Management of nonsteroidal anti-inflammatory drug (NSAID)-induced gastrointestinal (GI) complications has been an issue of interest to clinicians in an almost universal way during the last several years. With the introduction of cyclooxygenase-2 (COX-2) inhibitors, the prevalence of NSAID use among the elderly in one Canadian province increased from 14% to nearly 20%; the increase has been correlated with an increase in the rate of hospitalizations for upper GI bleeding.1 Similar increases probably occurred elsewhere. Our understanding of the subject matter continues to change over time as the data evolve. This article’s goal is to review the most recent clinical and research observations related to management of this problem and provide an intervention framework for individual networks or practices.

NSAID-induced GI effects can be approached by examining 3 principal components—prevention, symptoms, and healing. Clinical approaches will vary with each component. When trying to manage symptoms, for example, various therapeutic strategies generally use acid-lowering mechanisms to reduce dyspepsia. This article focuses on symptom treatment and ulcer prevention since patients diagnosed with ulcers are generally managed by specialists rather than generalists. Generalists, including physicians, nurse practitioners, physician assistants, and pharmacists, are more likely to encounter the need to prevent ulcer formation when NSAIDs are prescribed or to manage symptom issues after initiation of NSAIDs.

Incidence of Endoscopic NSAID-Induced Gastric or Duodenal Ulcer

The precise incidence of NSAID-induced ulceration is dependent on the definition and monitoring methods used. If endoscopy is employed at baseline and then at regular intervals after NSAIDs are administered (e.g., 1, 2, 3 months), the incidence of NSAID-related ulceration approaches 40%. Specifically, gastric ulcers occur in 10% to 30% (mean=15%) of patients, and duodenal ulcers occur in 4% to 10% (mean=5%) of NSAID-treated patients. Thus, 4 of every 10 NSAID-treated patients develop an ulcer.2 This data can be slightly misleading; nowhere near 40% of individuals who take NSAIDs experience perceptible GI problems. Generalists must remember this axiom: most NSAID-related ulceration is asymptomatic. Its corollary is that we must not use the presence of symptoms to predict which NSAID users will be at risk for complications.

Studies have assessed patients presenting with NSAID-related upper GI bleeds to determine how many of those patients experienced symptoms prior to presenting with a bleed on an NSAID. Armstrong and Blower, in an early study, examined 235 consecutive patients with life-threatening peptic ulceration complications over a 36-month period. Of the 235 patients, 141 (60%) were taking an NSAID, and mortality associated with a peptic ulcer complication in NSAID-treated patients was more
Reducing Risk: Identify Risk Factors

It is possible to reduce the likelihood that an NSAID-related GI complication might occur. First, clinicians must identify risk factors in the at-risk population (Table 1). Risk factors are not quantitatively similar. Figure 1 describes how risk factors compare. Several risk factors significantly increase risk. Patients who have these risk factors are appropriate candidates for risk reduction using gastroprotective drugs or safer NSAIDs. Note also that patients having 4 risk factors (increasing age, history of peptic ulcer or bleeding, and cardiovascular disease) have a 9% risk for a major complication during 6 months of NSAID treatment. Most clinicians are aware of and appreciate age, GI ulceration, and concomitant medications as risk factors; these are described briefly. Other risk factors are covered in greater depth because they are less well known.

Age. Most risk assessment tools have included a threshold age above which or below which one either does or does not qualify for risk reduction. No magical age threshold exists that automati-

### Reducing Risk: Identify Risk Factors

#### identifying risk factors

Most risk assessment tools have included a threshold age above which or below which one either does or does not qualify for risk reduction. No magical age threshold exists that automatically places individuals at risk for having an NSAID-related event, however. Age-related risk increases incrementally, starting around 50 years, increasing about 2 percentage points per decade to age 70. Patients in their eighth decade are at a 6-fold increased risk of having an NSAID-related GI complication.3

**GI ulceration or a history of ulcer complications.** For patients with a history of a previous GI bleed, the risk is higher than 13 times the risk for those who have no history. It is essential that these patients have their risks reduced.3

**Concomitant warfarin or corticosteroids.** An NSAID user's risk for developing GI complications is 13 times greater when he or she is taking warfarin.29

**Multiple NSAID use.** Of these risk factors, “multiple NSAID use” has not been appreciated as well as it should be. Many clinicians wonder why someone would take multiple NSAIDs. After age, however, multiple NSAID use is the second most common risk factor. It frequently occurs when patients add over-the-counter (OTC) NSAIDs or low-dose aspirin to their prescribed COX-2 inhibitor or nonselective NSAID.3 Data addressing the GI effects of low doses of aspirin or the GI effects of OTC NSAIDs, explain why addition of aspirin to an NSAID or a COX-2 inhibitor might exacerbate toxicities.

Wilcox's trial highlights the high prevalence of OTC use and OTC NSAID use in bleeders. A gastroenterology consultative service evaluated 421 consecutive patients with upper GI hemorrhage at a large inner-city hospital over 2 years. OTC

### Table 1: Risk Factors for GI Complications With NSAIDs

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Bleed</td>
<td>13.5 (10.3-17.7)</td>
</tr>
<tr>
<td>Anticoagulant Use</td>
<td>12.7 (6.3-25.7)</td>
</tr>
<tr>
<td>Corticosteroid Use</td>
<td>4.4 (2.0-9.7)</td>
</tr>
<tr>
<td>Low-Dose NSAID</td>
<td>2.9 (2.2-3.8)</td>
</tr>
<tr>
<td>High-Dose NSAID</td>
<td>5.8 (4.0-8.6)</td>
</tr>
<tr>
<td>Age 70-80</td>
<td>5.6 (4.6-6.9)</td>
</tr>
<tr>
<td>Age 60-69</td>
<td>3.1 (2.5-3.7)</td>
</tr>
<tr>
<td>Age 50-59</td>
<td>1.6 (1.4-2.0)</td>
</tr>
</tbody>
</table>


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than double that of patients who did not report NSAID use. The first sign of ulceration was a life-threatening complication in 58.2% of NSAID-treated patients. Almost 80% of all ulcer-related deaths occurred in patients using NSAIDs. NSAID use was associated with older age, more preexisting medical conditions, and larger ulcers.3

Singh’s later prospective observational study evaluated event rates for all NSAID-induced GI complications in 1,921 patients with rheumatoid arthritis (RA), with particular attention to the time course of events and prophylactic therapy’s role. Using information from validated patient self-reports collected every 6 months and supplemented by review of hospital records for all hospitalizations, they found that approximately 15% of patients reported an NSAID-induced GI side effect during the 2.5-year observation period. Forty-two patients had a serious GI complication requiring hospitalization; 34 (81%) of these 42 patients did not have a preceding GI side effect. Asymptomatic patients taking antacids and H2 receptor antagonists were at significantly higher risk for GI complications compared with those who did not take these medications.4 This underscores the point that NSAID-related symptoms are typically absent.

The incidence of complications is much lower when clinical symptoms are used to identify patients at risk of perforation. Clinically significant ulcers (ulcers that present with pain, perforation, or bleeding) occur in 1% to 4% of NSAID-treated patients, with an average of about 2%. Although a 2% incidence of adverse events for several classes of medicines causes little concern, because NSAIDs are the most commonly taken medications worldwide, the impact is significant—NSAID-associated mortality causes greater than 16,000 deaths in the United States annually.1 Since symptomatic presentation cannot be used to risk-stratify, other characteristics must be considered prior to initiation of NSAID therapy to identify patients at risk.

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#### Table 1: Risk Factors for GI Complications With NSAIDs

- Age (>65 years)
- GI ulceration
- A history of ulcer complications
- Concomitant warfarin or corticosteroids
- Multiple NSAID use, including low-dose aspirin use for cardioprophylaxis
- Cardiovascular disease
- Helicobacter pylori infection

**GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.**

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**FIGURE 1**

Risk Factor for Serious GI Adverse Events With NSAIDs: Relative Risks

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Bleed</td>
<td>13.5 (10.3-17.7)</td>
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</tr>
</tbody>
</table>

Management of NSAID-Associated Upper Gastrointestinal Problems

**SIDEBAR** The REDUCE Campaign

The American Gastroenterological Association (AGA) in association with the American Pharmacists Association has developed an educational effort called the REDUCE campaign. Its goal is to educate the public on the risk of analgesic-related events, especially in light of prevalent OTC and NSAID use and many of the misconceptions about these agents’ safety. Their informative brochure, available from the AGA or on the Internet at http://www.2reduce.org/, prompts patients to self-assess for risk using a checklist. If patients determine they are at risk, the brochure encourages them to talk with their pharmacist or physician.

**REDUCE** = Risk Education to Decrease Ulcer Complications and Their Effects from NSAIDs; OTC = over-the-counter; NSAID = nonsteroidal anti-inflammatory drug.

Aspirin or nonaspirin NSAID use during the week before admission was reported in 145 patients (35%) and 36 patients (9%), respectively. Fifty-six patients (14%) reported prescription nonaspirin NSAID use, and 27 patients (6%) reported prescription aspirin use. In other words, 21% of patients were taking nonaspirin NSAIDS and 44% were taking aspirin. Overall, 56% of patients had used an NSAID during the week before admission, and this was associated with ulcer-related bleeding and upper GI hemorrhage.11

In more recent trials, 80% of patients who present with upper GI bleeds have recently taken an NSAID.12 NSAID use may represent a more important cause of peptic ulcer disease and ulcer-related hemorrhage than previously appreciated. It clearly surpasses *Helicobacter pylori* (*H. pylori*) as a cause of ulcer complication in patients.

Blot and McLaughlin conducted independent analyses of data from an American College of Gastroenterology case-control study to evaluate and quantify potential GI bleeding risks associated with use of OTC analgesics. Information on use of multiple analgesics within the past week and data on other factors (e.g., alcohol and tobacco) were collected from 627 patients and 590 procedure-matched controls. GI bleeding risk was 2- to 3-fold greater among recent users of aspirin, ibuprofen, and other NSAIDs at OTC doses. Risk increased in a dose-related manner. Risk was unchanged among acetaminophen users. Alcohol consumption doubled risks of GI bleeding among drinkers.11 Even with doses that are within the OTCs recommended label dosages, risk of GI bleeding increases.

The American Gastroenterology Association has tried to understand the patterns of OTC use (see Sidebar), and recently reported the results of 2 surveys separated by a 6-year interval. Daily use of OTC analgesics is fairly common, but of greater concern, 50% of OTC users report taking an amount of an OTC NSAID that falls within the prescription-dose range (that is, greater than the OTC dosage), thus increasing risk (see Sidebar).14

NSAID-related bleeding is also related to comorbidities or overall health status, and 15% to 20% of the patients in this study considered themselves in less than good health. Additionally, two thirds were unconcerned about the side effects, and one third of users who took OTC products believed combining OTC products with a prescribed NSAID was safe. About 50% of OTC NSAID use was ibuprofen, but the use of low-dose aspirin as an OTC product is increasing. Most studies indicate that about 20% of the population has indications for low-dose aspirin; in future years, aspirin use will increase.14

**Low-dose aspirin.** A study from the United Kingdom assessed dose-related differences associated with low-dose aspirin use. At 75 mg (comparable to a dose of 81 mg aspirin), risk of Gl adverse events doubled, and risk was 3.9 times greater with 300 mg (comparable to 325 mg aspirin). They concluded, “No conventionally used prophylactic aspirin regimen seems free of the risk of peptic ulcer complications.”15

A specific interest is whether a dose of aspirin exists that, if taken daily, would either have no GI risk or be associated with a lower risk of GI toxicity. When subjects were randomized to receive 10 mg (n = 8), 81 mg (n = 11), or 325 mg (n = 10) aspirin daily for 3 months, all doses significantly reduced gastric mucosal prostaglandin levels to approximately 40% of values measured at baseline. All doses reduced significant gastric injury, and 325 mg caused duodenal injury. Aspirin at 325 daily significantly reduced rectal mucosal prostaglandin levels to approximately 60% of the baseline value. The findings indicate there is no dose of aspirin that will not induce Gl events.16

Kelly and colleagues proved that enteric-coated aspirin does not provide a risk reduction benefit with non-enteric-coated or plain preparations of aspirin. They interviewed 550 patients (a cohort from the Framingham study) with upper GI bleeding after hospital admission and 1,202 controls identified from population census lists about use of aspirin and other NSAIDs during the 7 days before the onset of bleeding (cases) or interview (controls). The relative risks of upper GI bleeding for plain, enteric-coated, and buffered aspirin at average daily doses of 325 mg or less were 2.6, 2.7, and 3.1, respectively.18

**Helicobacter pylori.** Chan and colleagues addressed the uncertainty of whether infection with *H. pylori* is a risk factor for NSAID-induced upper GI bleeding. In a group of *H. pylori*-infected patients with bleeding upper GI ulcers, after subjects’ ulcers were healed, half of the group received *H. pylori* eradication therapy for 1 week while the other half remained *H. pylori*-infected and took the proton pump inhibitor (PPI) omeprazole, 20 mg daily, for 6 months. Both groups were given 500 mg of naproxen twice daily for 6 months. Compared with the group that received *H. pylori* eradication, the omeprazole-treated group had an approximately 80% reduction in rates of recurrent upper GI bleeding, supporting the ability of PPI cotherapy to be very effective in the reduction of NSAID-associated upper GI bleeding.17

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Reducing Risk

Researchers have studied several interventions to prevent serious GI events with nonselective NSAID use. An early strategy was to use a different NSAID formulation, specifically enteric-coating the

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drug to reduce topical interaction of that NSAID with the stomach. However, after 4 weeks of administration, this strategy does not reduce risk compared with nonenteric formulations of NSAIDs. The NSAID used most often as an enteric-coated formulation is aspirin. Enteric-coated aspirin will lessen dyspepsia, but the reduction in dyspepsia will not correlate with reduction in risk.

A second strategy was to use a different route of NSAID administration. Researchers suggested that bypassing the stomach (administering the NSAID parenterally) might be associated with a reduction in risk. The most familiar example is that of ketorolac. Rather than reducing risk, parenterally administered NSAIDs such as ketorolac are more ulcerogenic. Therefore, ketorolac’s recommended duration of use is limited.

With failure of these approaches, researchers moved toward 2 approaches currently considered acceptable strategies (assuming that prescribers are using the lowest effective dose of NSAID):

- cotherapy with misoprostol or a PPI or
- use of safer NSAIDs that specifically inhibit COX-2.

### The Gold Standard: Coadministration of Misoprostol

The 6-month Misoprostol Ulcer Complication Outcomes Safety Assessment (MUCOSA) study was a randomized, double-blind, placebo-controlled trial to investigate whether concurrent administration of misoprostol reduces the occurrence of serious upper GI complications. This large trial enrolled 8,843 NSAID-treated patients receiving any of 10 specified NSAIDs for control of symptoms of RA. Patients were randomly assigned 200 micrograms of misoprostol or placebo 4 times a day. Serious upper GI complications were detected by clinical symptoms or signs (but not endoscopically). Misoprostol-treated patients had a 40% reduction in serious GI events compared with placebo-treated patients.

### H2 Receptor Antagonists

Many guidelines recommend H2 receptor antagonists to prevent NSAID-related GI events. Although each of the H2 blockers has been studied at usual ulcer-healing doses, none can adequately reduce the incidence of NSAID-related ulcerations.

In a double-blind, placebo-controlled trial, investigators studied the efficacy of 2 doses of famotidine (low-dose 20 mg and high-dose 40 mg, each given orally twice daily) compared with placebo in 285 patients without peptic ulcers who were receiving long-term NSAIDs. Clinical and endoscopic evaluation occurred at baseline and after 4, 12, and 24 weeks of treatment. The primary end point was the cumulative incidence of gastric or duodenal ulceration at 24 weeks. Placebo-treated patients had a cumulative incidence of gastric ulcers of 20%. Gastric ulcers occurred in 13% (a rate still unacceptably high) of the famotidine 20 mg twice-daily group, and 8% of the famotidine 40 mg twice-daily group. The reduction in occurrence of duodenal ulcers was similar (13% in the placebo group, 4% in the low-dose famotidine group, and 2% in the high-dose famotidine group). Famotidine was well tolerated.

Researchers have examined higher doses of cimetidine, ranitidine, or nizatidine and for reasons that were initially unclear, only famotidine has demonstrated some benefit, albeit not as much as misoprostol or the PPIs. Thus, H2-blockers, in general, at usual ulcer-healing doses, should not be viewed as effective strategies for risk reduction for people who are taking NSAIDs.

### COX-2 Specific Inhibitors

The list of 25 available NSAIDs in the United States includes 2 COX-2 inhibitors: celecoxib and valdecoxib. Prior to rofecoxib’s withdrawal from the market, the 3 COX-2 inhibitors constituted about 50% of the prescribing for NSAIDs in the United States.

The cyclooxygenase (COX) isoform specific to the stomach is primarily COX-1. COX-1 is responsible for prostaglandin production, which protects against injury.

When COX-1 is inhibited by nonselective NSAIDs, prostaglandin production and GI protection are reduced. COX-2 selective inhibitors spare inhibition of GI COX-1 and confer a protective effect within the GI tract. Several studies have been designed to examine this concept from the outcomes perspective, and the Vioxx Gastrointestinal Outcomes Reserarch (VIGOR) and Celecoxib Long-term Arthritis Safety Study (CLASS) trials are 2 of the most important. Each enrolled upwards of 8,000 patients. It is important to consider, however, whether the trials allowed use of low-dose aspirin or not.

Table 2 summarizes these trials’ key points. In the CLASS (celecoxib) trial, 21% of patients took 81 mg or 325 mg aspirin daily, concomitant with either celecoxib, ibuprofen, or diclofenac. In the VIGOR trial, low-dose aspirin use was not allowed. Each of these studies was conducted for about 1 year. However, the CLASS trial, published in the Journal of the American Medical Association, reported data at 6 months.

The 6-month data from the CLASS trial indicate that ulcer complications or symptomatic ulcers were markedly reduced in the celecoxib group compared with the NSAID group, but the findings lacked statistical significance. However, 21% of patients were on low doses of aspirin that may have been responsible for

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**TABLE 2** GI Outcomes Trials: Design

<table>
<thead>
<tr>
<th></th>
<th>VIGOR (n = 8,076)</th>
<th>CLASS (n = 7,982)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Rofecoxib 50 mg QD</td>
<td>Celecoxib 400 mg BID</td>
</tr>
<tr>
<td></td>
<td>(2x maximum chronic dose)</td>
<td>(2x maximum chronic dose)</td>
</tr>
<tr>
<td>Patients</td>
<td>RA</td>
<td>OA (72%), RA (28%)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Naproxen 500 mg BID</td>
<td>Ibuprofen 800 mg TID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diclofenac 75 mg BID</td>
</tr>
<tr>
<td>Low-dose ASA</td>
<td>No</td>
<td>Yes (21%)</td>
</tr>
<tr>
<td>Duration</td>
<td>Median 9 months</td>
<td>Maximum 13 months</td>
</tr>
<tr>
<td></td>
<td>Maximum 13 months</td>
<td>6 months reported</td>
</tr>
</tbody>
</table>

ASA = aspirin; BID = twice daily; OA = osteoarthritis; QD = once daily; TID = thrice daily; RA = rheumatoid arthritis.
some of the ulcerations observed in the trial. To tease out celecoxib's effects on GI risk reduction with an NSAID, excluding patients taking aspirin is appropriate. In the subgroup of patients (79%) who were only taking celecoxib, ibuprofen, or diclofenac, a statistically significant reduction in risk was observed.\textsuperscript{21} During the U.S. Food and Drug Administration (FDA) proceedings evaluating the CLASS and VIGOR trials, the 13-month trial dataset was assessed. There was no statistically significant difference between celecoxib versus ibuprofen, diclofenac, or the 2 NSAIDS combined.

The VIGOR trial data were more straightforward because the trial was conducted in the absence of aspirin use. During a median follow-up of 9 months, 2.1 confirmed GI events per 100 patient-years occurred with rofecoxib compared with 4.5 per 100 patient-years with naproxen. Rates of complicated confirmed events (perforation, obstruction, and severe upper GI bleeding) were 0.6 per 100 patient-years for rofecoxib and 1.4 per 100 patient-years for naproxen. The incidence of myocardial infarction was lower among naproxen-treated patients than among rofecoxib-treated patients. For each of its end points, either primary or secondary, there was a statistically significant reduction with rofecoxib compared with naproxen.\textsuperscript{21}

**Addition of PPI to Low-Dose Aspirin**

What can be done to protect low-dose aspirin users? A Chinese study group studied 123 H. pylori-infected patients who had ulcer complications after using low-dose aspirin continuously for more than 1 month. Once ulcers were healed and H. pylori infection eradicated, patients were randomly assigned to lansoprazole 30 mg daily or placebo in addition to 100 mg of aspirin daily. During a median follow-up of 12 months, 14.8% of the 61 patients in the placebo group and 1.6% of the 62 patients in the lansoprazole group had ulcer recurrences. In the group of high risk (previously had a bleeding ulcer) aspirin users, 15%, or 1 of 6 participants, had a recurrent bleeding ulcer by the end of 1 year. Lansoprazole-treated patients were significantly less likely to have a recurrence of ulcer complications than placebo-treated patients. Mortality in the 2 groups was similar.\textsuperscript{24}

Risk reduction was examined in a cohort study based on record linkage between a population-based prescription database and a hospital discharge registry in North Jutland County, Denmark, over 4 years. Occurrence of upper GI bleeding in 27,694 users of low-dose aspirin was compared with occurrence in the general population. Two hundred seven exclusive users of low-dose aspirin were admitted to the hospital with their first episode of upper GI bleeding. The standardized incidence rate ratio was 2.6. The standardized incidence rate ratio for combined use of low-dose aspirin and other NSAIDS increased to 5.6. Risk was similar among users of noncoated low-dose aspirin (2.6) and coated low-dose aspirin (2.6).\textsuperscript{23}

Thus, multiple NSAID users who combine a traditional NSAID with low-dose aspirin, because their risks of upper GI bleeding are unacceptably high, need risk reduction strategies. Does the risk of combined use of low doses of aspirin plus a nonselective NSAID extend to the COX-2 specific inhibitors? Returning to the 6-month CLASS trial data, when aspirin was administered concurrently with celecoxib, the risk of having a GI event increased 4- to 6-fold.\textsuperscript{21} Similar to the Danish study, rates of ulceration in the aspirin users, whether it be nonselective NSAID or COX-2 inhibitor, persist.

Average rates of clinically apparent ulceration for NSAID users range from 2% to 4%, but low-dose aspirin use increases the rate to 5% to 6%. Low-dose aspirin use confers sufficiently high risk that these individuals need an alternative approach. Even the safer NSAIDs (the coxibs) have limitations.

**PPI Efficacy in Recurrent NSAID-Associated Ulcers**

A prospective, double-blind, multicenter, active- and placebo-controlled study assessed 537 long-term NSAID users who were not infected with H. pylori and who had a history of endoscopically documented gastric ulcer. Patients were randomized to 1 of 3 groups: (1) placebo, (2) 200 micrograms of misoprostol 4 times a day, or (3) 15 or 30 mg of lansoprazole once daily for 12 weeks. Endoscopy was performed at 4, 8, and 12 weeks. Lansoprazole-treated patients receiving either dose remained free from gastric ulcer longer than placebo recipients. Figure 2 shows patients free of gastric ulcers at week 12. Misoprostol was associated with a significantly higher number of adverse events (diarrhea was seen in about approximately 20% of patients) and early withdrawal from the study. Factoring in withdrawals, therapy was successful for 69% in each of the active treatment groups, but only 35% of placebo-treated patients.

For the prevention of NSAID-induced gastric ulcers, PPIs and misoprostol are similarly effective and both are superior to placebo. If poor compliance and potential adverse effects are considered, the PPI approach becomes more attractive.\textsuperscript{19} Subgroup analysis is
revealing. Ninety percent of patients taking naproxen in combination with low-dose aspirin with misoprostol or lansoprazole were ulcer-free at 2 weeks.

**COX-2 Specific Inhibitor or Nonspecific NSAID + PPI**

Two studies examined high-risk NSAID users in a head-to-head comparison of NSAID plus PPI versus a COX-2 inhibitor alone. One study assessed GI adverse events with celecoxib compared with diclofenac plus omeprazole in high-risk subjects. Patients with a past history of ulcers and who were negative for H. pylori were randomly assigned to either celecoxib 200 mg twice daily plus placebo daily or diclofenac 75 mg twice daily plus 20 mg of omeprazole daily for 6 months. Intention-to-treat analysis of 287 patients (144 receiving celecoxib and 143 receiving diclofenac plus omeprazole) revealed that the probability of recurrent bleeding during the 6-month period was 4.9% for celecoxib-treated patients and 6.4% for diclofenac plus omeprazole-treated patients. Approximately one quarter of celecoxib-treated patients experienced renal adverse events (hypertension, peripheral edema, and renal failure), as did 30.8% of those receiving diclofenac plus omeprazole.26

Lai’s study of 115 H-pylori-negative patients with prior ulcer bleeding documented that recurrent ulcer complications with naproxen plus lansoprazole occurred with approximately the same frequency as recurrences with celecoxib alone.27

**General Principles for NSAID-Associated Problem Management**

Management of symptoms and management of risk are 2 different clinical considerations. Endoscopic evaluation of patients with dyspepsia typically reveals that few have ulcers on endoscopy. Conversely, few patients with bleeding ulcers have had symptoms prior to presentation. Thus, symptom management differs from management of upper GI risk. What do the data say about the management of symptoms?

A recent study that assessed dyspepsia in a group of NSAID-taking patients analyzed the ability of a PPI, in this instance esomeprazole, to reduce symptoms. In 2 identically conducted studies, the PPI either at 40 or 20 mg was able to significantly reduce more symptoms in these NSAID users than placebo.27

High-risk NSAID patients, defined as patients aged 60 years or older or with a history of ulcers within the last 5 years, were taking either a COX-2 inhibitor or an NSAID continuously at the time of study entry. These high-risk NSAID or COX-2 users were then randomized to placebo or the PPI, esomeprazole, 20 or 40 mg.

One very interesting observation was that high-GI-risk COX-2 users did not have a significant reduction in ulceration compared with nonselective NSAID users. But more importantly as it relates to the consideration of PPI plus NSAID, combining a PPI either with a nonselective NSAID or a COX-2 inhibitor markedly reduced ulcer rates. A question of great interest is whether use of a PPI plus COX-2 results in fewer ulcers than PPI plus NSAID.

### TABLE 3 Comparison of FDA-Approved Proton Pump Inhibitors

<table>
<thead>
<tr>
<th>Indications</th>
<th>Lansoprazole</th>
<th>Esomeprazole</th>
<th>Rabeprazole</th>
<th>Pantoprazole</th>
<th>Omeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heartburn and other GERD symptoms</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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</tr>
<tr>
<td>Erosive esophagitis</td>
<td>✔ ✔ ✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Maintenance of healed erosive esophagitis</td>
<td>✔ ✔</td>
<td>✔</td>
<td>✔</td>
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</tr>
<tr>
<td>Helicobacter pylori eradication with antibiotics to reduce the risk of DU recurrence</td>
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<td>✔</td>
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</tr>
<tr>
<td>Active DU</td>
<td>✔</td>
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<tr>
<td>Maintenance of healed DU</td>
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<tr>
<td>Active benign GU</td>
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<td>Healing of NSAID-associated GU recurrence</td>
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<td>✔</td>
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<tr>
<td>Risk reduction of NSAID-associated GU recurrence</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Hypersecretory conditions, including Zollinger-Ellison syndrome</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

**DU** = duodenal ulcer; **FDA** = U.S. Food and Drug Administration; **GERD** = gastroesophageal reflux disease; **GU** = gastric ulcer; **NSAID** = nonsteroidal anti-inflammatory drug.

### TABLE 4 Management Guideline for NSAID Risk Reduction: Patient Profiles

<table>
<thead>
<tr>
<th>No/Low NSAID GI Risk</th>
<th>NSAID GI Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No aspirin Traditional NSAID</td>
<td>COX-2 selective agent or, if on PPI, add traditional NSAID</td>
</tr>
<tr>
<td>Aspirin Traditional NSAID or COX-2 selective + gastroprotective agents</td>
<td>A gastroprotective agent must be added irrespective of type of NSAID prescribed</td>
</tr>
</tbody>
</table>


Unfortunately that was not answered by this study. The numerical difference between PPI plus COX-2 and PPI plus NSAID was not statistically different. This esomeprazole study has unfortunately not answered the question of whether ulcer rates differ with PPI plus COX-2 inhibitor compared with PPI plus traditional NSAID.

Another study assessed the PPI lansoprazole and showed that it was more effective than placebo or misoprostol in preventing symptoms of heartburn, abdominal pain or the composite of GI symptoms.27 In summary, management of symptoms in patients who take NSAIDs can be easily managed with acid suppression. Currently 5 PPIs are available in the United States.
(Table 3); there is a range of potential indications for which these agents might be used. Only 2 currently are FDA-approved for NSAID-related considerations: lansoprazole and esomeprazole.

### A Clinicians’ Guide to NSAID Therapy

Assimilating this information into a management strategy to reduce NSAID-induced ulceration or complications is not difficult. Older approaches asked clinicians to assign numerical values to risk factors and use a formula to calculate a likelihood index for NSAID-related bleed. Reasonable in concept, they were difficult to implement in practice because it took too long on any individual patient encounter to conduct the assessment.

A simpler approach (Table 4) requires us to ask 2 questions when determining patient risk: 28

1. What is the patient’s risk?
2. Is the patient taking aspirin?

Using the answers, clinicians can find the quadrant of the decision table in which the patient rests. Aspirin-free patients without GI risk have very low risk of developing an NSAID-related event and should be able to take a traditional NSAID. For patients who have GI risk and are not taking aspirin, data support using a COX-2-specific inhibitor or, alternatively, using a PPI plus traditional NSAID. This paper reviewed 2 studies to support that these approaches are comparable for GI risk reduction in patients who do not take aspirin. 28

Low-dose aspirin users at low risk for NSAID-related GI events could be treated with a traditional or COX-2 selective NSAID plus aspirin with or without a gastroprotective agent. Use of a gastroprotective agent is debatable. Patients with GI risk who take low-dose aspirin (COX-2 inhibitor or a nonselective NSAID) are at high risk; a gastroprotective agent is indicated regardless of the type of NSAID used. Recent data support combining a PPI plus an NSAID or a PPI plus a COX-2 inhibitor.

### Conclusion

Three major points summarize this review:

- For patients who take NSAIDS, management of upper GI symptoms and management of GI risks are separate therapeutic considerations;
- Patients who take multiple NSAIDS, commonly combining low-dose aspirin with a traditional NSAID or with a COX-2 selective NSAID, are an underappreciated group at high risk for NSAID-induced upper GI ulcer complications; and
- Treating NSAID users with a PPI is a strategy that successfully manages upper GI symptoms as well as reduces risks of upper GI ulcer complications.

### DISCLOSURES

This article is based on the proceedings of a Foundation for Managed Care Pharmacy symposium held on July 17, 2004, in Napa Valley, California, and supported by an educational grant from TAP Pharmaceutical Products, Inc. The author received an honorarium from TAP Pharmaceutical Products, Inc for participation in the symposium.

### REFERENCES


Shortly after the program on which this supplement is based was presented, the entire American pain management landscape changed when rofecoxib’s manufacturer announced that it was voluntarily withdrawing this COX-2 inhibitor from the market. Anticipating reader questions, the Journal of Managed Care Pharmacy asked Dr. Cryer to update his presentation by responding to several important questions.

**APPENDIX** NSAID Therapy—An Update

1. How do the recent concerns with COX-2s and naproxen affect the 4 quadrants of the decision table (A Clinicians’ Guide to NSAID Therapy)? Are the COX-2 recommendations still valid? Should naproxen still be used?

Recommendations to confer gastrointestinal (GI) safety to patients who take nonsteroidal anti-inflammatory drugs (NSAIDs) need to be revised in light of new cardiovascular (CV) concerns with cyclooxygenase-2 (COX-2) inhibitors. With regard to the nonselective NSAID naproxen, the results from the one report suggesting that over-the-counter doses of naproxen might increase CV risks were not statistically significantly different from placebo and, therefore, could have entirely been attributed to chance. More importantly, that study results are outliers from the well-established body of literature indicating that naproxen actually decreases CV risks.

In light of the above considerations, management recommendations for reducing GI risks with NSAIDs have been recently revised. Decisions for appropriate therapy for patients requiring NSAIDs should be primarily based on 2 considerations: (1) assessment of the patient’s baseline GI risk (no/low NSAID-GI risk versus NSAID-GI risk) and (2) assessment of the patient’s baseline CV risks (no CV risk versus CV risk). Based on the various combinations of GI and CV risks, evidence-based recommendations for 4 different patient scenarios are:

- **Patient with no CV and no NSAID-GI risk.** Patients with low CV risk assumes that low-dose aspirin is not taken. For patients at low NSAID-GI risk who are not taking aspirin, the likelihood of a GI event is very low. Therefore, these patients can be given a traditional NSAID without gastroprotective therapy. A very low number of these patients will develop GI complications. However, the low risk of GI events weighed against the high financial costs of GI risk-reduction favors a recommendation for traditional NSAIDs alone for the majority of these patients.

- **Patient with no CV but with NSAID-GI risk.** In patients with modest GI risk for NSAID-related complications, data indicate that use of a COX-2 specific inhibitor alone or use of a traditional NSAID + a proton pump inhibitor (PPI) are approaches that achieve comparable levels of GI risk reduction. Thus, either approach seems reasonable for patients with this combination of risk. There is, however, one important exception to this recommendation. Patients at highest risk for GI events—those with a previous history of GI bleeding—may not be sufficiently risk-reduced with either strategy. Therefore, patients with a previous history of GI bleeding should be given a COX-2 selective agent plus a PPI. *Since NSAID-GI risk reduction can be achieved at a much lower cost with etodolac when compared with labeled COX-2 inhibitors, etodolac should be the preferred COX-2 selective agent.*

- **Patient with CV risk and no/low NSAID-GI risk.** Until long-term studies are available evaluating CV effects of the remaining COX-2 inhibitors, the most prudent approach for patients with CV risks is to use a traditional NSAID (± a PPI*). The degree of GI risk or the need for low-dose aspirin will direct whether the PPI* should be added or not.

- **Patient with CV risks and NSAID-GI risk.** These patients’ baseline risk for NSAID-GI complications is high, and a major GI bleed could lead to significant CV complications. Thus, non-NSAID therapy should be considered. If a traditional NSAID is prescribed, a PPI* should be added.

* Misoprostol can be substituted for a PPI.

<table>
<thead>
<tr>
<th>A Clinicians’ Guide to NSAID Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No/Low NSAID GI Risk</strong></td>
</tr>
<tr>
<td>No CV risk (no aspirin)</td>
</tr>
<tr>
<td>Highest risk: COX-2 + PPI</td>
</tr>
<tr>
<td>CV risk (consider aspirin)</td>
</tr>
<tr>
<td>A PPI* must be added if a traditional NSAID is prescribed</td>
</tr>
</tbody>
</table>

*Misoprostol can be substituted for a PPI. Adapted from Fendrick AM et al. Pharm Ther. 2002;27:579.

2. Should existing COX-2 patients be converted to a nonselective NSAID with gastroprotection?

As discussed above, this decision should be based on patients’ baseline CV risks and GI risks. Based on the combination of those considerations, clinicians can use the above table to select the best form of NSAID therapy and GI protection for their patients.

3. What is the potential interaction between ibuprofen and aspirin?

The data suggesting a potential interaction between ibuprofen and aspirin are largely based on intermediate markers of platelet function (platelet aggregation and platelet thromboxane) rather than clinically significant end points such as CV thrombotic events. Furthermore, the data on a potential ibuprofen-aspirin interaction with intermediate markers of platelet function have been conflicting. Therefore, until the appropriate prospective, controlled studies have been conducted, there is currently not sufficiently compelling available information to change current prescribing recommendations for patients who concurrently take ibuprofen and aspirin.