REVIEW

Coprescribing proton-pump inhibitors with nonsteroidal anti-inflammatory drugs: risks versus benefits

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Abstract: Nonsteroidal anti-inflammatory drugs (NSAIDs) are often coadministered with proton-pump inhibitors (PPIs) to reduce NSAID-induced gastrointestinal (GI) adverse events. This coadministration is generally regarded as safe, and is included in many of the guidelines on NSAID prescription. However, recent evidence indicates that the GI risks associated with NSAIDs can be potentiated when they are combined with PPIs. This review discusses the GI effects and complications of NSAIDs and how PPIs may potentiate these effects, options for prevention of GI side effects, and appropriate use of PPIs in combination with NSAIDs.
Keywords: PPIs, COX2 inhibitors, NSAIDs, enteropathy, gastrointestinal

NSAIDs: one of the most widely used therapeutic agents

Nonsteroidal anti-inflammatory drugs (NSAIDs), including both traditional non-selective NSAIDs (ns-NSAIDs) and selective COX2 inhibitors, are among the most widely used of therapeutic agents. Taken alone or in combination with other classes of drugs, they are used for symptomatic treatment across multiple clinical indications, including short- and long-term pain states and a range of musculoskeletal disorders.[1,2] Both prescription and over-the-counter NSAIDs are widely used for their anti-inflammatory (AI) and analgesic effects. NSAIDs are an essential choice in pain management, because of the combined role of the COX pathway in inflammation.[3] In a meta-analysis examining the sales and essential-medicine lists in countries of different incomes, diclofenac was found to be the most popular NSAID, followed by ibuprofen, mefenamic acid, and naproxen (Figure 1).[1] Etoricoxib was also commonly prescribed in Bangladesh, Malaysia, Hong Kong, and Singapore.[1]

NSAID-induced GI injury and the coprescription of PPIs

NSAIDs are a leading cause of drug-related morbidity, especially in the elderly and patients with comorbidities.[4] Adverse events associated with NSAIDs are a challenge in treatment optimization for pain.[5] Adverse events include alterations in renal function, effects on blood pressure, hepatic injury, and platelet inhibition, which may result in increased bleeding. However, the most important adverse effects of NSAIDs are the gastrointestinal (GI) and cardiovascular adverse effects. A considerable amount of money is spent treating and preventing just the GI events. A Canadian study found that

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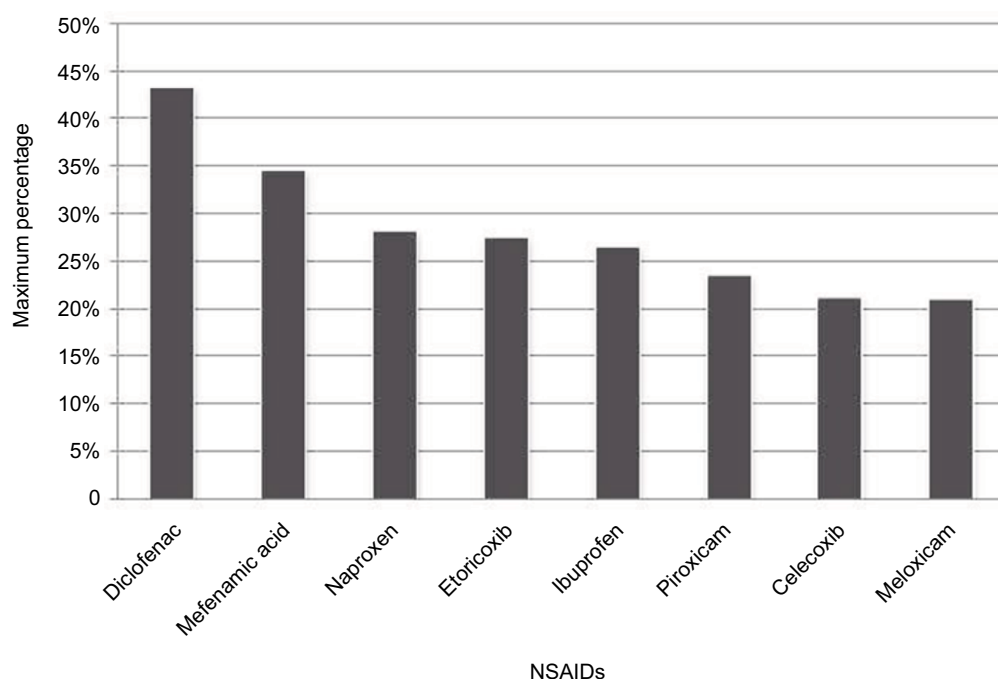Fax +65 6722 4188
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Figure 1 Individual NSAID use as percentage[a] of total NSAID sales in all countries in 2011.
Notes: [a]Proportion of total NSAID sales in all countries studied. High/high middle-income countries, Australia, China, Hong Kong, Malaysia, New Zealand, Singapore, Taiwan, Thailand, UK/England, Canada; Low/low middle-income countries, Bangladesh, Indonesia, Pakistan, Philippines, Vietnam. Intercontinental Medical Statistics Health (IMS Health) tracks over 80% of global pharmaceutical use by sampling individual country sales through multiple supply routes to retail pharmacies and hospitals. These sales include both indirect sales from wholesalers and direct sales from manufacturers. In some countries, hospital audits are based on data sourced from hospital pharmacies. In each country, the sampling data are projected to estimate sales for the whole country. Data extracted from McGettigan and Henry.[1]
Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

the GI iatrogenic cost factor for NSAIDs was 1.73, meaning that an additional CA$0.73 was spent on the prophylaxis and treatment of NSAID-related GI events for each Canadian dollar of direct cost spent on NSAID.[6] The deleterious GI effects of ns-NSAIDs are a cause for concern, because of their frequency and seriousness.[3]

Proton-pump inhibitors (PPIs) have been proven efficacious in healing NSAID-associated ulcers, as they provide potent and long-lasting inhibition of gastric acid secretion.[7] As such, they are often coprescribed with NSAIDs. However, this leads to excessive cost for both patients and governments, and also induces a potential risk for iatrogenic harm.[8] In the past two decades, the coadministration of NSAIDs and PPIs has resulted in a decrease in upper-GI tract adverse events, but has been associated with an increased frequency of lower-GI tract events. This enteropathy induced by the combination of an NSAID and PPI is common, and lesions induced by these drugs in the small intestine could be of considerable clinical importance.[9] The subsequent sections of this manuscript focus on the GI effects/complications of NSAIDs, options

for prevention of GI side effects, and appropriate use of PPIs in combination with NSAIDs.

NSAID-related upper- and lower-GI complications
Clinical significance

The extensive use of NSAIDs in prescriptions and by over-the-counter NSAID users has made GI complications a severe problem.[10] These complications generally include bleeding gastric and/or duodenal ulcers, and to a lesser extent obstructions and/or perforations.[11,12] NSAIDs can cause both upper- and lower-GI complications.[13] Although the incidence of upper-GI mucosal damage has decreased over the years, due to the use of PPIs, lower-GI mucosal damage has been steadily increasing.[13,14]

Although the risk of ulcer complications may decrease after the first few months of NSAID use, it still does not disappear with long-term therapy.[15] Also, NSAID use is associated with heightened risks in some patients, and thus awareness of the risk factors and the use of preventive therapy for NSAID-related

upper-GI injury is important.[16] Table 1 highlights some of the GI complications associated with NSAID use.

Upper- versus lower-GI complications associated with NSAIDs

Upper-GI complications

The two main mechanisms that are involved in upper-GI complications are systemic inhibition of gastric mucosal protection, through inhibition of COX activity (mostly COX1) of the gastric mucosa, resulting in reduced synthesis of mucus and bicarbonate, an impairment of mucosal blood flow, and an increase in acid secretion; and physicochemical disruption of the gastric mucosal barrier.[17] Acid injures the

mucosa by H^+-ion back-diffusion from the lumen, causing tissue acidosis, and also increases drug absorption, which is inversely proportional to drug ionization.

Clinical impact

According to estimates from the US, nonvariceal upper-GI bleeding results in 400,000 hospital admissions every year, costing more than an annual US$2 billion.[18] In addition, despite advances in therapy, rebleeding is common (7%–16%) and the in-hospital mortality rate remains high (3%–14%).[19] An observational study conducted in the Spanish national health service found that the incidence of hospital admissions due to major GI events of the entire GI tract was 121.9 events/100,000 persons/year, but those related to the upper GI tract were six times more frequent.[20]

Upper-GI risk profile of various NSAIDs

Different NSAIDs have different upper-GI risks. In a systematic review and meta-analysis of observational studies, different NSAIDs, including COX2 inhibitors, showed different risks of upper-GI complications.[21] The NSAIDs with the lowest relative risk included celecoxib and ibuprofen, while piroxicam had one of the highest (Figure 2).[21] The use of high daily doses of individual NSAIDs was associated with approximately a two- to threefold increase in relative risk for upper-GI complications compared with the use of low–medium doses, except for celecoxib, for which a dose response was not observed.[21] In addition, in the recently published CONCERN trial, where the primary end point was recurrent upper-GI bleeding within 18 months, it was found that celecoxib, a COX2 inhibitor, had a 5.6% cumulative
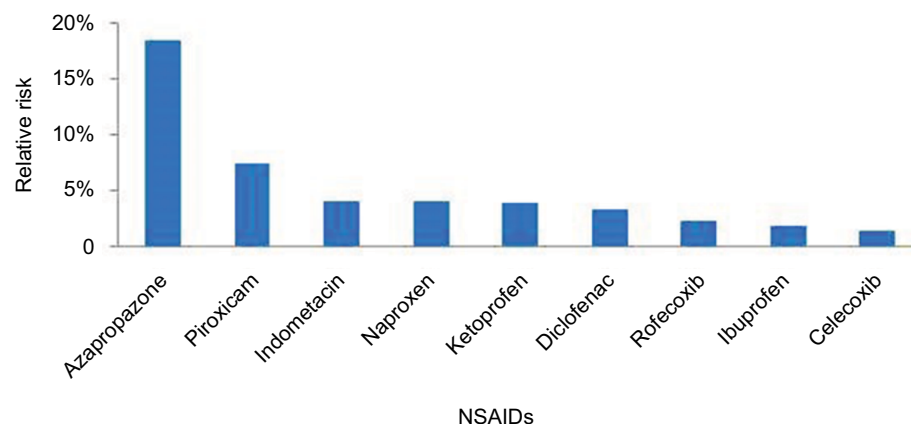
Table 1 Risk factors for GI complications associated with NSAID use

Risk factors

- Age 60 years and above
- Dyspepsia history
- Current high dose of NSAID
- Multiple NSAID therapy
- Concomitant use of ASA
- Uncomplicated peptic ulcer history
- Concomitant use of corticosteroids
- Concomitant use of oral anticoagulants
- Peptic ulcer bleeding
- *Helicobacter pylori* infection
- Cigarette smoking
- Alcohol use
- Chronic debilitating disorders, especially cardiovascular disease

Note: Information obtained from several studies.[49,99,100]
Abbreviations: GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; ASA, acetylsalicylic acid (low-dose aspirin).

Figure 2 Relative risk of upper-GI complications with different NSAIDs.
Note: Data compiled from Castellsague et al.[21]
Abbreviations: GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

incidence of recurrent bleeding, which was significantly lower than naproxen, which had a 12.3% cumulative incidence.[22] This significant difference was observed despite PPIs being given in both the study groups.

Lower-GI complications

Mechanism

The mechanism of NSAID-induced lower-GI damage is very different from upper-GI damage, and is proportional to the acidity of the molecule used and the extent of increased lower-intestine permeability generated by NSAIDs. This increase in permeability always leads to inflammation.[23] The development of small-intestine inflammation usually starts with an initial increase in small-intestine permeability.[24]

Inhibition of both COX1 and COX2 causes small-bowel damage in the long-term. A capsule-endoscopy study found that even though COX2-selective agents resulted in a lower prevalence of damage compared to ns-NSAIDs, there was still a high prevalence of damage seen with COX2-selective agents.[25] There has also been increasing evidence that COX2 is needed for the maintenance of mucosal integrity and ulcer healing, and thus gastric and intestinal lesions develop only when both COX1 and COX2 are suppressed.[26] ns-NSAIDs are also weakly acidic and are invariably lipophilic, giving them detergent-like properties (Table 2). As such, they interact with phospholipids, an essential constituent of the brush border, causing damage to the surface epithelium.[27] Moreover, lower-GI injury is not dependent on acid production.[28] Therefore, the use of antisecretory agents does not help reduce its incidence.[29] However, a lower pK_a value for individualized NSAIDs is associated with increased intestinal permeability.[30]

Table 2 Acidity comparison among NSAIDs

Compound	Acidity (pK_a)
Valdecoxib[101]	9.8
Celecoxib[62]	9.7
Nimesulide[62]	6.4
Ibuprofen[62]	5.2
Lumiracoxib[102]	4.7
Etoricoxib[103]	4.5
Indomethacin[62]	4.5
Naproxen (enteric-coated)[62]	4.2
Diclofenac[104]	4.0
ASA (enteric-coated)[62]	3.5

Notes: The lower the pK_a value, the more acidic the drug. NSAID acidity is linked to increased intestinal permeability and lower-GI tract damage (inflammatory enteropathy).[27]
Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; ASA, acetylsalicylic acid (low-dose aspirin); GI, gastrointestinal.

NSAIDs also uncouple mitochondrial oxidative phosphorylation, which decreases intracellular adenosine triphosphate concentration. This change results in loss of intercellular integrity, as the intercellular junctions are under the control of adenosine triphosphate-dependent actin–myosin complexes, and hence an increase in intestinal permeability and subsequent mucosal damages.[27,31]

Many studies have suggested that bacteria also play a role in the pathogenesis of NSAID enteropathy. One key observation is that germ-free rats and mice develop little or no intestinal damage when given an NSAID, but become susceptible to NSAID-enteropathy when colonized by Gram-negative bacteria.[32] A number of studies have also reported protective effects of antibiotics against NSAID enteropathy, particularly when the antibiotics were effective in attenuating Gram-negative bacteria.[32] For example, in a randomized controlled trial in which healthy volunteers were given slow-release diclofenac plus omeprazole and rifaximin extended intestinal release, or slow-release diclofenac plus omeprazole and extended intestinal-release rifaximin, the results showed that fewer rifaximin-treated volunteers developed small-bowel lesions compared with placebo-treated subjects.[33] This strengthens the evidence of the role of enteric bacteria in the development of NSAID enteropathy.

Bile and enterohepatic circulation are also important factors in the induction of intestinal damage.[32,34] The combination of NSAIDs with bile has been shown to damage cultured intestinal epithelial cells.[35] Also, the presence of bacteria can result in the formation of secondary bile acids, which are particularly damaging to these cells.[36] There is evidence that the ligation of the bile duct prevents/reduces intestinal damage when NSAIDs are administered to rats.[37,38] In addition, animal models have shown that NSAIDs that do not undergo enterohepatic recirculation do not cause significant intestinal damage. This may be related to the recurring injury to the epithelium induced by the NSAID recirculating through the intestine.[39]

Clinical impact

Association of NSAIDs with damage to the lower-GI tract has not been widely studied and remains poorly characterized. NSAID-induced enteropathy has recently gained much attention, due to the introduction of new diagnostic modalities, such as capsule endoscopy and device-assisted enteroscopy, as well as the increased use of acetylsalicylic acid and NSAIDs. The clinical significance and frequency of risks and complications with ns-NSAIDs in the lower-GI tract

have been increasingly reported.[13,25] Lower-GI complications also have worse clinical outcomes compared to upper-GI complications (Figure 3):[40] they lead to higher mortality and longer hospitalization.[41] Although PPIs are prescribed together with NSAIDs as a form of gastroprotection, not only do they not inhibit NSAID enteropathy[29] but also frequent use of PPIs can worsen NSAID-induced small-intestine injury by modifying intestinal microbiota.[9]

In recent years, large randomized controlled trials have begun to analyze the effect of NSAIDs on the entire GI tract, rather than just the upper GI tract. In such studies as CONDOR[42] and GI-REASONS,[43] the primary end point was defined as clinically significant events occurring throughout the GI tract. It was seen that celecoxib, a COX2 inhibitor, generally caused fewer upper- and lower-GI events compared to such ns-NSAIDs as naproxen, ibuprofen, and diclofenac. Table 3 highlights a comparison of lower-GI outcomes in a few major studies.

Most patients (80%–100%) have active mucosal lesions in the small bowel after 2 weeks of low-dose NSAID and PPI therapy.[44] Evidence from shorter studies in healthy volunteers has also shown that short-term NSAIDs use can also cause NSAID enteropathy. Maiden et al reported that slow-release diclofenac use for 2 weeks resulted in macroscopic injury to the small intestine in up to 75% of subjects.[45] Goldstein et al also reported that the background incidence of small-bowel lesions in healthy adults was not insignificant, and 2 weeks of naproxen plus omeprazole resulted in small-bowel mucosal breaks in more than half of volunteers. In comparison, celecoxib was associated with significantly fewer small-bowel mucosal breaks than naproxen plus omeprazole (17% versus 55%).[46] Another study comparing celecoxib with ibuprofen/

omeprazole found similar results (percentage of subjects with small-bowel mucosal breaks was 25.9% for ibuprofen plus omeprazole compared with 6.4% for celecoxib and 7.1% for placebo).[47]

Prevention of NSAID-related GI complications: options
Proton-pump inhibitors
PPIs are antisecretory agents that reduce acid secretion for up to 36 hours.[48] They are commonly used to prevent NSAID-induced peptic ulceration and mucosal injury.[49] Although PPIs have shown to be effective in reducing upper-GI events, video-endoscopy studies have shown that there is a high occurrence of small-intestine damage, despite the fact that patients were given PPIs. Furthermore, animal studies have suggested that PPIs worsen NSAID enteropathy when given together with an NSAID.[39]

Histamine 2-receptor antagonists
Histamine 2-receptor antagonists (H$_2$RAs), which inhibit acid secretion, have also been evaluated for reducing NSAID-associated complications. A meta-analysis of 14 trials found that H$_2$RAs (eg, famotidine and ranitidine) were protective at high doses, but at commonly prescribed doses they reduced the risk of duodenal but not gastric ulcers.[50]

Misoprostol
Misoprostol (a prostaglandin analogue) protects the GI mucosa by stimulating mucus/bicarbonate secretion and stabilizing barrier function.[51] It decreases NSAID-related upper-GI complications by approximately 40% compared with NSAIDs alone.[52,53] High-dose misoprostol
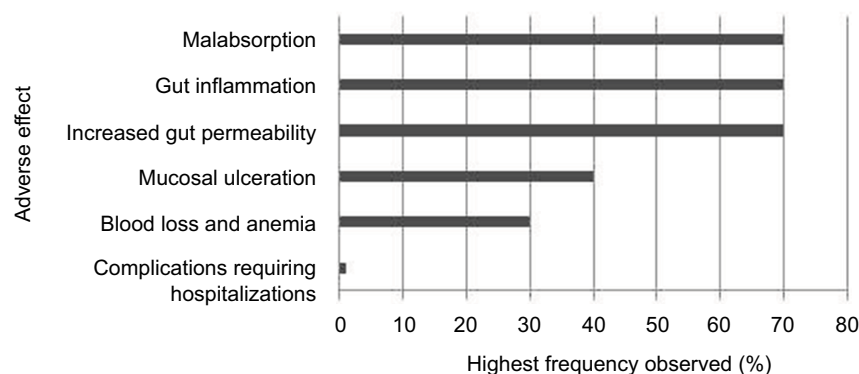

Figure 3 Main adverse effects of NSAIDs in the lower-GI tract.
Note: Data extracted from Lanas and Sopeña.[40]
Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; GI, gastrointestinal.

Table 3 Comparison of lower-GI outcomes

	CONDOR[42]	GI REASONS[43]	MEDAL program[105]	PRECISION[106]
Patients	4,484	8,067	34,701	24,081
Study design	Randomized, double-blind, parallel-group	Prospective, randomized, open-label, blinded end point	Data pooled from three randomized double-blind studies: MEDAL, EDGE, and EDGE II	Randomized, double-blind, parallel-group
Study setting	Investigating centers in 32 countries or territories	Investigating centers in the US	Investigational sites in 46 countries	Investigational sites in 13 countries[107]
Key inclusion	Age ≥60 years Age 18–59 years, increased GI risk[a] Test negative for *Helicobacter pylori*, or confirmed eradication of infection on rescreening visit	Age ≥55 years OA, require daily NSAIDs At least moderate GI risk	Age ≥50 years OA or RA Need chronic NSAIDs, not candidates for paracetamol as first-line therapy, due to severity of symptoms	Age ≥18 years RA or OA that requires daily NSAIDs High CV risk or established CV disease
Primary objective	GI-safety evaluation	GI-safety evaluation	CV-safety evaluation	CV-safety evaluation
Intervention	Celecoxib	Celecoxib	Etoricoxib	Celecoxib
Comparator	Diclofenac SR + omeprazole	ns-NSAIDs	Diclofenac	Naproxen or ibuprofen
Aspirin (low dose)	Excluded	Excluded	Recommended for selected patients[b]	Allowed: 35% target, 46% actual
Primary end point	Clinically significant events occurring throughout the GI tract (CSULGIEs)[c]	CSULGIEs over 6 months[d]	First occurrence of any thrombotic CV events, both venous and arterial	First occurrence of an adverse event that met APTC criteria
Lower GI outcome	Proportion of patients reaching the primary end point during the 6-month study period was 0.9% (95% CI 0.5%–1.3%) in the celecoxib group and 3.8% (95% CI 2.9%–4.3%) in the diclofenac + omeprazole group HR 4.3 (95% CI 2.6–7) in favor of celecoxib	Significantly more ns-NSAID users met the primary end point (2.4%) compared to celecoxib (1.3%) Those taking ns-NSAIDs, even with concomitant PPI use, were at increased risk of mucosal damage throughout the entire GI tract compared with the relative GI-mucosa protection offered by COX2 inhibition via celecoxib	Discontinuations due to GI adverse events were significantly less frequent with etoricoxib than diclofenac Rates of lower-GI clinical events were similar for the two drugs: 0.32 per 100 (95% CI 0.25–0.39) patient-years for etoricoxib and 0.38 per 100 (95% CI 031–0.46) patient-years for diclofenac, yielding an HR of 0.84 (95% CI 0.63–1.13)	Event rate for the composite outcome of serious GI events lower in the celecoxib group than the naproxen group (HR 0.71, 95% CI 0.54–0.93; P=0.01) and lower in the celecoxib group than the ibuprofen group (HR 0.65, 95% CI 0.5–0.85; P=0.002)

Notes: [a]Documented history of gastroduodenal ulceration or GI hemorrhage more than 90 days before screening RA or OA, require regular NSAID treatment for at least 6 months; [b]prophylaxis in patients with established CV, peripheral arterial, cerebrovascular disease, or diabetes; [c]components of the primary end point were gastroduodenal, small-bowel, or large-bowel hemorrhage, gastric-outlet obstruction, gastroduodenal, small-bowel, or large-bowel perforation, clinically significant anemia of defined GI or presumed occult GI origin (including possible blood loss from the small bowel), and acute gastrointestinal hemorrhage of unknown origin (including presumed small-bowel hemorrhage). Clinically significant anemia was defined in the protocol as a decrease in hemoglobin of 20 g/L or more or a decrease in hematocrit of at least 10 percentage points. [d]Included gastroduodenal hemorrhage, gastric-outlet obstruction, gastroduodenal, small-bowel or large-bowel perforation, small-bowel hemorrhage, large-bowel hemorrhage, clinically significant anemia of defined GI origin, symptomatic ulcers, small-bowel obstruction, acute GI hemorrhage of unknown origin, including presumed small-bowel hemorrhage, and clinically significant anemia of presumed occult GI origin, including possible small-bowel blood loss.
Abbreviations: GI, gastrointestinal; OA, osteoarthritis; RA, rheumatoid arthritis; CV, cardiovascular; ns-NSAIDs, nonselective nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitor; CSULGIEs, clinically significant upper- and lower-GI events; APTC, Antiplatelet Trialists Collaboration.

coadministered with indomethacin was found partially to alleviate indomethacin-induced increase in intestinal permeability.[54] Unfortunately, misoprostol is not always well tolerated, due to diarrhea and abdominal pain, preventing continued use; lower doses of misoprostol with a lower frequency of side effects may also be less effective at preventing GI events.[55]

Enteric-coated NSAIDs

Available data indicate that enteric-coated NSAIDs do not reduce the incidence of upper-GI events compared with other formulations,[16] but the use of sustained-release and enteric-coated NSAIDs may possibly shift the site of damage distally.[56] However, this phenomenon has not been widely studied. A small study done using video-capsule endoscopy

found that even short-term administration of enteric-coated daily aspirin is associated with mucosal abnormalities of the small-bowel mucosa.[57]

Topical NSAIDs

Topical NSAID formulations can produce higher concentrations of drug in the local tissue, with very low systemic exposure, as measured via plasma concentrations.[58] Use of topical NSAIDs may also be associated with fewer severe GI events compared to oral NSAIDs.[59] Although topical NSAID formulations have shown to be effective in acute pain[60] and for short-term use in chronic pain, there are contradictory results regarding topical NSAIDs providing effective long-term pain relief.[16]

Lower-dose NSAID formulations

New formulations of NSAIDs may reduce risks of adverse events by using lower doses, while providing effective analgesia. There is some evidence that a few NSAIDs, such as diclofenac, could provide effective pain relief at lower doses than are currently used, assuming that 80% inhibition of COX2 is necessary for therapeutic efficacy.[61]

Selective COX2 inhibitors

Selective inhibition of COX2 leads to decreased inflammation in musculoskeletal tissues, and by sparing COX1, there is a decrease in the incidence of GI mucosal injury.[49] Furthermore, some of these inhibitors are effective in preventing lower-GI events, which are largely mediated by the acidic nature of NSAIDs themselves.[62] According to the CONDOR[42] and GI-REASONS[43] trials, which looked at both upper- and lower-GI events, only celecoxib has been shown to reduce mucosal harm versus NSAIDs throughout the entire GI tract.

Helicobacter pylori eradication

Studies have shown that *Helicobacter pylori* infection has a high prevalence rate in Asia – 54%–76%.[63] This is of concern, as *H. pylori* is etiologically associated with gastroduodenal disease, particularly peptic ulcer disease and gastric malignancies.[64] In fact, the 2008 American College of Cardiology Foundation–American College of Gastroenterology–American Heart Association expert consensus document on reducing the GI risks of antiplatelet therapy and NSAID use recommends testing for and eradicating *H. pylori* in patients with a history of ulcer disease before starting chronic antiplatelet therapy.[65] The 2009 American College of Gastroenterology guidelines on the prevention of NSAID-related ulcer complications also concluded that

H. pylori infection increases the risk of NSAID-related GI complications.[49] One systematic literature review found that *H. pylori* eradication in infected patients was equally effective as the use of PPIs in preventing GI complications due to NSAID use.[66] However, another meta-analysis revealed that although *H. pylori* eradication reduces risk, PPIs provides superior ulcer prevention.[67]

PPIs as standard of care: benefits and risks

The American College of Gastroenterology in 2009 stated that PPIs significantly reduce gastric and duodenal ulcers and their complications in patients taking NSAIDs or COX2 inhibitors.[49] Nonetheless, coadministration of PPIs and NSAIDs contributes to an increased risk of adverse events.[68]

PPIs in comparison with other gastroprotective agents

PPIs control both basal and food-stimulated acid secretions, producing complete and longer-lasting acid suppression than H_2 receptor antagonists (H_2RAs).[8] Also, unlike H_2RAs, tolerance to PPIs has never been observed.[8] Controlled studies of the therapeutic effects of PPIs versus H_2RAs for NSAID-associated gastric ulcers have shown that PPIs had a significantly higher healing rate after 8-week treatment compared to H_2RAs.[7,69] The ASTRONAUT study, which compared omeprazole and ranitidine in the treatment of ulcers associated with NSAIDs, found that at 8 weeks, treatment was successful in a higher percentage of patients on omeprazole (80% for 20 mg, 79% for 40 mg) compared to those on ranitidine (63%).[70] Compared to misoprostol, PPIs also appear to be more effective. In a study comparing the two drugs, maintenance therapy with omeprazole was associated with a lower rate of relapse than misoprostol, although the overall rates of successful treatment of ulcers, erosions, and symptoms associated with NSAIDs were similar for 20 mg omeprazole, 40 mg omeprazole, and misoprostol.[71] However, a systematic review with network meta-analysis showed that selective COX2 inhibitors provide better GI protection compared with a combination of an ns-NSAID plus PPI.[72]

Risks associated with long-term use of PPIs

Patients also experience an increased risk of adverse drug reactions with PPIs.[68] These include an increased risk of chronic kidney disease, dementia, bone fracture, myocardial infarction, infections, micronutrient deficiencies, and GI

malignancies. Figure 4 highlights the potential adverse effects of PPIs, along with their relative risks. However, the overall quality of evidence is either low or very low.[68]

A randomized placebo-controlled trial comparing celecoxib plus PPI versus celecoxib plus placebo found that a significantly higher proportion of subjects in the COX2 plus PPI group developed small-bowel injury than the COX2 plus placebo group. This further proves that the use of PPIs increases the risk of short-term NSAID-induced small-bowel injury. Because PPIs alone cause neither small-bowel mucosal damage nor inflammation, alteration of the luminal environment by PPIs seems to be an exacerbating factor in NSAID-induced small-bowel injuries.[73]

In recent years, there has been growing evidence that PPIs can alter the composition of the gut microbiome, exacerbating NSAID-induced small-intestine injury.[74,75] Jackson et al reported that PPI users had a significantly lower abundance of gut commensals and lower microbial diversity.[75] A study examining the relationship between PPIs and NSAID-induced small-intestine injury also reported that PPIs increased the incidence and severity of NSAID enteropathy, partly due to dysbiosis.[28] This is because alteration of intestinal microbiota contributes to low-grade but chronic inflammation.[9] A meta-analysis evaluating the association between PPIs and small-intestine bacterial overgrowth concluded that that PPI use was statistically associated with small-intestine bacterial overgrowth risk, suggesting that

Figure 4 Potential adverse effects of PPIs and their relative risks.
Notes: Data collated from Freedberg et al.[68] Overall quality of evidence low/very low.
Abbreviations: SIBO, small-intestine bacterial overgrowth; GI, gastrointestinal; PPIs, proton-pump inhibitors; RCT, randomized controlled trial.

this effect could possibly be due to chronic acid suppression and the resultant hypochlorhydria associated with PPI use.[76] Considering that Gram-negative bacteria are an important factor in the pathogenesis of NSAID enteropathy, it is possible that suppression of acid secretion by a PPI could worsen NSAID-induced small-intestine damage.[28]

Appropriate use of PPIs: recommendations from international guidelines

There are several guidelines that provide recommendations on the use of PPIs when NSAIDs are used.

2016 Position paper on safe PPI use

Standard-dose PPIs are recommended for patients taking ns-NSAIDs at risk for upper-GI complications (bleeding and perforation) and for those having had an episode of previous GI bleeding and prescribed selective COX2 inhibitors.[77] In both ns-NSAID and COX2-selective NSAID users, PPI therapy reduces upper-GI symptoms, in particular dyspepsia.[77] However, NSAID-induced adverse events in the lower GI tract are not prevented by PPIs.

American Gastroenterological Association clinical practice updates 2017

The 2017 update recommends that patients take long-term PPIs for NSAID bleeding prophylaxis if at high risk.[68]

American College of Gastroenterology guidelines on management of bleeding ulcers

In patients with NSAID-associated bleeding ulcers who must resume NSAIDs, it is recommended to give a daily PPI together with a COX2-selective NSAID at the lowest effective dose.[78] In patients with low-dose aspirin-associated bleeding ulcers that have been resumed on aspirin for secondary prevention, long-term daily PPI therapy should also be provided.[78]

National Institute for Health and Care Excellence 2014 guidelines on the investigation and management of gastroesophageal reflux disease and dyspepsia in adults

In patients using NSAIDs with diagnosed peptic ulcers, a full-dose PPI or H_2RA for 8 weeks should be offered,
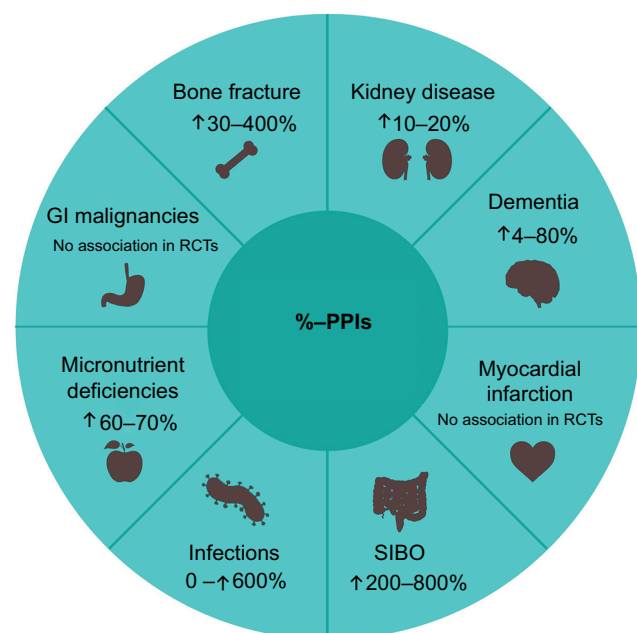
and NSAIDs should be stopped where possible.[79] Further, *H. pylori*-eradication therapy should be offered if bacteria are present. In high-risk patients (previous ulceration) for whom NSAID continuation is necessary, a PPI together with the NSAID should be prescribed. A COX2-selective NSAID is preferred over a standard NSAID.[79]

Deprescribing PPIs

Coadministration of NSAIDs–PPIs is widely used and still regarded as safe and standard medical practice.[9] Use of PPIs for ulcer prophylaxis in low-risk patients is often perceived by doctors as a harmless and relatively inexpensive remedy.[8] Also, many patients continue to take PPIs beyond the recommended course of treatment. This of course has potential for harm, as well as large economic implications.[80] Deprescribing PPIs, however, may be important and clinically relevant in many patients taking NSAIDs. For example, patients who require chronic pain medication tend to be older (≥65 years),[81] and thus more likely to have comorbidities. Hence, NSAID–PPI coprescription will likely contribute to polypharmacy and increase risks along with additive side effects, especially those affecting the lower GI.

Benefits of deprescribing

Prescribing a PPI together with an NSAID as ulcer prophylaxis is an example of a prescribing cascade. It can result in further harm to the patient.[82] As seen from evidence on the effects of PPIs on gut microbiota, we see how a prescribing cascade exacerbates the adverse events of NSAIDs. Deprescribing will reduce the risk of adverse events of NSAIDs. Deprescribing will also decrease risks of nonadherence. A cohort study in Italy found that among the 100 patients recruited, nonadherence was reported for 49 (55.1%) at the first follow-up and 55 (69.6%) at the second follow-up. The number of drugs prescribed at discharge was related to patient lack of adherence at follow-up.[83] This may have had a negative impact on the clinical and economic outcomes of patients' various conditions.

Despite the numerous guidelines on prescribing PPIs and NSAIDs, there is only one on the deprescription of PPIs. Recently, the College of Family Physicians of Canada developed a set of guidelines after a systematic review of PPI-deprescribing trials and examination of reviews of harm from long-term PPI use.[80]

Recommendations from Canada College of Family Physicians guidelines on deprescribing PPIs

When should PPIs be deprescribed?

Not all patients are suitable candidates for PPI deprescription. Patients with risk factors for GI bleeding or ulcers will have a high risk of relapse, and thus will not be suitable candidates.[78] Nonetheless, even though PPIs are widely used as they are seen to be generally safe and effective,[84] they should not be continued if they are not indicated. Recent studies have suggested that PPIs alter intestinal microbiota and are involved in the pathogenesis of NSAID enteropathy.[85] Adults who have completed a minimum of 4 weeks of PPI treatment for heartburn or mild–moderate gastroesophageal reflux disease or esophagitis whose symptoms are resolved are ideal examples where PPI deprescription should be considered. This should exclude patients with Barrett esophagus, severe esophagitis grade C or D, or documented history of bleeding GI ulcers.[80] PPIs, however, should not be deprescribed in chronic NSAID users with bleeding risk.[86]

How to deprescribe PPIs?

Reducing the dose or switching to on-demand use

The Canadian guidelines strongly recommend lowering the dose or switching to on-demand use.[80] Lowering the dose will lead to a lower risk of symptom relapse compared to switching to on-demand use. However, on-demand use will help to lower pill burden and cost.

Abrupt discontinuation or tapering

Alternatively, the PPI can just be discontinued abruptly or tapered slowly. There is evidence that an abrupt discontinuation increases the risk of symptom relapse, and thus patients should be tapered to the lowest effective dose before discontinuation.[80] Patients can also be provided symptomatic relief with on-demand PPI.

Monitoring and nonpharmacological management

The patient should be monitored at 4 and 12 weeks for such symptoms as heartburn, dyspepsia, regurgitation, or epigastric pain.[80] The patient may exhibit nonverbal symptoms, such as loss of appetite, weight loss, and agitation. If symptoms return, nondrug strategies can be used: avoid meals 2–3 hours before bedtime, elevate head of bed, address need for weight loss, and avoid dietary triggers.[87] Over-the-counter drugs, such as H_2RAs, PPIs, antacids,

and alginates, can also be used, although the use of daily H$_2$RAs is only weakly recommended, due to a higher risk of symptom relapse.

Appropriate use of PPIs in patients on NSAIDs: when and why?
Managing upper-GI damage

According to the guidelines available, PPIs are still essential in the treatment and prophylaxis of NSAID-induced upper-GI injury.[86] However, their prescription for this indication should be based on appropriate recommendations from worldwide published guidelines.[8] Also, it is essential to reduce their continuation after the patient's discharge from hospital by assessing the true need on a case-by-case basis and periodically reviewing the long-term intake.[8] Table 4 summarizes some risks and benefits of using PPIs.

Managing lower-GI damage

Much of the data available are catered toward upper-GI protection. Scarpignato et al[77] provided general guidance on prescription of NSAIDs and PPIs based on cardiovascular and GI risk of the patient. However, this was based only on upper-GI risk. At present, there are no comprehensive guidelines on how and when to prescribe PPIs for the prophylaxis of both upper- and lower-GI injury in NSAID users. Although several international guidelines touch on this issue, they do not explicitly state what to do in the event that a low-GI-risk patient becomes a high-risk one or what to do in the event that the first-line decision fails. Perhaps it is time to reconsider the use of PPIs together with NSAIDs.

Switching or starting with a COX2 inhibitor rather than an ns-NSAID

The most updated consensus on chronic NSAID prescription recommends that ns-NSAIDs can be used in patients with low GI risk, but COX2 inhibitors should be prescribed to those with high GI risk.[86] Therefore, if a patient develops GI problems during treatment with ns-NSAIDs, he/she could possibly be switched to a COX2 inhibitor. However, even if NSAID therapy is discontinued, lesions in the small intestine

tend to persist,[87] and thus switching agents may not aid in healing of ulcers. Also, Zhao et al reported that patients on ns-NSAIDs were more likely to switch therapy than those on COX2-specific inhibitors.[88]

As such, we should question whether switching to COX2 inhibitors is a suitable strategy after a patient who continues to need NSAIDs develops GI ulcers. A meta-analysis found that COX2 inhibitors when compared with NSAIDs plus PPIs significantly reduced the risk of perforation, obstruction, bleeding, diarrhea, and withdrawal due to GI adverse events.[89] Perhaps a better strategy would be to start patients on COX2 inhibitors, as they have a lower risk of causing GI events compared to ns-NSAIDs.

Use of probiotics in preventing lower-GI tract injury

Results for probiotic use in preventing NSAID-induced lower-GI injury are promising, showing that probiotic use reduces small-bowel injury in either aspirin or NSAID users.[90,91] This suggests a potential strategy for prophylaxis. However, the studies conducted had only a small sample size, and thus larger studies are needed. At present, there is insufficient evidence to recommend a specific probiotic strain to prevent lower-GI injury. However, some bacteria have demonstrated AI activity and a protective effect on intestinal mucosa.[85]

Use of H$_2$RAs for less profound suppression of acid

Most evidence indicates that PPIs are more effective than H$_2$RAs in the prophylaxis and treatment of NSAID-induced GI injury. Nonetheless, a recent study comparing the efficacy of PPIs vs H$_2$RAs in reducing risk of upper-GI bleeding and ulcers in high-risk users of low-dose aspirin showed that the two agents had similar efficacy in the prevention of recurrent ulcers. These patients had a history on endoscopically confirmed ulcer bleeding, and were restarted of aspirin plus PPI or aspirin plus H$_2$RA after the ulcer was healed.[92] Perhaps H$_2$RAs could be used to prevent both upper- and lower-GI injury. H$_2$RAs produce less profound suppression of acid compared to PPIs,[93] and could result in less alteration to the gut flora.

Table 4 Benefits versus risks for PPI use

Benefits	Risks
• Reduces the occurrence of NSAID-induced upper-GI events • Treats upper-GI bleeding and lesions	• Offers no lower-GI protection • Risk of adverse events, especially with long-term use • Problems associated with polypharmacy

Note: Information from Scarpignato et al.[86]
Abbreviations: PPI, proton-pump inhibitor; NSAID, non-steroidal anti-inflammatory drug; GI, gastrointestinal.

Regular monitoring

In a European survey investigating primary-care physician behavior and understanding, it was found that only half of the doctors measured their osteoarthritis patients' hemoglobin routinely as part of a complete blood count.[94] Although GI-injury prophylaxis is important, regular monitoring is still essential to allow early detection of injury so that treatment can be administered, and also to prevent development of complications. Hemoglobin levels can be used as an indicator of GI injury; low hemoglobin and hematocrit are attributable to blood loss in the absence of other evident causes.[95] The CONDOR trial, which looked at both upper- and lower-GI events, also investigated the frequency of clinically significant blood loss measured by decreases ≥2 g/dL in hemoglobin throughout the GI tract.[42] A drop in hemoglobin ≥2g/dL has been well recognized as a surrogate end point in clinical trials investigating the GI toxicity of NSAIDs conducted over the last 20 years.[42,94,96–98]

Conclusion

The coprescription of PPIs and NSAIDs has benefited patients at risk of upper-GI ulcers and bleeding. However, this common prescribing practice may have potentially deleterious effects on small-bowel mucosa, possibly through a combination of gut dysbiosis and increased intestinal permeability. Accumulating data from several recent large-scale human studies suggest that the use of a lower-acidity COX2 inhibitor may be a suitable strategy for patients who are at high risk of both upper- and lower-GI adverse events.

Author contributions

All authors were involved in conception, design, and analysis and interpretation of data. All authors were also involved in preparation of the manuscript, revising it for important intellectual content and final approval before submitting it for publication.

Acknowledgment

Disclosure

SS and GL are employees of Pfizer. VG underwent indirect patient-care pharmacy training for 3 months at Pfizer, Singapore. KAG reports no conflicts of interest in this work.

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