INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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**Review Article**

# Comprehensive Review of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Role in Gastric Ulcer Risk

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ARTICLE INFO

Published: 9 Jun 2026
Keywords:
NSAIDs, gastric ulcer, peptic ulcer disease, cyclooxygenase inhibition, proton pump inhibitors, gastrointestinal toxicity
DOI:
10.5281/zenodo.20617309

## ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used drugs worldwide due to their analgesic, antipyretic and anti-inflammatory properties. However, they are associated with significant gastrointestinal toxicity, in particular, the formation of gastric ulcers. This extensive review covers current knowledge of NSAID-induced gastric ulcers, including their epidemiology, pathogenesis, risk factors, and management. Worldwide, the prevalence of gastric ulcers in NSAID users ranges from 10% to 30% and varies widely between regions. The main mechanism of action is inhibition of the cyclooxygenase (COX) enzymes, especially COX-1, leading to decreased prostaglandin synthesis and reduced gastric mucosal defence. Key risk factors include advanced age, Helicobacter pylori co-infection, high-dose NSAID use, and co-morbid conditions. Management strategies are centred on risk stratification. The use of proton pump inhibitors (PPI) is more effective in both prevention and treatment. An alternative approach is the use of selective COX-2 inhibitors but careful assessment of cardiovascular risk is required. This review summarises the current evidence and provides clinicians with practical recommendations to reduce the risk of NSAID-related gastric ulceration while preserving therapeutic benefits.

## INTRODUCTION

NSAIDs are among the most commonly used drugs worldwide. They are widely used for controlling pain, inflammation and fever. They work for everything from osteoarthritis to acute musculoskeletal injuries. However, NSAIDs are associated with a substantial burden of gastrointestinal adverse effects, most notably gastric and duodenal ulcers [1 & 7].

NSAIDs-induced gastric ulcers have a clinical significance beyond mucosal erosion. These ulcers are associated with significant morbidity and mortality, particularly from complications such as gastrointestinal bleeding and perforation [4 & 10].

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**Relevant conflicts of interest/financial disclosures**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

It is estimated that NSAID-associated GI complications are responsible for approximately 100,000 hospitalisations per year in the United States alone, with significant associated health care expenditures [9].

The last three decades have seen extensive research into the pathogenesis of NSAID-induced gastropathy. Previous theories centred around the irritant effects of these drugs on the mucosa, but it is now appreciated that the inhibition of prostaglandin synthesis and the interference with gastric mucosal defence mechanisms are of prime importance [6 & 9]. The discovery of two different cyclooxygenase isoforms, COX-1 (constitutive) and COX-2 (inducible), revolutionised the understanding of NSAID pharmacology and paved the way for the design of selective inhibitors with the aim of minimising gastrointestinal toxicity. This review aims to provide a comprehensive overview of NSAIDs-induced gastric ulcers, including the current understanding of epidemiology, pathogenic mechanisms, risk factors, clinical management, and prevention strategies. The evidence synthesised herein is based on recent systematic reviews, clinical practice guidelines, and original research to provide practical guidance to clinicians managing patients requiring NSAIDs therapy.

## 2. EPIDEMIOLOGY AND GLOBAL BURDEN

### 2.1 Prevalence

NSAID-induced gastric ulcers have a high global burden. Studies report a prevalence rate of gastric ulcers of 10–30% in chronic NSAID users, with higher rates noted in older populations and in those with comorbidities [7]. The lifetime prevalence of peptic ulcer disease in industrialised countries is about 5% to 10%. The 2 major independent risk factors are the use of NSAIDs and infection with Helicobacter pylori [7 & 10].

### 2.2 Geographic Differences

There are important geographic differences in the epidemiology of NSAID-induced peptic ulcers. The Global Burden of Disease study (2019) reported a relatively low age-standardized prevalence rate of 81.0 per 100,000 population (95% uncertainty interval: 68.2 to 95.8) in high-income countries[7]. This lower rate is however, mainly due to systematic preventive strategies, despite increased volumes of NSAID prescriptions volumes, and is primarily attributable to systematic preventive strategies, particularly the routine co-prescription of gastroprotective agents[7].

### 2.3 Morbidity and Mortality

NSAID-induced ulcers are frequently asymptomatic and are diagnosed when complications develop[10]. The commonest complication is gastrointestinal bleeding that may range from chronic occult blood loss causing anaemia to acute, massive haemorrhage necessitating urgent intervention [7]. The risk of ulcers is greatly increased when NSAIDs are taken together with anticoagulants or corticosteroids [10].

## 3. PATHOGENESIS AND MECHANISMS OF INJURY

### 3.1 Inhibition of Prostaglandin Synthesis

The primary mechanism of injury to gastric mucosa by NSAIDs is through the inhibition of cyclooxygenase (COX) enzymes that convert arachidonic acid to prostaglandins [6 & 9]. Two isoforms of COX have been described:

| Isoform | Expression Pattern | Physiological Role |
|---|---|---|
| **COX-1** | Constitutive (present in most tissues) | Mucosal protection, platelet aggregation, and renal function |
| **COX-2** | Inducible (upregulated during inflammation) | Mediates pain, fever, and inflammation |

Traditional NSAIDs inhibit both isoforms non-selectively. Inhibition of COX-1 suppresses synthesis of cytoprotective prostaglandins (PGE2, PGI2), resulting in decreased secretion of mucus and bicarbonate, impaired epithelial cell proliferation and diminished mucosal blood flow [6 & 7].

### 3.2 Microcirculatory Disturbance

Recent evidences points to the microcirculatory disturbance as the central player in NSAID-induced gastric damage. Inhibition of Prostaglandin Synthesis Causes:

a) Constriction of blood vessels in the gastric mucosa

b) Increased leukocyte adhesion to endothelial cells

c) Induction of inflammatory cascades.

d) Ischaemic and hypoxic injury to epithelial and endothelial cells [9].

### 3.3 Direct Mucosal Damage

In addition to systemic COX inhibition, NSAIDs also directly interfere with the integrity of the mucosa due to their physicochemical properties. These agents are:

a) Disrupt phospholipids of mucus and of cell membranes

b) Uncouple mitochondrial oxidative phosphorylation.

c) Produce reactive oxygen species

d) Promote leukotriene production through the shunting of arachidonic acid into the lipoxygenase pathway [6].

The NSAID ulcerogenic potential is variable. In animal models, tiaprofen caused significantly less ulceration (ulcer index 6.6 ± 1.0) than indomethacin (20.6 ± 2.9, $p < 0.005$) while inhibiting PGE2 to a similar extent, suggesting that the difference may be due to prostacyclin levels.

## 4. RISK FACTORS OF NSAIDS-INDUCED GASTRIC ULCERS

### 4.1 Risk Factors Related to Patients

| Risk Factor | Effect | Odds Ratio |
|---|---|---|
| **Advanced age (>65 years)** | Reduced mucosal repair capacity | 4-5x |
| **Previous ulcer history** | Increased baseline risk | 3-5x |
| **H. pylori co-infection** | Synergistic effect | 19.11 (combined) |
| **High-dose NSAID use** | Dose-dependent toxicity | 3-10x |
| **Concomitant anticoagulants** | Bleeding risk potentiation | 5-10x |
| **Concomitant corticosteroids** | Additive mucosal injury | 2-4x |

### 4.2 H. pylori and NSAID Synergy

The combination of H. pylori infection and NSAID use has a synergistic effect on the development of gastric ulcer. NSAID use and H. pylori infection together have been shown to have an odds ratio of 19.11 for developing gastric ulcers, which is significantly greater than the sum of the individual ORs for NSAIDs alone (5.93) and H. pylori alone (5.74) [3].

However, such synergy was not observed in the complications of ulcer such as upper gastrointestinal bleeding, indicating different pathogenic mechanisms for ulcer formation and ulcer complications [3].

### 4.3 Drug-Related Risk Factors

NSAIDs vary considerably in their gastrointestinal toxicity profile:

**Classification of NSAIDs by Gastrointestinal Risk** :

| GI Risk Category | NSAID Classification |
|---|---|
| **Low Risk** | Ibuprofen, Aceclofenac, Celecoxib |
| **Intermediate Risk** | Rofecoxib, Sulindac, Diclofenac, Meloxicam, Nimesulide, Ketoprofen, Naproxen |
| **High Risk** | Indomethacin, Tenoxicam, Piroxicam, Ketorolac, Azapropazone |

## 5. CLINICAL PRESENTATION AND DIAGNOSIS

### 5.1 Clinical Manifestations

**S**ymptomatology of NSAID-induced gastric ulcers is varied. Many patients are asymptomatic (up to 50-60%), and ulcers are diagnosed only when complications develop [10]. The symptoms when they do occur are generally:

a) Epigastric pain: Burning or gnawing pain, often worse on an empty stomach

b) Nausea and loss of appetite

c) Early satiety

d) Iron deficiency anaemia as a presenting symptom of obscure gastrointestinal bleeding

e) GI bleeding Overt Haematemesis (blood vomiting) Melena (black, tarry stools).

### 5.2 Diagnostic Strategy

Endoscopy remains the best test for the diagnosis of NSAID-induced gastric ulcers. It provides:

a) Direct visualisation of lesions of the mucosa

b) Assessment of the size, site and depth of the ulcer

c) Biopsy for histology and H. pylori testing

d) Active bleeding therapeutic intervention

Important: The sensitivity of H. pylori testing is significantly reduced in the setting of acute gastrointestinal bleeding, and false-negative results may occur [4]

## 6. ADMINISTRATIVE ACTIONS

### 6.1 Withdrawal of NSAIDs

Withdrawal of the offending agent is the mainstay of therapy for NSAID-induced gastric ulcers. High healing rates of gastric and duodenal ulcers are obtained after withdrawal of NSAIDs [8]. However, for patients under ongoing antiplatelet therapy (e.g., for secondary cardiovascular prophylaxis), the decision to interrupt therapy has to be carefully risk stratified.

Guidelines recommend that aspirin should not be interrupted in the setting of acute upper gastrointestinal haemorrhage in patients taking low-dose aspirin for secondary prevention. If interruption occurs, aspirin should be restarted as soon as possible, ideally within three to five days, and preferably after starting proton pump inhibitor therapy [4].

### 6.2 Pharmacological Treatment

**Recommended Treatment Algorithm for NSAID-Induced Ulcers**:

| Clinical Scenario | Recommended Therapy | Evidence Level |
|---|---|---|
| **NSAIDs can be discontinued** | Anti-ulcer therapy (PPI preferred) | A (Strong) |
| **NSAIDs cannot be discontinued** | PPI as first-line therapy | A (Strong) |
| **H. pylori positive** | Eradication therapy + PPI | A (Strong) |

Recommended as first-line treatment when NSAIDs are required to be continued

Vonoprazan (VPZ) is a potassium-competitive acid blocker with potent and long-lasting acid suppression. Recently, it has been reported that VPZ effectively heals peptic ulcers and prevents recurrence of NSAID-related ulcers.

Proton Pump Inhibitors (PPIs) show better efficacy than H2 receptor antagonists and prostaglandin analogues:

- Significantly Higher Healing Rates with PPIs at 8 Weeks
- Suggested as the first-line therapy when NSAIDs are required

## 7. PREVENTION APPROACHES

### 7.1 Risk Stratification

Prevention of NSAID-induced ulcers requires an integrated approach considering both gastrointestinal and cardiovascular risks [7]:

**Comprehensive Prevention Strategy Based on Risk Profile [7]**:

| Cardiovascular Risk | Low GI Risk | High GI Risk |
|---|---|---|
| **Low CV Risk** | Non-selective NSAIDs | Selective COX-2 inhibitors OR Non-selective NSAIDs + PPIs |
| **High CV Risk** | Non-selective NSAIDs + PPIs | Avoid NSAIDs if possible; if necessary, use non-selective NSAIDs + PPIs |

### 7.2 Pharmacoprevention

- Effective prevention measures include:

a) Proton Pump Inhibitors: Better results in primary and secondary prevention

b) Misoprostol: Effective but causes diarrhea and reduces tolerability

c) Selective COX-2 Inhibitors: Lesser gastrointestinal toxicity but with cardiovascular side effects [5]

For patients with a history of ulcers on NSAIDs: PPIs alone or with celecoxib are preferable; VPZ is recommended in preventing recurrence of ulcers [8].

### 7.3 H. pylori Eradication

In NSAID-naive patients, H. pylori eradication is preferred for ulcer prevention (strong recommendation, evidence level A) [8]. Present guidelines recommend:

a) First-line: Vonoprazan with antibiotics

b) Second-line: PPIs or VPZ with antibiotics [8]

## 8. SPECIAL POPULATIONS AND CONSIDERATIONS

### 8.1 Geriatric Population

Advanced age is an important risk factor for gastric ulcers caused by NSAIDs due to:

a) Decreased mucosal healing ability

b) Increased inciden

c) ce of co-morbidities

d) Increased chances of polypharmacy

e) Greater NSAID use among the geriatric population [7]

In patients with duodenal ulcers, the proportion of geriatric patients is 27.5%, with statistically significant differences from non-geriatric patients ($p<0.01$) [3].

### 8.2 Patients Undergoing Antithrombotic Therapy

The combination of NSAIDs with either anticoagulant or antiplatelet drugs substantially increases the risk of bleeding. The choice between continuation and discontinuation of these drugs is based on a balance between:

- Risk of thrombosis if antiplatelet therapy is stopped
- Risk of bleeding if medications are continued

### 8.3 Patients with Cardiovascular Diseases

COX-2 selective inhibitors are associated with lower GI adverse effects but need careful cardiovascular risk evaluation. In patients at high cardiovascular risk, non-selective NSAIDs with proton pump inhibitors may be preferable to COX-2 inhibitors [7].

## 9. CONCLUSION

NSAIDs are still important tools in the management of pain and inflammation. The problem with NSAIDs, however, is the high risk for gastric ulceration. There is sufficient evidence to support the adoption of a risk stratification approach that will take into account the risk factors of individual patients, choose safer alternatives where possible, and adopt gastroprotective measures especially PPIs where applicable. Testing and eradicating H. pylori infection before commencing NSAID treatment is highly recommended.

Though a lot has been achieved on NSAID induced gastropathy, the high prevalence rate of asymptomatic ulcers and the burden of complications necessitates further research and adherence to guidelines on NSAID prescribing. A multidisciplinary approach that involves primary care physicians, gastroenterologists, cardiologists, and rheumatologists among others, is very important in optimizing pain control and reducing gastrointestinal toxicity.

Conclusion: NSAID induced gastric ulcers are common, preventable, and treatable. Risk assessment, proper drug choice, and use of gastroprotection as a standard practice will significantly reduce the morbidity and mortality associated with NSAIDs.

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HOW TO CITE: Avinash Kumar, Parveen Kumar, Comprehensive Review of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Role in Gastric Ulcer Risk, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 6, 2600-2606. https://doi.org/10.5281/zenodo.20617309