adverse gastrointestinal events of gastroduodenal ulcer formation, bleeding, perforation, obstruction, and death. Although large amounts of data have been accumulated to define the hypertension risk, cardiovascular risks, renal, and other myriad risks associated with chronic NSAID use, the more common problem has been consequent GI damage. Thus, assessing the GI risk of the patient to be treated along with gastroprotective strategies to mitigate it is an important part of the clinical decision process.

## Gastroprotective Strategies with PPI and High-Dose $H_2A$

As a starting point, we took a Cochrane review,[14] a U.K. analysis from NICE,[59] and supplemented using an electronic literature search for additional randomized trials and then re-analyzed outcome data.

***PPI.*** Seven trials in 6 reports compared PPI + NSAID with placebo + NSAID.[60–65] These trials lasted between 12 and 26 weeks, recruited 2,176 patients, of whom between 6% and 100% had a prior history of ulcer; naproxen was the most commonly used NSAID (Table 3). Two additional trials reported in 2010[65] added 860 patients to the total, so that 40% of the data analyzed were additional to the Cochrane review.[14]

**Table 3. Summary of Randomized Trials Evaluating Efficacy of Proton Pump Inhibitors (PPI) and $H_2RA$ for Protection Against Endoscopic Ulcers with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**

| Reference | Patients (*N*) | Previous Ulcers (%) | Duration (weeks) | NSAID | GPA (daily dose mg) |
|---|---|---|---|---|---|
| PPI | | | | | |
| Bianchi Porro et al.[60] | 95 | 15 | 12 | Diclofenac, ketoprofen, indomethacin | Pantoprazole 40 |
| Cullen et al.[61] | 168 | 24 | 26 | Naproxen | Omeprazole 20 |
| Ekstrom et al.[62] | 177 | 24 | 12 | Naproxen | Omeprazole 20 |
| Graham et al.[63] | 403 | 100 | 12 | Ibuprofen, naproxen, diclofenac, aspirin, piroxicam | Lansoprazole 15 or 30 |
| Hawkey et al.[64] | 429 | 30 | 26 | Diclofenac, ketoprofen, naproxen | Omeprazole 20 |
| Goldstein et al.[65] PN400-301 | 434 | 6 | 26 | Naproxen | Esomeprazole 40 |
| Goldstein et al.[65] PN400-302 | 420 | 10 | 26 | Naproxen | Esomeprazole 40 |
| High-dose $H_2A$ | | | | | |
| Hudson et al.[66] | 78 | 29 | 24 | Diclofenac | Famotidine 80 |
| Taha et al.[67] | 190 | 12 | 24 | Diclofenac, naproxen, indomethacin, ketoprofen, ibuprofen, fenbufen | Famotidine 80 |
| Ten Wolde et al.[68] | 30 | 100 | 52 | Diclofenac | Ranitidine 600 |
| Laine et al.[69] REDUCE-1 | 812 | 7 | 24 | Ibuprofen | Famotidine 80 |
| Laine et al.[69] REDUCE-2 | 570 | 6 | 24 | Ibuprofen | Famotidine 80 |

GPA, gastroprotective agents.

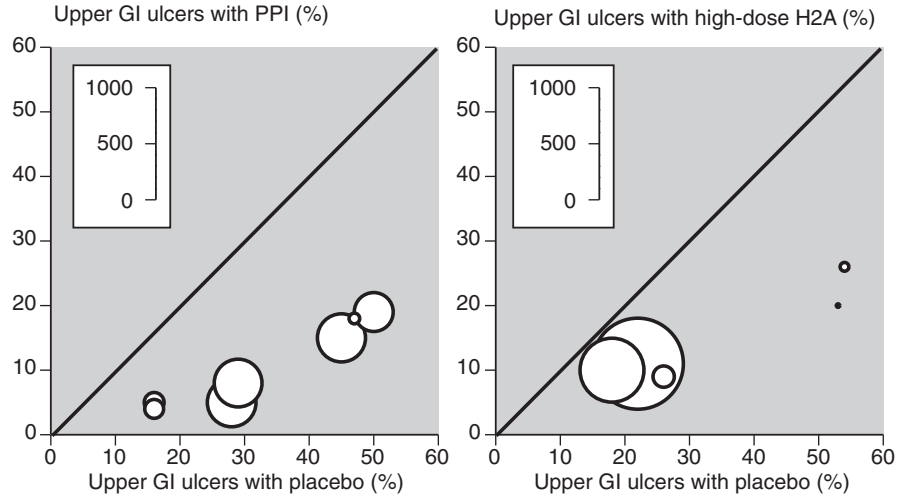


**Figure 2.** Plot of upper gastrointestinal endoscopic ulcer rates with nonsteroidal anti-inflammatory drug (NSAID) + gastroprotective agents (GPA) vs. NSAID + placebo. Size of symbol is proportional to size of study (inset scale).

Various PPIs were used, including omeprazole, pantoprazole, lansoprazole, and esomeprazole. Most trials provided results for both gastric and duodenal ulcers, although 1[63] provided results only for gastric ulcers, which are more common than duodenal ulcers associated with NSAID use. The total number of upper GI endoscopic ulcers was also reported except in two studies;[63,65] for the latter, the total was assumed to be the sum of gastric and duodenal ulcers, as the five studies reporting gastric, duodenal, and total upper GI ulcers had totals that were the sum of gastric and duodenal.

With NSAID + placebo, the incidence of upper GI ulcers ranged between 15% and 50% (Figure 2). PPI significantly reduced the incidence of endoscopic ulcers, however, described (Table 4). Using the outcome of all upper GI endoscopic ulcers, there was a 65% reduction in incidence across trials from 32% to 11%. For PPI vs. placebo, the overall NNTp for total upper GI endoscopic ulcers was about 5, with an NNTp of about 7 for gastric ulcers and 16 for duodenal ulcers (Table 4).

***High-dose $H_2RA$.*** Five trials in 4 reports compared high-dose $H_2RA$ + NSAID with placebo + NSAID.[66–69] These trials lasted between 12 and 52 weeks and recruited 1,680 patients, of whom between 6% and 100% had a prior history of ulcer; ibuprofen was the most commonly used NSAID (Table 3). Two additional

**Table 4. Summary of Analyses of Efficacy of Proton Pump Inhibitors (PPI) and $H_2RA$ in Studies Comparing Nonsteroidal Anti-Inflammatory Drugs (NSAID) + Gastroprotective Agents (GPA) with NSAID + Placebo, Over 12 weeks or Time Nearest 12 weeks**

| Outcome vs. Placebo | Number of | | Percent Ulcers with | | Relative Risk (95% CI) | NNTp 95% CI) |
|---|---|---|---|---|---|---|
| | Trials | Patients | Active | Placebo | | |
| PPI | | | | | | |
| Gastric ulcers | 7 | 2,076 | 10 | 25 | 0.34 (0.27 to 0.42) | 6.7 (55 to 8.6) |
| Duodenal ulcers | 6 | 1,729 | 1 | 7 | 0.16 (0.08 to 0.29) | 16 (12 to 24) |
| Upper GI ulcers | 5 | 1,216 | 14 | 34 | 0.35 (0.28 to 0.43) | 4.7 (3.8 to 6.1) |
| Upper GI ulcers (assumed) | 7 | 2,076 | 11 | 32 | 0.30 (0.25 to 0.36) | 4.8 (4.1 to 5.8) |
| High-dose $H_2A$ | | | | | | |
| Gastric ulcers | 5 | 1,680 | 10 | 19 | 0.52 (0.40 to 0.66) | 10 (7.5 to 17) |
| Duodenal ulcers | 5 | 1,680 | 1 | 7 | 0.23 (0.13 to 0.41) | 17 (13 to 28) |
| Upper GI ulcers | 5 | 1,680 | 11 | 24 | 0.49 (0.39 to 0.61) | 7.7 (5.9 to 11) |

GI, gastrointestinal; NNTp, number needed to treat to prevent.
Note that for PPI, all upper GI ulcers were assumed to be sum of gastric and duodenal ulcers in two studies

trials reported in 2010[69] added 1,382 patients to the total, so that 82% of the data analyzed were additional to the Cochrane review.[14] $H_2RA$s used were famotidine in four trials, and ranitidine in one. All provided results for both gastric and duodenal ulcers, as well as total number of upper GI endoscopic ulcers. One additional trial published in Russian had only a 4-week duration, but an English summary reported a 50% reduction in endoscopic ulcers with diclofenac plus famotidine vs. diclofenac alone in 224 patients, although based on small numbers of events.[70]

With NSAID + placebo, the incidence of upper GI ulcers ranged between 18% and 54% (Figure 2). High-dose $H_2RA$ significantly reduced the incidence of endoscopic ulcers, however, described (Table 4). Using the outcome of all upper GI endoscopic ulcers, there was a 46% reduction in incidence across trials from 24% to 11%. For high-dose $H_2RA$ vs. placebo, the overall NNTp for total upper GI endoscopic ulcers was about 8, with an NNTp of about 10 for gastric ulcers and 17 for duodenal ulcers (Table 4).

***Comparing PPI with High-dose $H_2RA$.*** These indirect comparisons of results with PPI and high-dose $H_2RA$ showed a somewhat greater reduction in the incidence in upper GI endoscopic ulcers with PPI than high-dose $H_2RA$, with a statistically lower (better) NNTp for PPI than $H_2RA$ ($z = 2.99$, $P = 0.003$). The PPI studies mostly used naproxen as the NSAID, while those with high-dose $H_2RA$ mostly used ibuprofen (Table 3). We know from observational studies that naproxen produces more GI problems than ibuprofen (Table 1) and that tendency probably describes the higher incidence of endoscopic ulcers with placebo in the PPI compared with the $H_2RA$ studies. While the starting points were

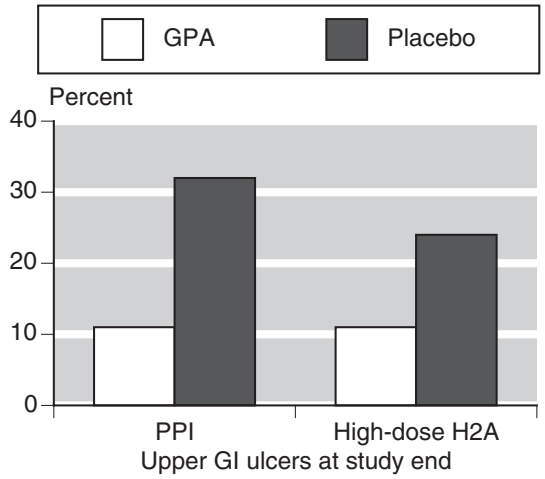


**Figure 3.** Overall incidence of endoscopic ulcers with nonsteroidal anti-inflammatory drug plus gastroprotective agents or placebo (percent).

different, the absolute risk of upper GI endoscopic ulcers endoscopic ulcer with treatment was the same (at 11%) with both gastroprotective interventions (Figure 3).

Direct comparisons of PPI and high-dose $H_2RA$ in the same trial are lacking. There are comparative studies, but in slightly different circumstances of healing established NSAID or aspirin-associated ulcers rather than those designed to determine prophylactic efficacy of gastroprotective agents. One study compared esomeprazole 20 mg or 40 mg with 300 mg (high dose) ranitidine daily;[71] 8-week healing rates were about 85% with esomeprazole compared with 76% with ranitidine, with no statistical difference.

In other examples, a randomized study compared 20 and 40 mg omeprazole with 150 mg (low dose) ranitidine in patients using NSAIDs with established ulcers or erosions.[72] Healing rates after 8 weeks were 80% with

omeprazole compared with 63% with low-dose ranitidine, with a maintenance phase after healing yielding a six-month ulcer-free rate of 72% for omeprazole and 59% for low-dose ranitidine. A similar comparison of lansoprazole 30 mg with low-dose famotidine 40 mg in patients with established ulcer using low-dose aspirin demonstrated identical healing rates (89%) after 8 weeks.[73] Observational studies that examine bleeding rates with NSAIDs find a somewhat greater protective effect with PPI than $H_2$RA; for example in a Spanish study, Lanas and colleagues[74] reported adjusted relative risk of peptic ulcer bleeding of 0.33 (0.27 to 0.39) with PPI compared to 0.65 (0.50 to 0.85) with $H_2$RA, but with no information about the actual drugs, and particularly the dose of $H_2$RA. Similar results are reported with low-dose aspirin, but again with no indications of GPA dose.[75]

There is consistent evidence across indirect and direct studies that the gastroprotective effects of PPI and high-dose $H_2$RA are broadly similar, but that low doses of $H_2$RA have lower effectiveness. There is no conclusive evidence of greater PPI efficacy compared with high-dose $H_2$RA.

Although there are other gastroprotective strategies including the addition of misoprostol to the NSAID regimen or developing a combination medication, the use of this medication is limited by dose-related symptoms directly related to the mechanism of action of replacing prostaglandins within the GI tract. Thus, when considering which gastroprotective therapy to use, we must consider the information learned about adherence to the medications offered.

### Adherence to Gastroprotective Strategies

***Prescribers' Adherence to Guidance.*** A systematic review of studies of adherence of prescribing gastroprotective agents (GPA) with NSAIDs conducted up to the end of 2005 and including 911,000 NSAID users found that GPAs were prescribed in about 26% of patients taking NSAIDs and having at least one gastrointestinal risk factor, like age, previous ulcers, etc.[11] An extension of the search from 2006 to August 2012 identified 21 additional studies (Table 5) with over 1,034,000 additional NSAID users.[76–96]

As in the earlier systematic review, there was a range of values for the percentage of patients using GPAs with NSAIDs, and this reflects differences in definitions of GPA cover. For example, several studies examined not just coprescribing, but the extent of coprescribing, with at least 80% of the NSAID exposure time covered by GPA defined as adequate.[82,86,87,92,95] There was a tendency for smaller studies (fewer than 5,000 subjects) to produce a somewhat better adherence of GPA prescribing than larger studies (Figure 4).

Combining the data from these 21 studies with those from the earlier systematic review (Figure 5), it becomes clear that there is a much greater variability between studies when they are smaller than when they are larger, but considerable variability still exists even with large studies.

Over time, GPA prescribing rates have increased. For example, in a Dutch study, GPA prescribing with NSAIDs increased from 40% in 2001 to 70% in 2007,[80] and in a study in three European countries, under-use of GPA fell between 2000 and 2008.[93] That increase is evident taking all the studies together; those in the review to the end of 2005 reported a weighted mean GPA prescribing rate of 26%, while the 21 later studies published since 2005 reported 49%. Overall, the rate was 38%.

Despite highly variable rates of adherence found between studies, and despite the tendency over time for adherence to prescribing guidance to increase, there is consistent evidence that about half of patients with gastrointestinal risk factors prescribed NSAIDs are not prescribed adequate or any gastroprotection.

***Patients' Adherence to Prescribed GPA.*** The proportion of patients who adhere to their coprescribed GPA is known to fall rapidly within the first year.[97] A more recent study in Spain suggests short-term adherence with GPA for NSAID use may be as high as 85%.[98] There is clear evidence that lack of adherence is associated with increased gastrointestinal harm.[92]

### Other Risks with NSAIDs and Pain

NSAIDs and coxibs are associated with other potential risks, fracture,[99] and renal failure in older patients given NSAIDs with longer half-lives.[100] The risk of fracture is much higher with opioids than with NSAIDs, with an incidence rate 5 times higher in older adults in a large propensity-matched study;[101] hospital admission for adverse events and all-cause mortality were also considerably higher with opioids. Meta-analysis of randomized trials of NSAIDs and coxibs indicate a 45% increased risk of a vascular event compared with placebo, amounting to a 0.3% increased absolute risk a year against a background risk of about 1% a year.[102]

**Table 5. Summary of Individual Studies and Meta-Analyses Published 2006 to 2012 Reporting Doctors' Adherence to Prescribing Guidelines for Patients Taking Nonsteroidal Anti-Inflammatory Drugs (NSAID), and with at Least One GI Risk Factor**

| Study | Details | Place | Number | Adherence (prescribed appropriate GPA) |
|---|---|---|---|---|
| Moore et al.[11] | Systematic review of GPA adherence to end 2005. Data from observational studies | Worldwide, mainly N America, Europe | 1.6 million, of whom 911,000 NSAID users | 26% |
| Bell et al.[76] | Survey of nursing home long-term residents | Finland | 1,087 total | 22% |
| Bianco et al.[77] | Nationwide GP survey | Italy | 3,943 | 81% |
| Coté et al.[78] | Review of patients discharged from medical service over 3 months | U.S.A. | 338 | 46% |
| Doherty et al.[79] | Record review of hospital inpatients | Ireland | 160 | 58% at end only 60 to 70% with several risk factors |
| Helsper et al.[80] | Retrospective cohort of medical records database | The Netherlands | 1.5 million, 7.5% using NSAIDs | 40% in 2001 70% in 2007 |
| Johnell and Fastbom[81] | National prescribed drug register | Sweden | 41,626 NSAID users | 22% |
| Koncz et al.[82] | Retrospective analysis of national GP database | U.K. | 26,371 NSAID users | Adequate gastroprotection 20% High risk 20% to 38% |
| Lanas et al.[83] | Patients visiting a national health service on 1 day with osteoarthritis | Spain | 17,105 | 56% low risk to 92% high risk with NSAID 33% to 76% with coxib |
| Lanas et al.[84] | Retrospective medical record study | Spain | 2,106 | 90% |
| Ljung et al.[85] | Nationwide registry study for persons aged 65 years and older | Sweden | 1.5 million 257,963 using NSAIDs | 40% |
| Lopez-Pintor and Lumbreras[86] | Cross-sectional study of community pharmacies | Spain | 670 | 64% (but only 20% had appropriate protection) |
| Morini et al.[87] | Cross-sectional studies of NSAID users in primary care over 1 week | Italy | 869 | Appropriate protection in 34% |
| Pasina et al.[88] | Analysis of prescription health database | Italy | Over 1 million population of whom 21,553 were regular NSAID users ≥ 35 years | 17% |
| Thiéfin and Schwalm[89] | Cross-sectional analysis of patients in primary care | France | 1,002 | 39% |
| Tsumura et al.[90] | NSAID users who had undergone upper GI endoscopy | Japan | 128 regular users | 84% |
| Valkhoff et al.[91] | Analysis of integrated primary care database | The Netherlands | 50,126 | 39% |
| Valkhoff et al.[93] | Case–control study using information from 3 primary care databases for coxib treatment | The Netherlands, U.K., Italy | 14,146 | > 80% cover in 49% taking coxib for ≥ 1 month |
| Valkhoff et al.[93] | Population-based cohort study in 3 European countries | U.K., Italy, The Netherlands | 617,000 total NSAID users, 314,000 with GI risk factor | Under-use of GPA in 66 to 76% in 2008, reducing over time |
| van Soest et al.[94] | Nested case–control study of new NSAID users with GI risk factors | The Netherlands | 38,201 | 15% |
| van Soest et al.[95] | Nested case–control study of new NSAID users aged ≥ 50 years who also used a GPA | The Netherlands, U.K., Italy | 61,8684 117,307 nsNSAID plus GPA | > 80% cover in 53% taking coxib for ≥ 1 month |
| Van der Linden et al.[96] | Retrospective analysis of prescription database | The Netherlands | 58,770 | ≤ 20% |

GPA, Gastroprotective agents.

Similar risk was evident for all coxibs or NSAIDs, with the exception of naproxen in these randomized trials, for which there was no increased risk.

There is increasing evidence that the presence of chronic pain, particularly severe pain[103,104] or pain resulting in inactivity,[105] is associated with increased all-cause mortality. Large, long-term observational studies fail to corroborate increased cardiovascular risk with NSAIDs; indeed, they suggest that long-term treatment with NSAIDs or coxibs is associated with reduced incidence of cardiovascular events and all-cause mortality.[106,107] The degree of the reduction is substantial and appears to be true of all cardiovascular events, cardiovascular mortality, and all-cause mortality. NSAIDs and coxibs tend to have lower rates of significant harm than opioids in large-matched cohorts.[101] One

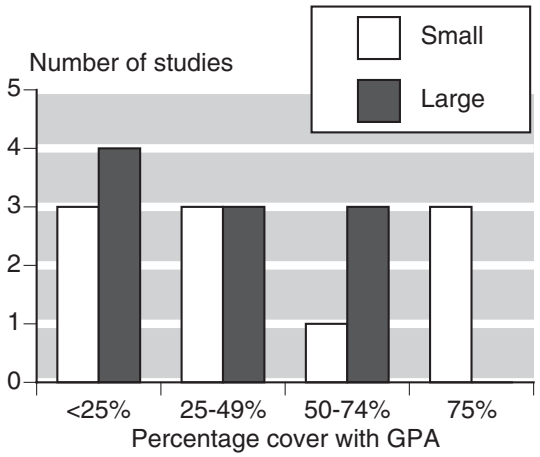


**Figure 4.** Degree of adherence to gastroprotective agents prescribing with nonsteroidal anti-inflammatory drugs according to study size (smaller studies had fewer than 5,000 subjects each).

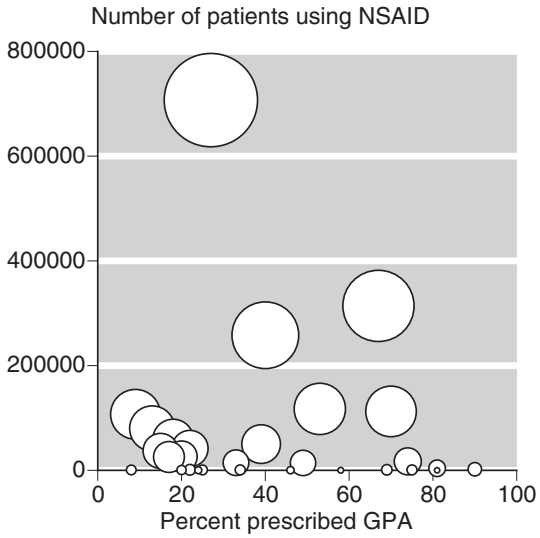


**Figure 5.** Prescribing of gastroprotective agents with nonsteroidal anti-inflammatory drugs in patients with at least one gastrointestinal risk factor in individual studies.

possible explanation for the association between chronic severe pain and increased all-cause mortality is lack of mobility, and the removal of the cardioprotective benefits of active living, although this is no more than speculative.

## Other Risks with GPA

Rare but serious harm may also be associated with long-term use of gastroprotective agents. A number of systematic reviews have examined risk with GPAs, particularly PPIs.

***PPIs.*** Proton pump inhibitors have been associated with higher rates of fracture. A substantial number of studies and meta-analyses have demonstrated a modest increase with PPIs but not other acid-suppressing medicines.[108–115] The link between PPI use and fractures has been downplayed because there is no proven mechanism. The reported magnitude of the risk elevation associated with the use of PPIs was only weak, and the likelihood of residual confounding despite adjustment for known comorbidities and drug use cannot be ruled out.[113,116]

A number of other potential risks have been associated with long-term use of PPIs, including cancer, enteric infections (mainly Clostridium difficile-associated diarrhea), pneumonia, hypomagnesaemia, and drug interactions, particularly with clopidogrel.[117,118] All have evidence of some effects, mainly moderate in magnitude, and with the possibility of confounding by indication. These are not reviewed in detail here, but are mentioned for completeness. Concern regarding the safety of PPIs has been highlighted in a number of recent U.K. Medicines and Healthcare Regulatory Agency (MHRA) safety updates.

***$H_2$RAs.*** We could not find reviews or large studies indicating increased risks associated with long-term $H_2$RA use and no increased risk of colorectal adenoma.[119]

## Patient and Physician Attitudes to Risk and Benefit

While the requirement for risk minimization is clear, the purpose for prescribing NSAIDs is to reduce pain, the symptom (probably with decreased function) that brings the patient to the clinic in the first place. This makes it expedient to examine the risk and benefit from the patient's perspective.

Patients with chronic conditions are willing to accept relatively high levels of risk of harm to obtain effective therapy, despite the significant barriers to describing benefit and risk in terms understood by patients in the clinical setting.[120,121] Table 6 summarizes results from recent studies of patient attitude to risk and benefit in a variety of chronic conditions, including menopausal flushing and sweats,[122] Crohn's disease,[123] osteoarthritis,[124,125] multiple sclerosis,[126] idiopathic thrombocytopenic purpura,[127] and irritable bowel syndrome.[128] They are characterized by patients regarding maximum acceptable risk of harm for successful treatment of 1 in 300 to 1 in 30 to get successful treatment. The

**Table 6. Studies Reporting Patients' Judgement of Acceptable Risk with Treatment in Chronic Conditions**

| Reference | Study Design | Acceptable Risk | Probable Actual Risk |
|---|---|---|---|
| Johnson et al.[122] | Internet questionnaire survey of 523 U.S. women regarding risks of cancer or heart disease for various levels of benefits for hot flushes, sweats and increased fracture risk | Maximum acceptable risk was: Heart attack, 1 in 50 to 1 in 30 Cancer, 1 in 140 to 1 in 70 | Heart attack 1 in 250 Cancer 1 in 250 |
| Johnson et al.[123] | Survey of 580 U.S. patients with Crohn's disease, and attitudes to serious infection, lymphoma, and progressive multifocal leukoencephalopathy related to moderate to mild or severe to remission changes | About 50% of patients would accept risk of 1 in 200 a year for change in symptoms from moderate to mild, and 80% would accept 1 in 200 risk for change from severe to remission | Risk of progressive multifocal leukoencephalopathy in persons with autoimmune disorders in below 1 in 1,000 |
| Richardson et al.[124] | 196 Canadian patients with OA, and attitudes to risk of increased heart attack or GI bleed for 2 or 5 point (out of 10) pain reduction | About 70% willing to accept increased risk of both, with about 20% not willing to accept any increased risk Maximum acceptable risks of the order of 1 in 50 | Depends on drug, but probably less than 1 in 1,000 |
| Johnson et al.[126] | 651 U.S. patients with multiple sclerosis presented with choices of treatment benefits and associated risks | Maximum acceptable risks for liver failure, leukaemia, and progressive multifocal leukoencephalopathy were 1 in 300 to 1 in 100 for various levels of benefit | Natalizumab has reported incidence of 1 case of progressive multifocal leukoencephalopathy per 384 MS patients |
| Hauber et al.[127] | 1,542 patients with chronic idiopathic thrombocytopaenic purpura and risk of thromboembolism | Maximum acceptable risk about 1 in 50 for > 50% chance of treatment success | Risk of any venous thromboembolism is about 1 in 50 following splenectomy |
| Johnson et al.[128] | 589 U.S. women with diarrhoea predominant irritable bowel syndrome and attitudes to risk of impacted bowel, severe colitis, and perforated bowel for different levels of symptom relief | Maximum acceptable risk was 1 in 100 to 1 in 30 for good improvement or complete symptom relief | Incidence of ischaemic colitis with treatment about 1 in 2,000, and serious gastrointestinal complications about 1 in 1,000 |
| Hauber et al.[125] | 294 U.K. patients with OA questioned about the benefits of different outcomes and risks | For improvement in ambulatory pain to mild pain or less, acceptable risk for bleeding ulcer, heart attack, or stroke was around 1 in 100 to 1 in 50 | Actual increased risks probably 1 in 1,000 or less for any treatment |

acceptable risk is typically similar to or higher than the actual risk.

Physicians see things differently, especially in the treatment of arthritis. A survey in the U.K. found that physicians graded a very substantial reduction in pain (from 75/100 mm to 25/100 mm, that is from severe to mild pain) as less important than an increased risk of heart attack from 0% to 1.5% (roughly 1 in 70 risk). Physicians were willing to accept an increased risk of bleeding of 0.7% (roughly a 1 in 140 risk) for a reduction in pain from 75/100 mm to 25/100 mm, that is, from severe to moderate pain.[129] It would appear that benefits generally regarded as substantial or moderate in importance[43] are neglected compared with small or moderate increases in absolute risk.

## DISCUSSION

Important issues in clinical practice are to establish that the NSAID or coxib prescribed delivers good pain relief and that these patients, who may need to use NSAIDs or coxibs in the long term, are prescribed gastroprotection and use it. The evidence on both counts gives cause for concern. A 2011 survey of 1,260 osteoarthritis patients across 6 European Union countries showed that only 46% experienced adequate pain relief;[130] those with inadequate pain relief are put at risk for no benefit. The proportion of patients who adhere to their coprescribed GPA is known to fall rapidly within the first year.[97]

Clinical guidance on gastroprotection is consistent across many guidelines. When an NSAID is prescribed and there is an increased risk of gastrointestinal harm, some form of gastroprotection should be prescribed. The NICE guidance on osteoarthritis, for instance, suggests coprescription with a PPI in every patient, irrespective of risk and whether the patient is prescribed an NSAID or a coxib.[15]

The issues are as follows:

1. To ensure patients have a good level of pain relief. Any single NSAID or coxib will deliver good pain

relief to only about 25% of those patients who try it.

2. How best to ensure that gastroprotection is guaranteed for the NSAID or coxib that delivers good pain relief. One argument for the use of coxibs was convincing evidence that they did deliver reduced gastrointestinal harm across a range of different outcomes[11] and, at doses used, had at least equal efficacy.[46] Fixed-dose combination products of esomeprazole plus naproxen, omeprazole plus ketoprofen, and high-dose famotidine plus ibuprofen are available. Therefore, there is a range of options that could deliver good pain relief for patients and provide reliable gastrointestinal protection while they are being taken.

The knowledge that pain relief and other benefits of successful treatment have a bimodal distribution can simplify the assessment of benefit and risk. For those who are nonresponders, without significant reduction in pain or who have intolerable adverse events that impede any benefits because they prevent the tablets being taken, risk should be irrelevant because therapy should stop. Those who are responders will have large benefits to set against any potential risk, and while they should be cognisant of the risk, the evidence is that most would choose benefit over risk.

For an individual patient with chronic musculoskeletal pain, the key is to find the NSAID or coxib that gives both good pain reliefs with tolerable adverse events. If an NSAID works for that individual patient, we know that gastroprotection as concomitant but separate PPI, misoprostol, or high-dose $H_2$RA is often neither prescribed nor taken. The problem can be overcome for some NSAIDs because single tablet combination therapies are available for naproxen (Vimovo®, naproxen plus esomeprazole; AstraZeneca UL Ltd, Luton, UK), ibuprofen (DUEXIS®, ibuprofen plus high-dose famotidine; Horizon Pharma, Deerfield, IL, USA), and ketoprofen (Axorid®, ketoprofen plus omeprazole; Meda AB, Solna, Sweden). These combination products are variably available in the U.K. and Europe, and U.S.A. and Canada. If it is a coxib that provides good pain relief, then gastroprotection is built in, but guidance sometimes recommends GPA with coxibs. Finding a strategy that delivers gastroprotection is an important component of improving the balance of benefit over risk with NSAIDs for chronic musculoskeletal pain.

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