

Review Article

Non-steroidal anti-inflammatory drug-induced gastric ulcers: A review on some current issues

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for their analgesic, antipyretic, and anti-inflammatory effects, but with associated risks. A comprehensive literature search was conducted to identify mechanisms of NSAID-induced gastric ulcers, risk factors and conditions that exacerbate NSAID-induced gastric ulcers, local and systemic risks and management. Key risk factors, such as age, *Helicobacter pylori* infection, high-dose usage, and co-morbidities, exacerbate the risk of NSAID-induced ulcers and highlight the need for careful prescription practices. Effective preventive strategies using drugs such as proton pump inhibitors (PPIs), misoprostol, and selective COX-2 inhibitors, reduce ulcer risk with potential side effects. This review identifies several limitations in the current study, including methodological variability, underrepresentation of high-risk populations, and limited data on long-term effects. Future studies should focus on long-term investigations, genetic risk stratification, and alternative pain management approaches to mitigate the adverse effects of NSAIDs while preserving therapeutic benefits. A multi-disciplinary approach, incorporating pharmacologic and non-pharmacologic strategies, is essential to improving patient outcomes and minimizing NSAID-induced gastric ulcers.

Keywords: NSAIDs, Gastric ulcers, Pain, Patient safety

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for their analgesic, antipyretic, and anti-inflammatory effects, commonly prescribed for conditions such as arthritis, musculoskeletal disorders, and general pain management. These drugs primarily act by inhibiting cyclooxygenase (COX) enzymes involved in prostaglandin synthesis. They are

further categorized into several classes which include salicylates (e.g., aspirin), propionic acid derivatives (e.g., ibuprofen, naproxen), acetic acid derivatives (e.g., diclofenac, indomethacin), enolic acid derivatives or oxicams (e.g., meloxicam, piroxicam), fenamates (e.g., mefenamic acid), selective COX-2 inhibitors or coxibs (e.g., celecoxib), naphthylalkanones (e.g., nabumetone), and pyrazolones (e.g., metamizole) [1,2]. Widespread accessibility,

including the availability of over-the-counter medications, underscores their clinical and economic importance globally. For example, the global NSAIDs market was valued at approximately USD 21.56 billion and is projected to reach USD 33.55 billion by 2032 and this growth is driven by factors such as aging population, increasing prevalence of chronic pain conditions, and a preference for non-opioid pain relief options [3].

Despite the benefits, their association with gastrointestinal (GI) complications, particularly gastric ulcers, is a major health concern. Gastric ulcers are defined as localized erosions in the stomach lining resulting from an imbalance between gastric acid secretion and the stomach's protective mucosal barriers [4]. Non-steroidal anti-inflammatory drugs (NSAIDs) disrupt this balance by inhibiting the cyclooxygenase-1 (COX-1) enzyme, which plays a key role in maintaining the integrity of gastric mucosa. Without COX-1, the stomach becomes more susceptible to acid damage, leading to ulceration [5]. The relevance of studying NSAID-induced gastric ulcers has increased due to the prevalence of long-term NSAID use, especially among older populations who frequently suffer from chronic pain. This population is at a particularly high risk of developing NSAID-induced gastric ulcers, which may result in several GI complications including death [6]. Data suggest that approximately 30 - 40 % of chronic NSAID users develop gastric lesions, and around 10 - 20 % may experience symptomatic ulcers or ulcer-related complications [7]. Given these substantial risks, this review investigated the mechanisms by which NSAIDs induce gastric ulcers, identify risk factors, discuss the broader health impacts of NSAIDs, and review strategies to prevent and manage NSAID-induced gastric ulcers.

Mechanism of NSAID-induced gastric ulcer

Non-steroidal anti-inflammatory drugs (NSAIDs) exert their effect by inhibiting cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2. While COX-2 is predominantly involved in inflammatory responses, COX-1 is constitutively expressed and vital for physiological functions, particularly in the gastric mucosa where it facilitates prostaglandin synthesis [8]. Prostaglandins play a protective role in the stomach by stimulating mucus and bicarbonate secretion, maintaining mucosal blood flow, and promoting cellular repair. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit COX-1, thereby reducing prostaglandin levels, and making the gastric lining vulnerable to acid-

induced damage [9]. Numerous studies have highlighted the significant role of COX-1 inhibition in the development of NSAID-induced ulcers. In a meta-analysis involving over 10,000 NSAID users, Hernández-Díaz and Rodríguez [10] observed a fourfold increase in the risk of upper GI complications, including ulcers and bleeding, among those using non-selective NSAIDs (inhibit both COX-1 and COX-2). Similarly, Foong [11] demonstrated that the extent of COX-1 inhibition directly correlates with the degree of gastric mucosal injury, showing that NSAIDs with greater COX-1 selectivity are associated with higher ulcer risks.

Animal studies have provided insights into the biochemical pathways that exacerbate mucosal injury under NSAID treatment. Studies by Takeuchi *et al* [9] demonstrated that NSAIDs led to significant oxidative stress in gastric tissues, further weakening the mucosal barrier. This oxidative damage triggers inflammatory responses that amplify tissue injury, indicating a cascade effect initiated by COX-1 inhibition. In human studies, Sostres and Lanás [5] corroborated these findings, showing that NSAID-induced oxidative stress were detected through biomarkers like lipid peroxides in patients with gastric ulcers. Selective COX-2 inhibitors, such as celecoxib, offer a potential alternative by sparing COX-1 and thereby reducing gastric ulceration risks. Previous study [12] indicated that selective COX-2 inhibitors showed lower GI risk profiles compared to non-selective NSAIDs, with a reduced incidence of endoscopically detected ulcers. However, despite these advantages, selective COX-2 inhibitors have been associated with cardiovascular risks, limiting their usage among individuals with pre-existing heart conditions [13]. Consequently, the trade-off between gastric protection and cardiovascular safety complicates the decision-making process regarding NSAIDs selection.

Risk factors and conditions that exacerbate NSAID-induced gastric ulcers

Several risk factors predispose individuals to NSAID-induced gastric ulcers, encompassing patient characteristics, medication-related variables, and lifestyle factors. Age remains a primary risk factor, with older adults showing a higher susceptibility to ulcer formation due to age-related decrease in mucosal defense mechanisms and higher prevalence of comorbidities [5]. In a study analyzing NSAID-related hospital admissions, Valkhoff [14] found that individuals over 65 had a threefold increased risk of GI complications compared to younger

patients, underscoring age as a vital risk factor in NSAID-induced GI toxicity.

Presence of *Helicobacter pylori* (*H. pylori*) infection is another significant risk factor that amplifies NSAID-induced gastric mucosal injury. *H. pylori* infection itself is a well-known cause of peptic ulcers, and its co-existence with NSAID use has been shown to increase ulcer risk significantly. Lanas and Chan [15] demonstrated that patients with concurrent *H. pylori* infection and NSAID use have nearly double the risk of ulcer complications compared to those using NSAIDs alone. The bacterium exacerbates mucosal injury by inducing an inflammatory response and weakening mucosal defenses, thus potentiating the harmful effects of NSAIDs.

Medication-related factors such as dosage and duration of NSAID use are also pivotal. High-dose and prolonged NSAID therapy has been strongly linked to increased risk of ulceration. A large cohort study by Valkhoff [14] reported a dose-dependent increase in GI hospital admissions among NSAID users, with high doses correlating with a threefold higher risk of complications. Furthermore, NSAIDs taken in combination with corticosteroids or anticoagulants further elevate ulcer risk, as these medications also impair gastric mucosal defenses or promote bleeding tendencies [16].

Lifestyle factors such as smoking, and alcohol consumption also exacerbate NSAID-induced gastric injury. Smoking has been shown to impair mucosal blood flow and delay healing of ulcerative lesions, while alcohol irritates the gastric lining and increases acid secretion [17]. Collectively, these findings underscore the complex interplay between patient characteristics, co-morbidities, and lifestyle factors in developing NSAID-induced gastric ulcers.

Systemic and GI risks of NSAID

In addition to their role in gastric ulcer formation, NSAIDs are associated with a variety of adverse effects that impact other organ systems, including the kidneys, cardiovascular system, and lower gastrointestinal tract. These risks emphasize the importance of cautious NSAID use, especially in individuals with pre-existing health conditions.

Renal risks and NSAID-induced nephrotoxicity

Non-steroidal anti-inflammatory drugs (NSAIDs)-induced nephrotoxicity is a well-documented consequence of long-term use, especially among

populations predisposed to renal impairment, such as the elderly or those with pre-existing kidney disease [18]. Non-steroidal anti-inflammatory drugs (NSAIDs) usage may lead to acute kidney injury (AKI) by reducing renal blood flow through inhibition of COX enzymes responsible for prostaglandin production, which normally helps maintain renal perfusion. Previous study [19] indicated that chronic NSAID use was associated with significant increase in the risk of developing chronic kidney diseases (CKD), with frequent NSAID users exhibiting a nearly twofold increase in CKD prevalence compared to non-users. Furthermore, Whelton and Hamilton [20] revealed that even short-term NSAID use may renal complications in patients with compromised renal function, especially when administered alongside other nephrotoxic agents such as diuretics or angiotensin-converting enzyme inhibitors. These findings underscore the need for renal monitoring in patients prescribed NSAIDs, particularly those with additional risk factors for kidney disease [18].

Cardiovascular risks associated with NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs), particularly selective COX-2 inhibitors, have been linked to increased risk of cardiovascular effects, including myocardial infarction, heart failure, and stroke [13]. Inhibition of COX-2 in vascular endothelium reduces prostacyclin production, which normally counterbalances thromboxane and provides a vaso-protective effect. When this balance is disrupted, the risk of thrombotic events increases. In a meta-analysis of randomized controlled trials, McGettigan and Henry [21] reported that the use of selective COX-2 inhibitors like celecoxib and rofecoxib was associated with a 1.4-fold increased risk of myocardial infarction compared to non-selective NSAIDs. Non-selective NSAIDs also carry cardiovascular risks, particularly at higher doses or with prolonged use. A large cohort study by Barcella [22] found that diclofenac (a commonly prescribed NSAID) was associated with higher incidence of cardiovascular complications relative to ibuprofen or naproxen. These findings suggest that the choice of NSAID should be carefully considered in patients with cardiovascular risk factors.

Impact on the lower gastrointestinal tract

While gastric ulcers are the most recognized GI complications of NSAIDs, these drugs also cause damage to the lower GI tract, leading to conditions such as small intestinal ulcers, bleeding, and NSAID-induced enteropathy. Enteropathy caused by NSAID is marked by

increased intestinal permeability, inflammation, and ulcer formation, which lead to protein loss and anemia. Shin [23] conducted endoscopic studies and revealed that NSAID-induced damage in the small intestine occurred in 40 % of chronic NSAID users, often presenting without immediate symptoms that characterize upper GI complications. Management of NSAID-induced enteropathy is challenging because symptoms may remain subclinical until complications arise. Cryer and Feldman [3] suggested that periodic monitoring and consideration of alternative therapies, such as acetaminophen, may be prudent in patients at risk of lower GI complications. Furthermore, use of gastroprotective agents, while effective for upper GI protection, may have limited efficacy in preventing lower GI damage, highlighting a gap in the therapeutic management of NSAID-induced enteropathy.

Management and preventative measures for NSAID-induced gastric ulcers

Preventing NSAID-induced gastric ulcers involves both pharmacologic and non-pharmacologic strategies aimed at reducing acid production, enhancing mucosal defenses, and mitigating NSAID exposure. Recent advancements in gastroprotection have improved outcomes, particularly for high-risk NSAID users.

Use of proton pump inhibitors (PPIs)

Proton pump inhibitors (PPIs) are widely recommended for reducing risk of NSAID-induced gastric ulcers. They act by inhibiting the H⁺/K⁺ ATPase enzyme, thereby reducing gastric acid secretion and creating a less acidic environment in the stomach. Common PPIs including omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and dexlansoprazole. A randomized controlled trial by Garegnani [24] found that patients co-administered PPIs with NSAIDs had a 60 % reduction in the incidence of endoscopically detected ulcers compared to those on NSAIDs alone. Despite their efficacy, long-term PPI use has been associated with potential adverse effects, including an increased risk of *Clostridium difficile* infection and vitamin B12 deficiency, thus requiring a more balanced approach in using PPIs [4].

Histamine-2 (H2) receptor antagonists

H2 receptor antagonists, such as ranitidine and famotidine, are another option for acid suppression. While they are generally less effective than PPIs in preventing NSAID-induced

ulcers, H2 antagonists may still provide a viable option for patients intolerant to PPIs. A study by Taha [25] demonstrated that high-dose famotidine reduced the risk of gastric and duodenal ulcers among NSAID users, though not as effective as PPIs.

Synthetic prostaglandins

Misoprostol, a synthetic prostaglandin E1 analog, has been shown to provide mucosal protection by directly counteracting COX-1 inhibition caused by NSAIDs. Misoprostol replaces the lost protective prostaglandins, enhancing mucus and bicarbonate secretion and increasing mucosal blood flow. In a meta-analysis by Rostom [26], misoprostol was found to reduce the incidence of NSAID-induced gastric ulcers by 40-50 % among high-risk patients. However, its clinical use is often limited by adverse effects such as diarrhea and abdominal cramping, which have led to high discontinuation rates [27].

Selective COX-2 inhibitors

Selective COX-2 inhibitors offer a pharmacologic approach that potentially mitigates GI complications by selectively targeting COX-2 without inhibiting COX-1, thus sparing gastric mucosal protection. Celecoxib, a commonly prescribed COX-2 inhibitor, has shown a reduced risk of gastric ulcers in NSAID users, as documented in the Celecoxib Long-term Arthritis Safety Study (CLASS), which reported a 50% lower incidence of symptomatic ulcers compared to non-selective NSAIDs [28]. However, due to the elevated cardiovascular risks associated with COX-2 inhibitors, which include myocardial infarction, stroke, hypertension, edema, and heart failure, primarily due to the imbalance between pro-thrombotic and anti-thrombotic prostaglandins caused by selective COX-2 inhibition. Therefore, their use requires careful evaluation of cardiovascular risk factors [21].

Alternative pain management options

For patients at high risk of NSAID-induced gastric complications, alternative pain management strategies may be warranted. Acetaminophen, which lacks anti-inflammatory properties, is often considered for mild pain relief in patients contraindicated for NSAIDs. Additionally, non-pharmacological approaches, such as physical therapy, acupuncture, and lifestyle modifications, may provide adjunctive pain relief without the associated GI risks of NSAIDs [29].

Limitations of current studies on NSAID-induced gastric ulcers

Despite substantial studies on NSAID-induced gastric ulcers, several limitations persist, affecting the generalizability and depth of existing findings. Addressing these limitations may provide the necessary evidence for clinical management and preventive strategies.

Methodological variability

One of the primary limitations of NSAID-related studies is the methodological variability, including differences in sample populations, study durations, and NSAID dosages used [30]. Many studies focused on short-term outcomes, typically spanning a few months to a year, which limits insights into the long-term impact of NSAID use on GI health [14]. This short duration is insufficient to capture chronic complications like gastric ulcers, particularly since these often develop over prolonged NSAID use. As Foong [11] highlighted, longitudinal studies with extended follow-up periods are essential to accurately assess both the incidence and progression of NSAID-induced gastric complications.

Underrepresentation of high-risk populations

Many studies on NSAIDs lack adequate representation of high-risk populations, such as older adults, individuals with comorbidities (e.g., diabetes, CKD), and those with genetic predispositions to GI complications. Sostres and Lanas [5] revealed that older adults especially are vulnerable due to age-related reductions in mucosal defenses and the prevalence of polypharmacy. However, most clinical trials either exclude these high-risk groups or fail to provide subgroup analyses, limiting the relevance of such findings to these populations. A review by Scheiman and Hinley [12] emphasized that including diverse patient populations in clinical trials provides a more comprehensive understanding of NSAID-related risks and tailor management strategies.

Geographic and ethnic biases

Majority of studies on NSAID were conducted in North America and Europe, potentially overlooking regional variations in healthcare practices, NSAID availability, and genetic differences that influence drug metabolism and susceptibility to GI side effects. For example, studies have shown that certain genetic polymorphisms in Asian populations may alter the pharmacokinetics of NSAIDs, potentially

affecting ulcer risk [31]. Geographic diversity is critical in creating globally relevant guidelines for NSAID use, as regional studies may reveal unique risk factors or protective mechanisms influenced by genetic, dietary, or environmental factors [15].

Limited exploration of lower GI effects

While extensive research has focused on NSAID-induced gastric ulcers, there is comparatively less investigation into the effects of NSAIDs on the lower GI tract. For example, NSAID-induced enteropathy has only recently been recognized as a significant clinical issue, and there is limited evidence on effective prevention or treatment strategies [23]. Cryer and Feldman [3] pointed out that most preventive measures, such as PPIs, target the upper GI tract and may not protect the intestines. Expanding understanding on lower GI effects may address this gap, providing a more holistic understanding of NSAID-induced GI complications.

Recommendations for future studies

Addressing the limitations of current studies on NSAIDs requires targeted efforts to expand knowledge on long-term outcomes, at-risk populations, and comprehensive GI protection strategies. Nanoencapsulation has been popular in reducing adverse drug reactions (ADRs) of NSAIDs [32-34].

Longitudinal studies on NSAID use and gastric ulcers

There is a need for longitudinal studies that track patients over extended periods to capture the full scope of NSAID-induced gastric complications, including the transition from asymptomatic gastric damage to severe ulceration and bleeding. Studies like those of Hernández-Díaz and Rodríguez [10] highlighted the limitations of short-term data and suggested that follow-up periods of five years or more would better document the chronic effects of NSAIDs. Longitudinal studies may also examine the cumulative impact of low-dose NSAIDs, as even minimal NSAID exposure over long durations may increase ulcer risk, particularly in older adults.

Preventive strategies in high-risk populations

Studies should prioritize preventive and therapeutic strategies tailored to high-risk populations, including older adults, those with polypharmacy, and individuals with underlying

conditions such as diabetes and cardiovascular disease. Studies on co-therapies, such as PPIs combined with other gastro-protective agents like rebamipide (mucosal protective agent) or misoprostol (prostaglandin analog), specifically for high-risk groups, would be valuable. Additionally, investigating the efficacy of emerging agents, like bismuth-based therapies, for both upper and lower GI protection in vulnerable patients may provide more targeted guidelines [12].

Exploration of NSAID-induced lower GI damage

With the increasing recognition of NSAID-induced enteropathy, prevention and treatment of lower GI complications are warranted. Shin *et al* [23] revealed that NSAID-induced enteropathy may involve different pathogenic mechanisms from gastric ulceration, necessitating specialized therapies. There is need to examine the potential role of probiotics and herbal remedies, selective COX-2 inhibitors, or novel anti-inflammatory agents with a safer GI profile in reducing the risk of NSAID-induced lower GI damage [35].

Genetic and biomarker-based risk stratification

As precision medicine advances, identifying biomarkers or genetic polymorphisms that predict susceptibility to NSAID-induced GI complications may improve patient outcomes. McEvoy *et al* [36] propose that pharmacogenetic studies may reveal specific genetic variants influencing NSAID metabolism and GI toxicity, allowing for personalized NSAID prescriptions. Additionally, developing biomarker panels to assess oxidative stress or inflammation in response to NSAID use may aid early detection of mucosal damage, enabling timely intervention before severe complications arise.

Non-pharmacologic approaches to pain management

Given the GI risks associated with NSAIDs, there is a compelling need for alternative pain management that circumvent these risks. Non-pharmacologic methods such as physical therapy, acupuncture, and lifestyle modifications have shown positive outcomes in managing chronic pain without the adverse effects linked to NSAIDs [29]. Comparative effectiveness studies may assess relief provided by these methods relative to NSAIDs, offering evidence-based recommendations for patients who are at high risk for GI and other complications [37,38].

CONCLUDING REMARKS

The use of NSAIDs presents a delicate balance between therapeutic benefits and potential adverse effects, particularly gastrointestinal complications (e.g., gastric ulcers), as well as systemic risks such as nephrotoxicity and cardiovascular events. To optimize safety, clinicians must assess individual risk factors, especially in vulnerable populations and consider protective strategies like co-administration of PPIs or use of COX-2 inhibitors, despite their limitations. It is important to prioritize long-term safety studies, targeted preventive therapies, and personalized approaches, including genetic profiling, to reduce NSAID-related harm and promote safer pain management alternatives.

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Ethical approval

None required.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author or Mohd Sofian Omar Fauzee on reasonable request.

Conflict of interest

No conflict of interest associated with this work.

Contribution of authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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