Review
# Balancing the gastrointestinal benefits and risks of nonselective NSAIDs

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## Abstract

Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used classes of medications to treat pain and inflammation. However, gastrointestinal complications associated with NSAIDs are prevalent, largely due to the frequent use of these agents. Adverse events associated with NSAIDs include minor side effects, such as dyspepsia, as well as serious complications, such as bleeding and perforation. Although the probability that any given individual user of an NSAID will suffer a serious gastrointestinal complication is fairly low, widespread patient exposure can translate into a major national health burden. The increasing use of aspirin in the prevention of cardiovascular events and the availability of select over-the-counter NSAIDs represent additional challenges to clinicians in their efforts to make the most appropriate therapeutic decisions while minimizing the potential gastrointestinal risks associated with the use of these agents. Side effects such as dyspepsia do not provide adequate warning of gastrointestinal complications, because most complications occur without the presence of antecedent symptoms. Therefore, accurate risk assessment and the management of controllable risk factors are crucial to the safe administration of NSAIDs. This review focuses on the gastrointestinal effects of aspirin, acetaminophen, and other nonselective NSAIDs, and discusses those factors that are associated with increased risk for adverse gastrointestinal events in certain individuals.

## Introduction

Gastrointestinal complications are strongly associated with the use of conventional nonsteroidal anti-inflammatory drugs (NSAIDs) and are recognized as the most prevalent and severe cause of drug toxicity in the USA [1]. Millions of patients use NSAIDs for the relief of various types of arthritis pain, stiffness, and related symptoms. Selective NSAIDs such as cyclo-oxygenase (COX)-2 inhibitors were first introduced with the purpose of providing symptomatic pain relief along with lesser gastrointestinal risk. Recent studies indicated that COX-2 inhibitors were prescribed more often than NSAIDs in patients who are older, sicker, and have risk factors associated with NSAID gastropathy [2].

However, rofecoxib (Vioxx®; Merck & Co., Inc., Whitehouse Station, NJ, USA) was voluntarily withdrawn in September 2004; valdecoxib (Bextra®; Pfizer, Inc., New York, NY, USA) was withdrawn and a 'black box' warning was added for celecoxib (Celebrex®; Pfizer, Inc., New York, NY, USA) in April 2005; and a joint hearing of the US Food and Drug Administration Arthritis Committee and the Drug Safety and Risk Management Committee found that the use of COX-2 inhibitors is associated with increased risk for cardiovascular events [3]. These recent events have led many physicians to consider the use of traditional NSAIDs in combination with a proton pump inhibitor (PPI) to reduce the gastrointestinal side effects of NSAIDs. Indeed, major treatment guidelines recommend PPI prophylaxis in patients with a previous gastrointestinal event and in those at high risk for complications [4].

NSAID-induced gastrointestinal complaints are among the most commonly reported adverse events. Balancing these benefits and risks is an important clinical goal in the post-Vioxx and post-Bextra era. Reducing the risk for gastrointestinal complications requires a thorough understanding of potential complications and underlying predisposing risk factors, which is a particularly important consideration in light of the fact that many individuals develop complications without antecedent warning signs or symptoms. This review provides updated information on traditional NSAIDs, including details regarding their efficacy and safety, and a discussion of the major risk factors that are commonly associated with gastrointestinal complications.

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ACR = American College of Rheumatology; CI = confidence interval; COX = cyclo-oxygenase; NSAID = nonselective nonsteroidal anti-inflammatory drug; OA = osteoarthritis; OTC = over-the-counter; PPI = proton pump inhibitor; RA = rheumatoid arthritis; RR = relative risk.

## Spectrum of gastrointestinal risk

The association between NSAIDs and gastrointestinal erosions and ulcers is well established. The relative risk for experiencing serious adverse gastrointestinal events is approximately three times greater for NSAID users than for nonusers [5]. Furthermore, patients with rheumatoid arthritis (RA) are nearly twice as likely as those with osteoarthritis (OA) to suffer a serious complication from NSAID treatment [6]. Compared with RA, OA is a milder disease and requires lower doses of NSAIDs, which may explain why patients with OA appear to be at lower risk for gastrointestinal complications.

NSAID gastrointestinal damage is mediated through several mechanisms that compromise mucosal integrity. In addition, NSAIDs, particularly aspirin, inhibit platelet function even at low dosage, giving rise to bleeding that most commonly affects the gastrointestinal tract. The distinction between erosions and ulcers depends on pathological and endoscopic definitions, with ulcers defined as lesions that penetrate to the level of the submucosa (involving endoscopically evident depth) and erosions defined as lesions confined to the mucosa (without endoscopically appreciable depth). Ulcers give rise to major bleeding, perforation, or obstruction.

NSAID-related gastrointestinal adverse events can be classified into three broad categories [7]: 'nuisance' symptoms such as heartburn, nausea, dyspepsia, and abdominal pain; mucosal lesions (which may or may not be symptomatic), such as ulcers; and serious gastrointestinal complications, such as perforated ulcers and catastrophic bleeding. Nuisance or minor gastrointestinal side effects, including nausea, dyspepsia, anorexia, abdominal pain, flatulence, and diarrhea, are common and affect between 10% and 60% of NSAID users. Mucosal lesions are also common, with nearly half of all patients who take NSAIDs on a regular basis having gastric erosions and 15–30% having endoscopically detectable ulcers. The majority of these lesions do not cause significant symptoms [8,9]. Clinically significant upper gastrointestinal events occur in 3–4.5% of NSAID users annually. The majority of these events are symptomatic ulcers whereas a smaller percentage (approximately 1%) are clinically serious and associated with gastrointestinal bleeding, perforation, or obstruction [10,11].

Throughout the 1980s, the overall risk for hospitalization resulting from gastrointestinal complications was estimated at approximately 1% per year in persons taking NSAIDs [1]. Recent data indicate that the incidence has declined substantially, to 0.5%, as a result of a number of factors, including lower doses of NSAIDs, use of gastroprotective agents (PPIs and misoprostol), and the introduction of the selective COX-2 inhibitors [12]. However, patients taking NSAIDs are 6.45 times more likely to be hospitalized for a gastrointestinal complication than are nonusers [1,6] (Table 1).

The number of deaths associated with NSAID-induced gastrointestinal damage, as acquired from ARAMIS (the Arthritis, Rheumatism, and Aging Medical Information System), which included postmarketing surveillance of more than 36,000 patients from 17 centers in the USA and Canada, are staggering and are comparable to mortality statistics for AIDS and other terminal diseases (Fig. 1) [6,11].

## Magnitude of risk for gastrointestinal complications associated with NSAIDS

Although only a relatively small proportion of NSAID users actually develop major gastrointestinal complications, the importance of these complications is magnified by the widespread use of these agents, thus translating this proportion into a large absolute number of toxicities. More than 30 million individuals are estimated to take NSAIDs daily [6]. Over 111 million NSAID prescriptions were written in the year ending in August 2000 [6]. Additionally, more than 30 billion over-the-counter (OTC) NSAIDs are purchased annually [13].

The prevalence of at least a once weekly NSAID dose among elderly patients aged 65 years or older has been reported to be as high as 70% (original source [7]; primary source [14]). This is particularly significant when it is considered that increasing age is an independent risk factor for gastrointestinal complications.

Several risk factors are known to increase substantially an individual's risk for NSAID-induced gastrointestinal events [7]. These include a history of ulcer, presence of *Helicobacter pylori* infection, use of more than one NSAID (including aspirin), use of high-dose NSAIDs, concurrent anticoagulant or corticosteroid use, a serious underlying disease, and age greater than 75 years. The severity of RA may also be directly related to an increased risk for gastrointestinal events. In contrast, dyspepsia and other upper gastrointestinal symptoms do not reliably predict the development of upper gastrointestinal events [7].

The role played by *H pylori* in the development of gastrointestinal complications remains a subject of controversy. In a recent meta-analysis of 25 studies [15], *H pylori* infection in NSAID users was associated with a 3.53-fold increased risk for peptic ulcer disease above the risk associated with NSAID use alone. The use of NSAIDs and *H pylori* infection increased the risk for ulcer bleeding 4.85-fold and 1.79-fold, respectively; the risk for ulcer bleeding increased to 6.13-fold when both factors were present. Therefore, although both NSAIDs and *H pylori* independently confer increased risk, these findings also a synergistic interaction between these two factors, which leads to increased incremental risk.

The highest relative risk for gastrointestinal events is associated with a history of complicated ulcer or multiple NSAID use (Table 2) [5,7,16-18]. In one study, in which 1457 patients with a history of bleeding were compared with 10,000 control individuals, patients on multiple NSAID

**Table 1**

**Gastrointestinal complications in osteoarthritis versus rheumatoid arthritis**

|  | OA hospitalizations | RA hospitalizations | RA deaths |
|---|---|---|---|
| Number of patients | 1283 | 3883 | 2921 |
| Person years of observation | 3234 | 19,961 | 12,224 |
| Person years taking NSAID | 2199 | 15,638 | 8471 |
| Number of GI events | 19 | 228 | 25 |
| Number of GI events while taking NSAID | 16 | 205 | 19 |
| Rates/year (%) while taking NSAID | 0.73 | 1.31 | 0.22 |
| Rates/year (%) while not taking NSAID | 0.29 | 0.19 | 0.05 |
| Relative risk while taking NSAID | 2.51 | 6.77 | 4.21 |

GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; RA, rheumatoid arthritis. Reproduced with permission from [6].

**Figure 1**
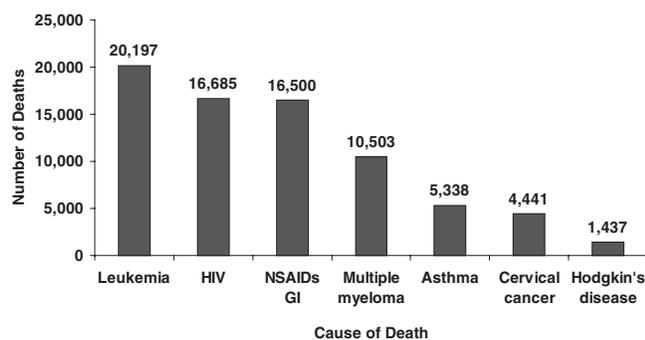


Deaths associated with NSAID induced gastrointestinal damage versus other causes. GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug. Data from Singh and Triadafilopoulos [6].

**Table 2**

**Risk factors for aspirin and NSAID associated ulcer complications, in order of relative importance**

| Rank | Risk factor |
|---|---|
| 1 | Personal history of complicated ulcer disease |
| 2 | Concurrent use of more than one NSAID (including aspirin) |
| 3 | Use of high doses of NSAIDs |
| 4 | Concurrent use of an anticoagulant |
| 5 | Personal history of uncomplicated peptic ulcer disease |
| 6 | Age >70 years |
| 7 | Concurrent use of steroids |

NSAID, nonsteroidal anti-inflammatory drug. Reproduced with permission from Elsevier [16].

regimens were nine times more likely to experience upper gastrointestinal bleeding than were control individuals [19].

The correlation between multiple NSAID use and upper gastrointestinal bleeding should be placed in a broader perspective, not only because of the widespread use (and considerable under-reporting) of OTC medications but also because patients do not recognize the potential complications that can develop with NSAIDs. A survey of more than 800 people found that approximately 65% said that they suffer gastrointestinal symptoms before the onset of a gastrointestinal event, despite considerable evidence that serious gastrointestinal complications occur in asymptomatic patients [20].

Many patients taking OTC NSAIDs and/or aspirin or other drugs do so without their physician's knowledge or approval, and are unaware of the increased relative risk for experiencing a gastrointestine related event. This widespread use of NSAIDs underscores the importance of a thorough assessment of potential gastrointestinal risk in patients who are administered these agents for the management of pain and inflammation. Obtaining accurate information regarding concomitant medications from patients taking NSAIDs may also help to identify those at additional risk from concurrent multiple NSAID, anticoagulant, or corticosteroid use.

## Assessment of gastrointestinal risk factors

It is imperative that clinicians carefully screen patients for risk factors for gastrointestinal complications due to NSAID use. Although dyspepsia is a frequent side effect of NSAIDs use, it is not – in contrast to common perception – an accurate predictor of gastrointestinal complications [6,7]. Approximately 15% of patients experience dyspepsia during NSAID therapy, but such symptoms correlate poorly with the severity of mucosal injury. As many as 50% of patients with dyspepsia have mucosa that appears normal on endoscopic examination. In fact, the majority of patients who develop gastro-

intestinal complications do so without any antecedent symptoms [21], further highlighting the importance of thorough risk assessment in patients receiving NSAIDs.

Some advocates of *H pylori* screening recommend that *H pylori* eradication be considered in chronic NSAID users at average risk for gastrointestinal complications, as well as in chronic NSAID users at increased risk for gastrointestinal complications [22]. However, patients with gastric and duodenal ulcers may or may not have evidence of *H pylori* infection [23], and *H. pylori* eradication may reduce but not completely eliminate the risk for recurrent ulcers or complications [24]. Therefore, this issue remains controversial.

It should be noted that the period of greatest risk to an individual taking NSAIDs occurs during the first 3 months of NSAID therapy. Although the underlying mechanism for this is not well understood, one theory holds that gastric mucosa adapts to NSAID use over time [5]. However, clinical findings from a study in which 1600 individuals receiving NSAID therapy were followed for up to 15 years [6] demonstrated that the stomach does not adapt to NSAID use, and that the risk for complications continues over the long term [6]. Further elucidation of the mechanisms that are involved in early NSAID associated gastrointestinal events may help to ascertain which individuals are at greatest risk for early gastrointestinal events.

## Comparison of gastrointestinal effects: aspirin, acetaminophen, and NSAIDs

The anti-inflammatory, analgesic, and antipyretic drugs are a heterogeneous group of compounds that share certain therapeutic actions and side effects, although they are chemically unrelated. Attempts to rank toxicity and efficacy have not been consistent. Earlier studies conducted by Henry and colleagues [25] established a comparative toxicity range for a select group of drugs (using ibuprofen as the reference comparator); for example, the relative risk (RR) for aspirin was found to be 1.6, for diclofenac it was 1.8, for naproxen it was 2.2, and for ketoprofen it was 4.2. A more recent nested case controlled analysis [26] showed that aspirin was associated with a RR of 2.9 for uncomplicated peptic ulcer, compared with a RR of 4.0 for nonaspirin NSAIDs.

Low-dose aspirin and NSAIDs are among the most widely used drugs worldwide. Because of their anti-inflammatory and analgesic (NSAIDs) or antiplatelet (low-dose aspirin) effects, these drugs can benefit patients substantially but at the cost of increased risk for gastrointestinal complications. The benefits of low-dose aspirin in the prevention of myo-cardial infarction and vascular events are well established [27]. The American Heart Association recommends the use of low-dose aspirin (75–160 mg) in patients whose 10-year risk for a cardiovascular event is 10% or greater, except in persons at high risk for gastrointestinal bleeding or hemorrhagic stroke [28]. Long-term use of aspirin in the

prevention of cardiac disease, especially in elderly populations, is of increasing concern because it is wide-spread and is known to cause irritation and injury to the gastrointestinal tract [29].

Recent clinical findings suggest that no aspirin regimen is free from risk for upper gastrointestinal bleeding [30]. Even lose-dose aspirin is associated with a significant increase in upper gastrointestinal bleeding. In a Danish registry of 27,694 users of low-dose aspirin (100–150 mg) the incidence of upper gastrointestinal bleeding upon admission to the hospital was 2.6-fold greater than in the general population [30]. The risk for upper gastrointestinal bleeding (incidence ratio 5.6) is even greater among patients taking other NSAIDs in combination with aspirin and is not dose dependent [30,31].

In contrast to aspirin, the use of low-dose acetaminophen (<2000 mg) is not associated with an increased risk for upper gastrointestinal complications. There are limited data that suggest that doses greater than 2 g are associated with an increased risk for gastrointestinal bleed or perforation by a factor of 3.6 [32]. *In vitro* analyses of human whole blood assays suggest that acetaminophen is a weak nonselective inhibitor of both COX-1 and COX-2 [33].

Currently, the American College of Rheumatology (ACR) recommends acetaminophen as first-line treatment for OA of the knee or hip. This is largely because of the perception that acetaminophen is safer than NSAIDs [34,35]. However, the selection of treatment depends on a balance of factors, including efficacy, safety, tolerability, availability, cost, and patient acceptance. The recent emergence of coxibs has raised further questions regarding the role of selective NSAIDs in the treatment of OA. Until recently, few comparison data were available with which to evaluate the relative efficacy and safety of acetaminophen and NSAIDs. Data from clinical trials demonstrated that celecoxib and diclofenac are both superior to acetaminophen in the treatment of OA [36,37]. Furthermore, a survey of 1799 patients found that the majority of patients with OA (>60%) prefer NSAIDs to acetaminophen in the symptomatic treatment of the condition based on perceived better efficacy [38]. However, newer data from several meta-analyses and pooled analyses evaluating the comparative efficacy and safety of NSAIDs versus acetaminophen indicate that, although NSAIDs are slightly more effective in relieving pain, acetaminophen is associated with fewer adverse reactions and less frequent gastrointestinal discomfort than are NSAIDs.

In a meta-analysis of seven clinical trials performed by Lee and colleagues [39], the efficacy and safety of NSAIDs, including coxibs, in the treatment of symptomatic hip and knee OA were compared with those of acetaminophen. Lee and coworkers determined that NSAIDs are statistically

superior to acetaminophen in reducing walking and rest pain; however, NSAIDs were also associated with an elevated, but statistically insignificant, risk for withdrawals due to adverse events (odds ratio 1.45, 95% confidence interval [CI] 0.93–2.27).

Based on the results from another meta-analysis of 10 randomized controlled trials ($n = 1712$), in which patients with symptomatic OA of the knee, hip and knee, or multiple joints were evaluated, Zhang and colleagues [40] reported that acetaminophen was significantly more effective than placebo (effect size 0.21, 95% CI 0.02–0.41) but that NSAIDs were better than acetaminophen for pain relief (effect size 0.20, 95% CI 0.10–0.30), clinical response rate (RR 1.24, 95% CI 1.08–1.41), and symptom relief (as measured using Western Ontario and McMaster Universities Osteoarthritis Index scores). The number of patients who preferred NSAIDs was more than twice the number of patients who preferred acetaminophen (RR 2.46, 95% CI 1.51–4.12).

Although NSAIDs exhibited superior efficacy in the meta-analysis conducted by Zhang and coworkers [40], the excellent safety profile of acetaminophen must be weighed against the therapeutic benefits of NSAIDs. In this meta-analysis, NSAIDs were associated with more frequent gastro-intestinal discomfort, including abdominal pain, gastro-intestinal distress, nausea, vomiting, and dyspepsia, than was acetaminophen (RR 1.35, 95% CI 1.05–1.75). It should be noted, however, that the studies examined in this meta-analysis included only short-term trials in which serious gastro-intestinal events, such as bleeding or ulcer complications, were not evaluated. In balancing the efficacy and safety data for acetaminophen and NSAIDs, Zhang and colleagues concluded that acetaminophen at 4 g/day demonstrates significant efficacy for pain relief in OA, and that the current ACR guidelines that recommend acetaminophen as first-line treatment for OA are supported by the evidence. Overall, however, acetaminophen is not adequate therapy for the majority of patients with daily OA pain.

Acetaminophen is generally thought to be safer than NSAIDs, although the therapeutic index is narrow and a single acetaminophen overdose with twice the highest labeled dose is associated with life-threatening acute liver failure [41,42]. There have been few case reports of acetaminophen-induced acute liver failure at therapeutic doses [43]. In a prospective study of acute liver failure at 17 tertiary care centers in the USA [44], involving 308 patients with liver failure over the course of more than 3 years, liver failure due to acetaminophen overdose accounted for 39% of all cases. Comparatively, viral hepatitis (A and B), a common cause of liver failure, accounted for only 12% of cases. Although acetaminophen overdose has replaced viral hepatitis as the most frequent putative cause of acute liver failure, it remains extremely rare given the ubiquitous use of this OTC analgesic.

The evidence for decreased gastrointestinal risk in patients receiving COX-2 is reviewed extensively elsewhere. However, the data presented here provide a context for discussion of the benefits and risks of these agents. Endoscopic studies, meta-analyses of serious gastrointestinal adverse events from clinical trials, and outcome studies have demonstrated the improved gastrointestinal safety of coxibs compared with most NSAIDs studied. Concerns over cardiovascular risk, however, have cast a shadow over the perceived overall safety profile of chronic coxib therapy. In addition, in patients with RA who are at risk for serious adverse gastrointestinal complications, the ACR recommends the use of one of the following [18]: low-dose prednisone instead of an NSAID; a nonacetylated salicylate; a highly selective COX-2 inhibitor; or a combination of NSAID and a gastroprotective agent. A safety issue related to NSAID and coxib safety that is not fully addressed in such guidelines, which are now 3 years old, is that low-dose aspirin (75–300 mg/day) for the prevention of stroke and myocardial infarction is increasingly common, especially in older patients. Because the concurrent use of aspirin with NSAIDs is common, the potential impact on safety should be weighed in patients receiving both selective and nonselective NSAIDs. Data available to date suggest that the potential gastrointestinal safety benefit of coxibs compared with NSAIDs is lost with aspirin cotherapy.

## Cardiovascular risk

Before the development of COX-2 inhibitors, the risks associated with NSAIDs precluded robust study of such agents for various preventive indications. These indications have included prevention of cancer, Parkinson's disease and Alzheimer's dementia. The perceived safety of patented COX-2 selective inhibitors generated the financial and ethical support for long-term exposure in a setting in which it was ethical to conduct a comparison with placebo. Previously, only symptomatic conditions were studied, and so long-term placebo control was not possible. Results of placebo controlled, long-term clinical trials with over 2 years of exposure have indicated that there is cardiovascular risk associated with rofecoxib. Similar trials using celecoxib have been less consistent.

Somewhat unexpectedly, the single long-term, placebo controlled study of a nonselective NSAID, namely naproxen, has been preliminarily reported as suggesting that there is cardiovascular risk with this agent, although a final report is not yet available. There have been at least seven large pharmacoepidemiologic studies on this topic published since 2001, with over 5 million person years of exposure. However, it is not clear whether all COX-2 selective agents entail cardiovascular risk, whether nonselective agents entail risk, or what effect dose and duration have on magnitude of risk [45]. The Food and Drug Administration has requested that all NSAID and COX-2 selective agents carry warnings that the product may increase the risk for cardiovascular events [46]. (This issue is addressed in greater detail elsewhere in this supplement [3,47].)

Thus, it is important to reassess the ACR recommendations in the light of newer safety information. Co-use of NSAIDs and gastroprotective agents appears to be more attractive. Gastroprotective agents, which are considered to be effective in decreasing NSAID-associated gastrointestinal ulceration, include high-dose $H_2$ blockers, PPIs, and the oral prostaglandin analog misoprostol. Although symptoms of dyspepsia often improve in patients treated with $H_2$ blockers, their routine use is not recommended because of findings in 1921 patients from the ARAMIS cohort that prophylactic treatment with these agents may increase the risk for subsequent serious gastrointestinal complications [21].

Numerous studies indicated that, when used in conjunction with NSAIDs, PPIs and the oral prostaglandin analog misoprostol significantly reduce gastric and duodenal ulcers in patients with and without a prior history of ulcers [8,48-52]. A recent study conducted by Chan and coworkers [53] raises the question regarding whether such a strategy is adequate in those who are at particularly high risk, based on a past history of upper gastrointestinal bleed. Despite these recent conflicting findings, the protective effects of these agents are well established (their efficacy is further evaluated in another review in this supplement [54]).

## Conclusion

Thorough risk assessment and prevention strategies together offer the best opportunity to prevent harmful gastrointestinal events in patients receiving NSAIDs. When selecting therapeutic agents, physicians should consider recent findings that further characterize the comparative safety and efficacy profiles of acetaminophen and NSAIDs, and should discuss with patients the potential benefits and risks of various treatments. Tailoring the options outlined in this article to a particular patient is the challenge for those caring for patients with OA. Future studies may help to quantify better the benefit of PPI cotherapy for chronic NSAID users compared with acetaminophen or COX-2 selective agents.

## Competing interests

DAP has received honoraria from TAP and AstraZeneca for speaking. LG is a consultant to Altana, Novartis and TAP.

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