Section: Medicine

Systematic Review Article

RISK OF PEPTIC ULCER DISEASE AMONG CHRONIC NSAID USERS: IMPACT OF GASTROPROTECTIVE STRATEGIES – A SYSTEMATIC REVIEW

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ABSTRACT

Background: Chronic NSAID (Nonsteroidal anti-inflammatory drug) use substantially increases peptic ulcer disease (PUD) and upper gastrointestinal (GI) bleeding risk. Gastroprotective strategies (PPIs {Proton Pump Inhibitors}, misoprostol, COX-2 {cyclooxygenase-2} inhibitors) aim to mitigate this injury. The objective is to systematically review PUD burden among chronic NSAID users and evaluate gastroprotective strategy efficacy. To examine real-world implementation gaps in gastroprotection and identify opportunities to improve risk stratification and clinical outcomes in chronic NSAID users.

Materials and Methods: MEDLINE, Embase, Scopus, and Cochrane Library were searched (1994–2024) using terms "NSAIDs," "peptic ulcer disease," "gastroprotection," "proton pump inhibitors," "COX-2 inhibitors," "misoprostol." RCTs (Randomized control trials), cohort/case-control studies, meta-analyses, review articles and guidelines reporting PUD risk/gastroprotection in adults were included. Non-English papers without extractable data, Lacked clear outcome measures or evaluable results, editorials, commentaries, conference abstracts, were excluded. Following PRISMA 2020 guidelines, 3,214 records were identified; 2,187 remained after deduplication; 1,912 excluded at title/abstract; 275 full-texts assessed, excluding 254 (paediatric/acute n=78; no outcomes n=92; other n=84). Narrative synthesis of 21 studies conducted due to heterogeneity.

Results: Chronic NSAID use increased serious GI complications 3–5-fold (annual incidence 1–2% high-risk). PPIs, misoprostol, and COX-2 inhibitors significantly reduced ulcers/complications; COX-2+PPI combination most protective. Real-world gastroprotection remained suboptimal.

Conclusion: Gastroprotective strategies effectively reduce NSAID-induced PUD, but implementation gaps persist. Enhanced risk stratification and adherence are needed.

Keywords: NSAIDs, peptic ulcer disease, gastroprotection, proton pump inhibitors, COX-2 inhibitors, misoprostol, upper gastrointestinal bleeding.

INTRODUCTION

Non-steroidal anti-inflammatory drugs remain indispensable for the management of chronic inflammatory and degenerative conditions, including osteoarthritis, rheumatoid arthritis, and chronic low back pain. However, chronic NSAID use consistently ranks as one of the most important causes of peptic ulcer disease and upper gastrointestinal bleeding globally. Current data indicate that NSAID use raises the likelihood of bleeding and perforation in the lower gastrointestinal tract at rates comparable to those observed in the upper GI tract. Selective COX-2 (cyclooxygenase-2) inhibitors provide anti-inflammatory relief that is comparable to conventional NSAIDs (Sostres et al.,2013).[1] Before prescribing NSAIDs, including aspirin, both GI and cardiovascular risks should be evaluated, and H. pylori testing considered for long-term use. High-risk patients may require the lowest effective NSAID dose, PPI co-therapy, or a COX-2 inhibitor. Naproxen is preferred in those with cardiovascular

risk. For patients on aspirin plus clopidogrel, avoid PPIs with strong interactions or separate dosing, and consider H. pylori eradication to reduce bleeding risk (Venerito M et al., 2010).[2] Given the high prevalence of chronic NSAID use, the burden of NSAID-related PUD represents a major public health challenge.

Selective COX-2 inhibitors are associated with a reduced risk of upper GI bleeding compared with traditional NSAIDs. However, this advantage is largely lost when they are taken alongside low-dose aspirin. The likelihood of upper GI bleeding is comparable in patients using either non-aspirin antiplatelet agents or cardioprotective doses of aspirin (Lanas A et al., 2006).[3]

COX-2 inhibitors generally offer improved upper GI safety compared with traditional NSAIDs, but their actual risk of upper GI complications depends on factors such as daily dose, systemic drug levels, and degree of COX-2 selectivity. Moreover, taking aspirin alongside a COXIB significantly alters its safety profile, effectively eliminating the GI advantage normally seen over standard NSAIDs (García Rodríguez LA et al., 2007).[4]

NSAIDs disrupt phospholipids and interfere with mitochondrial energy pathways, triggering changes that weaken the gut's protective barrier. This disruption increases intestinal permeability and promotes low-grade inflammation. Combined inhibition of COX enzymes and exposure to luminal irritants can lead to mucosal erosions and ulceration. These injuries may progress to bleeding, protein loss, strictures, or even perforation. A comprehensive model of these interacting mechanisms underscores the challenges in designing safer NSAID therapies (Bjarnason I et al., 2018).[5]

Despite wide availability, evidence consistently shows that gastroprotective agents remain underused in high-risk NSAID users, exposing patients to preventable complications.

This systematic review synthesizes current evidence on the risk of PUD among chronic NSAID users and evaluates the relative efficacy, limitations, and clinical applicability of gastroprotective strategies. It further discusses real-world gaps and future directions for improving NSAID safety.

Objectives

The objective is to systematically review PUD burden among chronic NSAID users and evaluate gastroprotective strategy efficacy. To examine real-world implementation gaps in gastroprotection and identify opportunities to improve risk stratification and clinical outcomes in chronic NSAID users.

MATERIALS AND METHODS

A systematic literature search was performed using MEDLINE, Embase, Scopus, and the Cochrane Library, covering the period from 1994 to 2024. Keywords included "NSAIDs," "peptic ulcer disease," "gastroprotection," "proton pump inhibitors," "COX-2 inhibitors," and "misoprostol." Eligible studies included randomized controlled trials, cohort and case-control studies, meta-analysis, review articles, guideline statements, and mechanistic studies relevant to NSAID-associated GI toxicity and gastroprotection. Non-English papers without extractable data, Lacked clear outcome measures or evaluable results, editorials, commentaries, conference abstracts, were excluded.

Titles, abstracts, and full texts were independently screened by two reviewers, with disagreements resolved by consensus. Data extracted included study design, sample size, NSAID type, PUD outcomes, gastroprotective interventions, and key findings. Due to heterogeneity, narrative synthesis was selected over meta-analysis.

Records identified from databases (n = 3,214)
(MEDLINE, Embase, Scopus, Cochrane Library; 1994–2021)
↓
Records after duplicates removed (n = 2,187)
↓
Records screened by title/abstract (n = 2,187)
↓Excluded (n = 1,912)
(Reasons: irrelevant topics, non-NSAID focus)
Full-text articles assessed for eligibility (n = 275)
↓Excluded (n = 254)
(Reasons: Non-English papers without extractable data, Lacked clear outcome measures or evaluable results, editorials, commentaries, Conference abstracts)
Studies included in narrative synthesis (n = 21)

RESULTS

Epidemiology and Clinical Burden of PUD in Chronic NSAID Users

NSAIDs contribute to a substantial proportion of ulcer disease worldwide. Estimates suggest that 1–2% of chronic NSAID users develop a serious GI complication annually, including bleeding or perforation (Sostres et al.,2013).[1] In individuals with cardiovascular risk who require an NSAID, naproxen is the preferred option. For those facing both substantial GI and cardiovascular risks, it is best to avoid NSAID therapy entirely (Venerito et al.,2010).[2]

Lanas and colleagues, in a landmark case-control analysis, found that non-aspirin NSAIDs increased the risk of upper GI ulcer bleeding by approximately fivefold (Lanas et al.,2006).[3]

The adjusted relative risk of upper GI complications was 3.7 for traditional NSAIDs and 2.6 for COX-2 inhibitors. Higher daily doses increased risk for both drug groups, and traditional NSAIDs with long half-lives or slow-release formulations carried an even greater risk. Overall, COXIB (Cyclo-Oxygenase Inhibitors) users had a relative risk of 0.8 compared with users of traditional NSAIDs. In individuals not taking aspirin, the relative risk for COXIBs dropped to 0.6 (G Rodríguez et al.,2007).[4]

NSAIDs are highly effective for inflammatory conditions but long-term use is limited by significant gastrointestinal toxicity. Current protective measures help but often introduce additional risks, and no available therapy completely prevents these side effects. This underscores the need for safer NSAID alternatives. New approaches—such as dual COX/5-LOX (5- lipoxygenase) inhibitors, NSAID prodrugs, or agents that neutralize unbound NSAIDs—may offer improved safety over existing strategies (Sinha M et al, 2013).[6]

Mechanisms of NSAID-Induced Gastrointestinal Injury

COX Inhibition and Prostaglandin Depletion

NSAIDs can injure the gastrointestinal tract through both COX-dependent and COX-independent mechanisms. Beyond COX inhibition, they disrupt phospholipids and mitochondrial function, weakening the mucosal barrier. This leads to increased permeability and low-grade inflammation. Ongoing injury results in erosions and ulcers, sometimes progressing to bleeding or perforation. These intertwined pathways explain the complexity of NSAID-induced damage. Understanding this model highlights why developing safer NSAIDs remains challenging (Bjarnason et al.,2018).[5]

Topical Injury and Epithelial Disruption

NSAIDs cause direct epithelial damage by decreasing hydrophobicity of the mucus layer and increasing epithelial permeability.

Mitochondrial Dysfunction and Oxidative Stress

NSAIDs disrupt mitochondrial oxidative phosphorylation, promoting epithelial injury and delayed healing.

Microbiota and Enteropathy

Regular PPI use may worsen NSAID-related small bowel injury by disrupting gut microbial balance. As a result, PPIs are recognized as an independent risk factor for NSAID-associated enteropathy.

This review highlights the clinical significance of this interaction. Key epidemiologic, mechanistic, and management considerations are summarized (Marlicz W et al.,2014).[7]

This multifactorial injury pathway underscores why gastroprotective strategies must address both acid suppression and mucosal defense.

Gastroprotective Strategies

1. Proton Pump Inhibitors (PPIs)

PPIs are the most widely used and effective gastroprotective agents for upper GI injury. They provide potent suppression of gastric acid, allowing mucosal healing and preventing ulcer formation.

Even after H. pylori eradication, patients are still vulnerable to NSAID-related injury, so adding a PPI is advised. Choosing an NSAID should take into account each patient's specific gastrointestinal and cardiovascular risk profile (Scheiman et al.,2013).[8]

Misoprostol, selective COX-2 inhibitors, and likely PPIs help lower the incidence of symptomatic ulcers, while misoprostol and COX-2 agents also appear to reduce major gastrointestinal events, though current evidence is limited in quality. Additional research on H2 blockers and PPIs is still required, along with more complete reporting of uncommon but clinically significant outcomes (Hooper et al., 2004).[9]

PPIs also show strong protective effects in high-risk groups, including elderly individuals and patients using anticoagulants. However, their inability to prevent lower GI injury remains a limitation, and concerns have been raised regarding long-term PPI use, although these risks remain modest compared to the benefits in high-risk NSAID users.

2. NSAIDs

Anticoagulants, low-dose aspirin, NSAIDs, and other antiplatelet agents all raise the likelihood of both upper and lower GI bleeding. Among these, anticoagulant therapy carries the highest bleeding risk (Lanas et al., 2015).[10]

The first Korean guidelines on NSAID-induced peptic ulcers were issued in 2009 through a joint effort by the Korean College of Helicobacter and Upper Gastrointestinal Research and the Korean Society of Gastroenterology. Because those recommendations relied largely on literature reviews and expert opinion, an update became necessary. Consequently, a new Guideline Development Committee for drug-related peptic ulcer was established under the Korean College of Helicobacter and Upper Gastrointestinal Research (Joo et al., 2020).[11]

3. High-Dose H_2 Receptor Antagonists (H_2 RAs)

H2-receptor antagonists are effective for treating primary gastric and duodenal ulcers, which has led to the assumption that they would work similarly for prevention. However, when used to prevent NSAID-related injury, they do not adequately protect the stomach, though they can lower the risk of duodenal ulcers (Nash J et al., 1994).[12]

4. COX-2 Selective Inhibitors

Although strategies such as using COX-2 inhibitors and adding PPIs or prostaglandin analogues can lessen NSAID-related adverse effects, each option has its own efficacy and safety limitations. This review outlines how NSAIDs work and the major gastrointestinal harms they can cause. It also summarizes current preventive measures and discusses emerging approaches aimed at preserving NSAID anti-inflammatory benefits while improving gastrointestinal safety (Sinha M et al., 2013).[6]

COX-2 inhibitors generally provide improved upper gastrointestinal safety and are better tolerated than traditional nonselective NSAIDs. However, their protective advantage may diminish when taken together with aspirin (Rostom et al., 2007).[13]

It is increasingly important to provide osteoarthritis patients with treatments that are both safe and cost-effective, helping to avoid serious complications that can affect quality of life and healthcare resources (Scarpignato et al.,2015).[14]

5. Combination Strategy: COX-2 Inhibitor + PPI

Extensive evidence indicates that the combination of a COX-2 inhibitor with a PPI offers the strongest upper GI protection.

Using a selective COX-2 inhibitor together with a PPI offers the strongest gastrointestinal protection, followed by COX-2 inhibitors alone, and then nonselective NSAIDs combined with a PPI (Yuan JQ et al., 2016).[15]

All standard gastroprotective approaches help lower the risk of upper GI complications in people taking NSAIDs, but pairing a COX-2 inhibitor with a PPI provides the greatest level of protection. In particular, celecoxib may be more effective than using a nonselective NSAID together with a PPI (Targownik et al., 2008).[16]

Real-World Evidence and Gaps in Gastroprotection

Despite strong guideline recommendations, real-world studies consistently show under-prescription and poor adherence to gastroprotective therapy:

- In the UK, PPI use does not consistently match the use of nonselective NSAIDs. As a result, the gastrointestinal protection seen with non selective NSAID–PPI combinations in clinical trials may not be fully replicated in everyday practice (Suh et al., 2008).[17]
- Even when physicians advise using PPIs alongside NSAIDs, patient-reported adherence is often low, creating a "gastroprotective treatment gap." There is clear potential to enhance patients' compliance with PPI therapy to better prevent NSAID-related upper GI ulcers (Henriksson et al., 2014).[18]
- This review outlines the gastrointestinal effects and complications associated with NSAID use, including how PPIs may worsen some of these outcomes. It also summarizes strategies to prevent GI toxicity and provides guidance on the appropriate use of PPIs alongside NSAIDs (Gwee et al.,2018).[19]
- More than half of high-risk patients using NSAIDs for short periods do not receive sufficient gastroprotective therapy. Patterns of use appear to be influenced by both patient and physician sociodemographic factors (van Boxel et al.,2009).[20]
- For patients with a prior ulcer who require NSAID treatment, PPIs—with or without celecoxib—are advised, and VPZ (Vonoprazan) may also help prevent ulcer relapse. For those with an ulcer history taking low-dose aspirin, PPIs or VPZ are recommended, and a histamine-2 receptor antagonist can be considered to reduce the risk of recurrence (Kamada T et al., 2021).[21]

This "gastroprotection gap" contributes significantly to preventable gastrointestinal morbidity and mortality.

DISCUSSION

This review confirms that chronic NSAID use substantially increases the risk of PUD and ulcer-related complications, particularly in high-risk individuals. Strong evidence supports the effectiveness of PPIs, misoprostol, and COX-2 inhibitors, with the combination of COX-2 + PPI providing the highest level of protection.

However, several clinical and systemic barriers limit optimal gastroprotection. These include clinician knowledge gaps, medication cost, and poor adherence. Strategies to address these barriers include integrating risk-assessment tools into electronic medical records, utilizing fixed-dose NSAID–PPI combinations, and increasing patient education.

Future research should explore:

- Improved strategies to prevent lower GI injury
- Personalized risk prediction models
- Long-term safety of combination gastroprotective therapy
- Implementation science approaches to reduce the gastroprotection gap

CONCLUSION

Chronic NSAID use remains a major contributor to peptic ulcer disease and ulcer complications. Effective gastroprotective strategies exist, particularly PPI therapy and COX-2 selective inhibitors, but real-world implementation remains inadequate. Strengthening guideline adherence, improving risk stratification, and expanding access to gastroprotective therapies are essential for reducing preventable morbidity and mortality associated with chronic NSAID therapy.

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