Review

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NSAID-induced Gastric Ulcer Disease: A Deleterious Connection

Hamza Islam[1,*], Areeba Siddiqui[2], Rabia Islam[1], Tamur Islam[3], Safia Ahmed[4], Mariam Fahim[5], Muneeb Khalid[4], Ghulam Mustafa Ali Malik[2], Hiba Imtiaz[6]

[1]Department of Internal Medicine, Punjab Medical College, 38000 Faisalabad, Pakistan
[2]Department of Internal Medicine, Dow University of Health Sciences, Civil Hospital, 74200 Karachi, Pakistan
[3]Department of Internal Medicine, Medicare Hospital, 38610 Faisalabad, Pakistan
[4]Department of Internal Medicine, Karachi Medical and Dental College, 74700 Karachi, Pakistan
[5]Department of Internal Medicine, Jinnah Sindh Medical University, 75510 Karachi, Pakistan
[6]Department of Internal Medicine, Fazaia Ruth Pfau Medical College, 74350 Karachi, Pakistan
*Correspondence: Hamzaislamdr@gmail.com (Hamza Islam)
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Gastric ulcers induced by non-steroidal anti-inflammatory drug (NSAID) usage have become a common public health problem, and several studies have established chronic NSAID usage to be one of the risk factors for the pathogenesis of peptic ulcers in patients. This review includes numerous articles that link NSAID usage with peptic mucosal erosion, especially among patients under anticoagulant therapy or with other risk factors. Risk factors for NSAID-induced peptic ulcers are reviewed, in addition to pathogenesis, clinical signs, symptoms, diagnosis, prevention, and treatments. We also emphasize effective methods for the prevention and management of peptic ulcers among NSAID users. Such methods include the use of selective Cyclo-oxygenase (COX-2) inhibitors as an alternative to aspirin or other Cyclo-oxygenase (COX-1) inhibitors, or using the lowest dosage possible in patients with other comorbidities. We have conducted a thorough review of the literature on diagnostic tests and alternative medication that can be used in the management of NSAID toxicity-induced ulcers.

Keywords: gastric ulcer disease; peptic ulcer disease; NSAID; *H. pylori*; PPIs; H2RA

Introduction

A gastric ulcer is a breach in the stomach's mucosal lining that typically measures more than 5 mm in diameter and 3 mm in deep extending into the muscularis mucosa layer [1]. A lifetime prevalence of 5 to 10% for peptic ulcer disease (PUD), which includes stomach ulcers, is likely a gross underestimate of the condition because some individuals may not be diagnosed, refuse treatment, or fail to notify their healthcare providers. Our stomach's primary means of defense against homeostatic disturbances that shift the balance between defensive and aggressive mechanisms are regular blood flow, mucus production, and release of bicarbonate ions [1]. An increase in acid production that exceeds the normal limit, decreased blood flow, and a reduction in the secretion of mucus and bicarbonate are the most common culprits. The three most significant risk factors for the formation of stomach ulcers are *Heliobacter* pylori infection, non-steroidal anti-inflammatory drug (NSAID) usage, and smoking [1].

NSAIDs are the most widely used and prescribed drugs around the world because of their versatility as analgesic, antipyretic, and anti-inflammatory agents. According to a report, 96% of individuals over 65 use NSAIDs [1]. NSAIDs are employed in healthcare settings to treat and prevent ailments like rheumatoid arthritis, osteoarthritis, collagen disease, ischemic cardiovascular disease, and neurodegenerative brain illness, which frequently arise in thromboembolic strokes and Parkinson's syndrome [2]. 30–50% of patients who use NSAIDs, often aspirin, have chronic lesions that can be visualized by endoscopy (ulcers, subepithelial hemorrhages, and erosions) [3]. NSAID use is known to raise the risk of serious gastroduodenal disorders such as peptic ulcers, bleeding, and perforations [2].

The pathophysiology of stomach ulcers caused by long-term NSAID use includes enterohepatic circulation, which slows down rapid drug absorption, enteric cell disturbances which trigger inflammation, and Cyclo-oxygenase (COX) suppression that lowers synthesis of prostaglandins—key mediators in the process of inflammation. When consuming NSAIDs, the stomach mucosa is more prone to damage from pepsin and gastric acid. Overall, the most detrimental physiological damage is caused by a drop in gastric blood flow and the mild ischemia it induces in the stomach mucosa [4].

15% to 35% of all cases of peptic ulcers are attributed to long-term NSAID usage [4]. According to their prescriptions, more than 30 million individuals worldwide consis-

tently use NSAIDs. Gastrointestinal (GI) toxicity was noted by Singh G [5] as a significant clinical problem that can be triggered by NSAIDs, and is responsible for about 25 percent of all reports of adverse drug interactions going back to 2000. An endoscopic study published in June 1993 by Hudson and Hawkey [6] found that NSAID users had a 15% chance of developing stomach ulcers and a 10% prevalence of duodenal ulcers.

Up to 40% of NSAID users experience upper GI symptoms, with gastroesophageal reflux disease (regurgitation and/or indigestion) and dyspeptic complaints (including pain in the epigastric area, burping, postprandial nausea, early satiety, and bloating) being the most frequently encountered [7]. The primary contributory factors for NSAID-related GI complications include age (>65 years, with an increased risk at >70 years), a history of simple or complicated ulcers, prior use of additional medications, notably aspirin, other non-aspirin antiplatelet agents, anticoagulants, steroids, or inhibitors of selective serotonin reuptake, severe illness, alcohol, and tobacco use, and *H. pylori* infection [8]. While protective treatment can sometimes obscure or delay the symptoms of ulcers in high-risk patients, any delay in accurately diagnosing these conditions can lead to heightened risks of complications and mortality. Therefore, prompt and accurate diagnosis and intervention are crucial to mitigate these potential outcomes and ensure timely recovery [8].

Proton pump inhibitors (PPIs) and H2 receptor antagonists (H2RAs) are the two medications that are frequently administered to treat the signs and symptoms of gastric ulcer disease. It has been shown that PPIs are useful for the treatment of NSAID-associated ulcers and for minimizing the risk of repeated gastroduodenal damage [9]. Widely agreed upon primary indications for the use of PPIs include treatment of gastroesophageal reflux disease and its complications, the eradication of *H. pylori* infection when administered with two or more antibiotics, the treatment of *H. pylori*-negative peptic ulcers, recovery from and prevention of NSAID-associated gastric ulcers, combination therapy with endoscopic procedures to control upper digestive bleeding, and medical therapy [10]. In their analysis, Alshamsi F *et al*. [11] reported that PPIs outperformed H2RAs in lowering the risk of clinically significant and overt GI bleeding without appreciably raising the risk of mortality or pneumonia in 19 trials including 2117 patients.

Because numerous studies have demonstrated a substantial correlation between chronic NSAID usage and the onset and progression of gastric ulcer disease, a review of the current evidence is warranted. In this review, we address the factors that increase the risk of developing gastric ulcers, the pathogenesis of NSAID-induced gastric ulcers, and the clinical symptoms that ultimately lead to the diagnosis of the condition. The goal is to provide the medical community with an in-depth and instructive evaluation of the negative effects of NSAIDs on the GI tract by providing a detailed analysis of the current literature and highlighting any new research findings.

Risk Factors of Gastric Ulcers

It is important to note the underlying predisposing factors associated with the pathogenesis of this disease. Gastric ulcers can arise from a combination of lifestyle choices and underlying medical conditions, some of which are illustrated in the diagram below (Fig. 1, Ref. [12]).

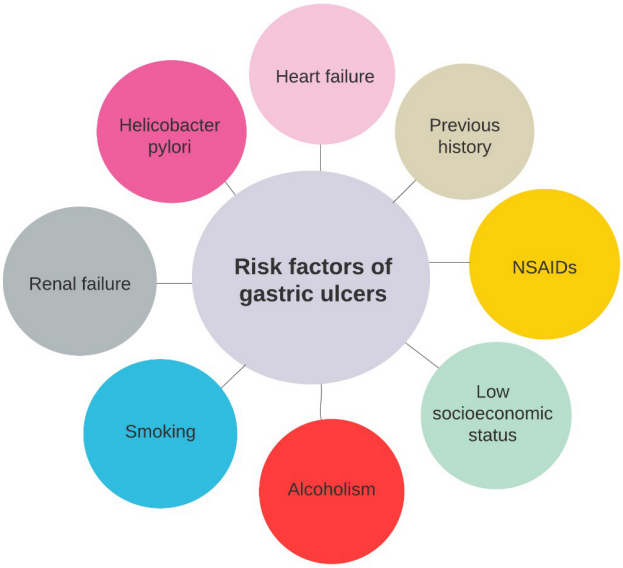

Fig. 1. Common lifestyle choices and medical conditions that act as risk factors predisposing patients to develop gastric ulcers [12]. NSAIDs, non-steroidal anti-inflammatory drugs.

NSAIDs

NSAID and aspirin users have a four-fold increased risk and a two-fold increased risk, respectively, of developing ulcer complications as compared to non-users [13]. Aside from aspirin, all NSAIDs enhance stomach motility at toxic levels [14]. They also increase the chances of bleeding, perforation, and gastric cancer, and can even lead to death [15]. In addition to the upper GI tract, the injury may also occur as frequently and severely in the lower intestinal tract, and patients may present with protein deficiency, bowel motility problems, abdominal pain, and iron deficiency anemia [16].

H. pylori Infection

H. pylori infection is the root cause of many GI disorders, such as duodenal ulcers, gastric ulcers, gastric cancer, and atrophic gastritis. According to estimates, more than half of the adult population globally has been infected by *H. pylori*, which accounts for 75% of occurrences of stom-

ach cancer [17]. *H. pylori* infects the metaplastic gastric epithelium, causing inflammation and tissue damage in the stomach as well as the duodenum [18]. It is also associated with an increased release of gastric acid from the stomach, which further contributes to ulcer formation. However, acid secretion decreases when the disease develops into gastric cancer, possibly due to acid depletion from a previous infection [19].

Comorbidities

Comorbidities can contribute to a higher risk of developing ulcers in the digestive tract. A considerably increased prevalence is linked to smoking, a history of dyspepsia, and a history of previously diagnosed peptic ulcers or recurrent chronic gastritis, while heart failure and diabetes continue to be major risk factors for peptic ulcers [20]. Moreover, according to research by Younossi *et al.* [21], patients with coronary artery stents who take warfarin plus aspirin prophylactically have a greater chance of gastrointestinal bleeding (GIB) than those who take aspirin, indicating a possible substantial risk from anticoagulants. Although diabetes has been suggested as a possible risk factor, this hypothesis has not been significantly explored in any research.

Smoking is another risk factor whose role in the development of gastric ulcers has been explored. Long-term cigarette smoking stimulates the vagus nerve and triggers functional parietal cells, leading to increased acid production in smokers [22]. It is also known to reduce blood flow to the gastric mucosa by mechanisms such as constriction of vessels supplying the gastric mucosa and decreased nitric oxide (NO) synthesis, which may affect the integrity of gastric mucosa. Moreover, by increasing the formation of enzymes such as myeloperoxidase, smoking may lead to the release of reactive oxygen species which may further damage the gastric mucosa. Furthermore, smoking delays wound healing by further aggravating apoptosis and decreasing important factors required for tissue repair such as NO and endothelial growth factor [23].

Furthermore, alcohol consumption has also been assumed to cause serious gastrointestinal complications. In a prospective study by Strate *et al.* [24], alcohol consumption was linked to a higher likelihood of experiencing significant upper GIB. Additionally, alcohol seemed to amplify the risk of NSAID-related GIB. In another study by Im *et al.* [25], there were notable positive correlations between alcohol consumption in men and several digestive conditions, including gastroesophageal reflux disease and gastric ulcers. In an animal study conducted on rats, oral administration of ethanol developed more extensive gastric lesions in hypertensive rats than in normotensive rats [26]. While these studies help link acute or chronic alcohol abuse to increased occurrences of gastric ulcers, there should be more research on this topic to gather clearer evidence. A study has also indicated that individuals with acute and chronic renal failure are susceptible to PUD [27]. However, comorbidities have been indicated to be more likely to cause GIB unrelated to ulcers, whereas the risk for peptic ulcer bleeding, which is more associated with aspirin and NSAID use, is marginally lower [28].

Socioeconomic Condition

Low socioeconomic status is frequently regarded as a risk factor for peptic ulceration. Those with low status are more likely to experience shift work, stress at work and home, as well as increased chances of smoking, excessive drinking, and *H. pylori* infection [29]. An individual's occupation is also important in determining their socioeconomic position and may impact both habitual physical activity and stress levels. Examples of high-risk occupations include night shift workers, bus drivers, conductors, air traffic controllers, and those in manager or supervisor positions [30]. Exercise is also another significant element; low-to-moderate exercise is beneficial because it reduces digestive secretions and boosts immunity, which lowers the probability of *H. pylori* infection. However prolonged, intense exercise increases the odds of gastric ulcers due to regular use of NSAIDs, decreased mucosal blood flow, and inhibition of immunological function [31]. The increased risk with heavy physical activity was also seen in an animal study by Tamzali *et al.* [32] to determine the prevalence of peptic ulcers in racehorses.

It is important to remember, however, that the existence of one or more predisposing factors does not ensure that an ulcer will form, as every individual will respond differently to the disease. Therefore, understanding the risk factors associated with gastric ulcers is crucial for preventing, detecting, and effectively managing this condition.

Pathophysiology of NSAIDs and Peptic Ulcers

NSAID Mechanism of Action

NSAIDs are widely used for conditions such as arthritis, musculoskeletal injuries, dysmenorrhea, and migraines due to their anti-inflammatory and analgesic properties. They work to relieve pain and reduce inflammation by interrupting prostaglandin synthesis due to inhibition of the COX isoenzymes (COX-1 and COX-2) [33]. Prostaglandins originate from a 20-carbon ω-6 fatty acid known as arachidonic acid (AA), which is stored in membrane phospholipids like phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol. Arachidonic acid is also the precursor for another group of eicosanoids called leukotrienes. Phospholipases release AA from the membrane phospholipids. Once free, AA undergoes oxidation via cyclooxygenases, initially forming endoperoxide prostaglandin G_2 (PGG_2) (an endoperoxide), which is then further peroxidized to produce prostaglandin H_2 (PGH_2), which in turn serves as a precursor to various prostanoids including prostaglandin

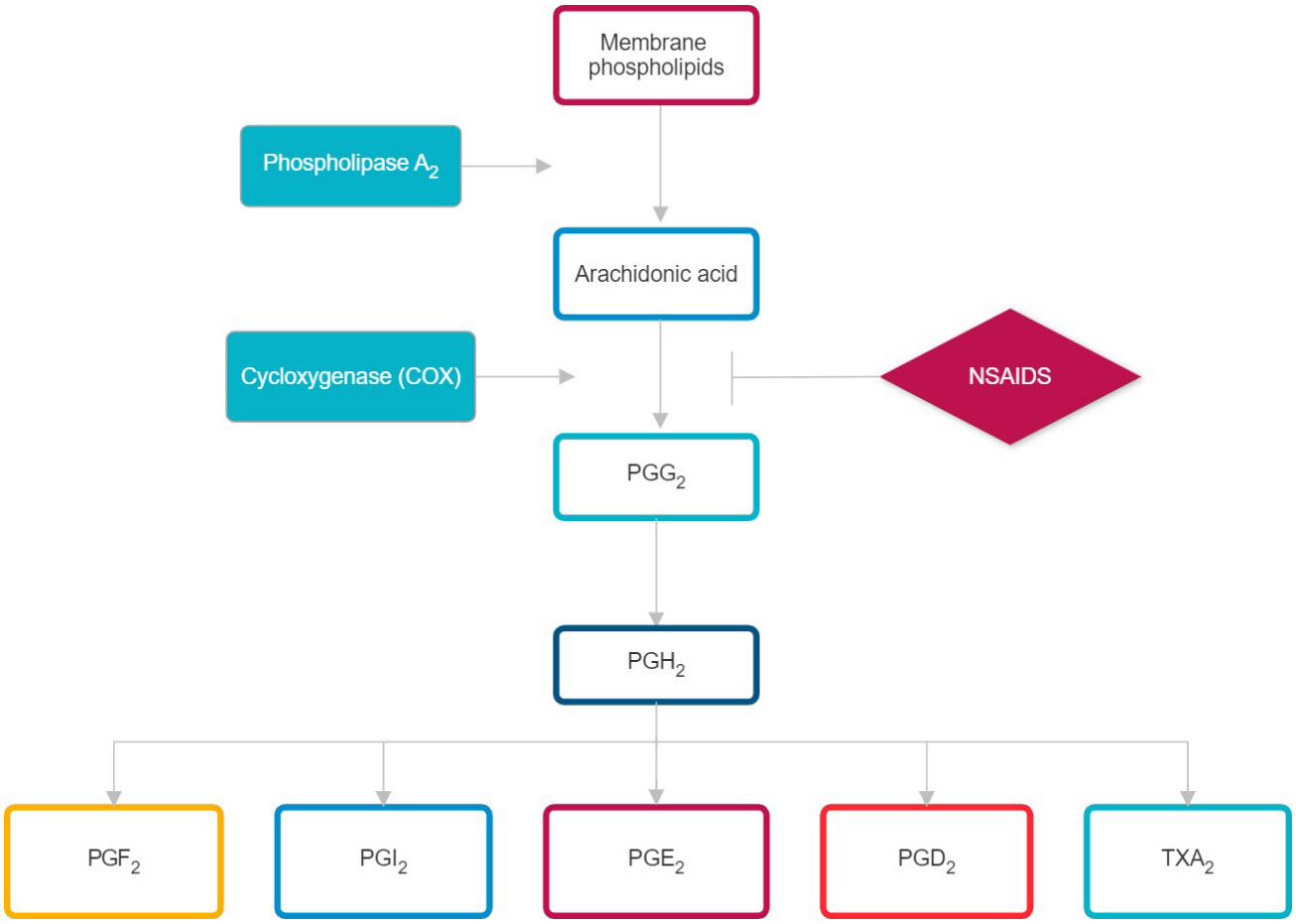

Fig. 2. Role of non-steroidal anti-inflammatory drugs (NSAIDs) in the synthesis of prostaglandins [34]. PG, prostaglandin; TXA_2, thromboxane A_2.

D_2 (PGD_2), prostaglandin E_2 (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), prostaglandin I_2 (PGI_2), and thromboxane A_2 (TXA_2) [34]. Due to the inhibition of the COX enzyme, prostaglandin production is interrupted (Fig. 2, Ref. [34]). This is the key to both the therapeutic and adverse effects of NSAIDs.

Therapeutically, prostaglandins are important mediators in the inflammatory response to injury, infection, or noxious stimuli. They are markedly increased in inflamed tissue and play a role in bringing about the typical signs of inflammation such as pain, fever, redness, and edema [35]. NSAID usage suppresses the inflammatory response and its markers due to reduced prostaglandin production, and results in the desired therapeutic effects. However, reduced prostaglandin production also has adverse effects, particularly on the GI tract and renal system [35].

NSAID Usage Through History—Aspirin

The first NSAID produced, and a prototype for subsequent forms, was Aspirin. Aspirin (acetylsalicylic acid) is still commonly used as an over-the-counter (OTC) drug for pain and inflammation, although due to its toxic effects, alternative drugs have come on the market. However, Aspirin still remains significant due to its antiplatelet properties that prevent blood clots from forming, and the cardiovascular benefits this yields for the management and prevention of myocardial infarction, stroke, and associated disorders [36]. The toxic effects of Aspirin, especially on the GI tract, led to efforts for the development of other NSAIDs that could be better tolerated. The toxicity associated with Aspirin is primarily due to the fact that it causes topical irritation in the upper GI tract and prostaglandin suppression [34]. This results in an increased risk for gastric disorders and injuries such as bleeding, perforation, and formation of ulcers [37].

Peptic Ulcer Disease Pathogenesis

Although the common denominator in PUD formation due to NSAID use is inhibition of prostaglandin biosynthesis, it is thought to be more complex and involves multiple factors such as gut hypermotility, neutrophil production, etc. [33]. However, it is evident that prostaglandin inhibition plays a key role since prostaglandins ensure the structural integrity of the mucosal tissue, increase blood flow to the gastrointestinal tract, and cause secretion of bicarbonate-rich mucus that protects against the corrosive effects of gastric hydrochloric acid. Decreased production

of prostaglandins leaves the stomach and duodenal mucosa exposed and more susceptible to injury, resulting in the pathogenic basis for ulcer formation (Fig. 3, Ref. [38]).

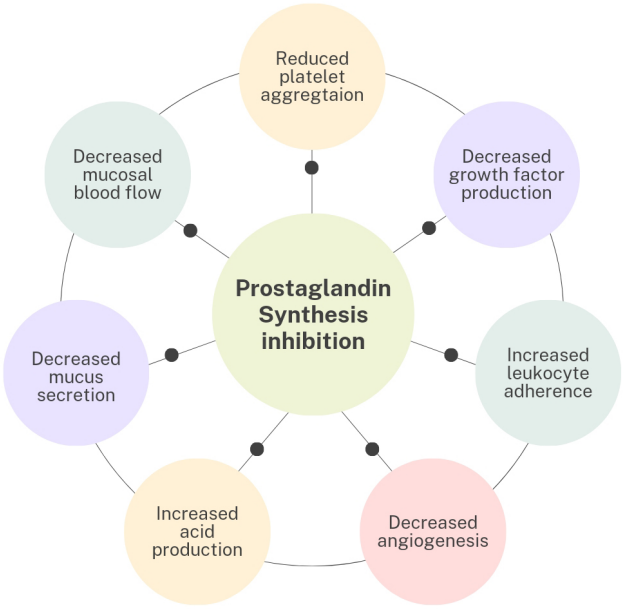

Fig. 3. Overview of the deleterious effects of decreased prostaglandin synthesis on physiological mucosal protective mechanisms [38].

Up to 70% of patients experience ulceration and erosion of the GI mucosa in association with long-term NSAID use, such as for arthritis management [3]. This is caused not only by prostaglandin biosynthesis suppression but also by topical irritation as explained below. Topical erosion of the GI mucosa is caused by NSAIDs with acidic residues that lead to ion trapping and consequent rupture of the cell [39]. Another reason behind topical irritation is the disruption of oxidative phosphorylation in the mitochondria, which decreases adenosine triphosphate (ATP) production and affects cellular activity [40]. NSAIDs have also been shown to damage the protective mucus barrier lining the mucosal surface by reducing its hydrophobicity and leading to increased acid permeability [41].

Disruption of prostaglandin-mediated vasodilation of the GI mucosa caused by NSAIDs can have deleterious effects as well. Decreased production of prostaglandins results in reduced blood flow to the gastric mucosa and can cause endothelial damage [42]. Researchers have also postulated that the primary ulcerogenic properties of NSAIDs arise from COX-1 inhibition, since it is the main 'housekeeping' enzyme of the GI mucosa and has a cytoprotective function [43]. COX-1 is also expressed in tissues all over the body and plays a vital role in mediating normal physiological processes, whereas COX-2 is selectively produced in response to inflammatory stimuli [44]. NSAIDs which are selective COX-2 inhibitors have been observed to have less damaging effects on the GI tract and show promising results in clinical trials for the prevention of peptic ulcers and mucosal damage [45].

Clinical Signs and Symptoms of NSAID-induced PUD

PUD is typically characterized by burning epigastric pain. The onset of this discomfort tends to be sudden and chronic. Patients commonly complain of this pain on an empty stomach [46]. Pain can be intermittent or persistent, and is worse at night [47]. The severity of the discomfort may even cause sleeplessness [48]. Although it begins in the upper abdomen, it can extend throughout the body, resulting in malaise [49]. The patient with PUD initially has pain alleviation with meal intake, but the discomfort returns after two to five hours [48]. The discomfort is frequently associated with dyspepsia symptoms such as bloating, abdominal fullness, and early satiety [50]. There may also be abdominal distention and discomfort [51]. Emesis is yet another symptom of NSAID-induced PUD [45]. It is less common and often manifests as nausea, GI pain, and flatulence [52].

Heartburn and regurgitation are additional symptoms reported by patients with NSAID-induced PUD. This is mostly a consequence of gastroesophageal reflux brought on by erosions caused by PUD [53]. Additionally, patients may also show signs of bleeding. The bleeding is a serious complication of PUD and is associated with alarming symptoms like melena and hematemesis [54]. One of the symptoms that a PUD patient may have is anorexia [46]. The anxiety of postprandial discomfort is frequently connected to this weight loss [47]. Anemia, which is typically brought on by GIB, or iron deficiency, may also be responsible for this [53]. Although typically found in individuals with recurrent ulcers from NSAID abuse, PUD may sometimes present with major life-threatening consequences like perforations and hemorrhage [55].

Severe epigastric pain is the most prevalent and standard indicator of NSAID-induced PUD among all the aforementioned symptoms. In the prospective study carried out by Okoye OG *et al.* [56] in Nigeria, 94.7% of the 132 patients suspected of PUD on examination showed severe epigastric pain, making it the most common symptom. In an observational study by Ali AM *et al.* [51], 51 patients with PUD were examined, and 42 of them reported having severe epigastric pain, resulting in a presenting rate of 82.4%, as shown in Table 1 (Ref. [51]).

Diagnosis of NSAID-induced PUD

Clinical signs including epigastric pain, nausea, and a sense of fullness are frequently used to identify NSAID-induced PUD; however, it is important to highlight that these signs and symptoms are rarely diagnostic [46]. A thorough history of the patient is required to form a more

Table 1. Signs and symptoms of peptic ulcer disease [51].

Sign and symptoms	Number of patients	Percentage of patients
Pain in epigastric region	42	82.4%
Abdominal tenderness on palpation	41	80.4%
Signs of peritonitis	38	74.5%
Distended abdomen	36	70.6%
Signs of emesis	31	60.8%
Systolic blood pressure less than 90 mmhg	15	29.4%

Table 2. Diagnostic tests for peptic ulcer disease [46].

Diagnostic tests for peptic ulcer disease (PUD)	
Esophagogastroduodenoscopy (EGD)	• Recommended in individuals with symptoms of hemorrhage, anorexia, chronic illness, or persistent Emesis. • Also indicated in those whose symptoms are unresponsive to medication and in those over 55 years of age. • Gastric and duodenal ulcers and malignancies diagnosis: >90% sensitivity.
Gastrografin (GGF) Contrast Radiography (double-contrast hypotonic duodenography)	• Indicated when endoscopy is neither feasible nor practical. • Recommended when complications like gastric outlet blockage are suspected. • With disease progression, diagnostic accuracy improves. • Duodenal ulcer detection: 80%–90% sensitivity.
Diagnostic tests for *Helicobacter Pylori* in PUD	
Endoscopic Biopsy	• Rapid urease test: sensitivity, 93–97%; specificity, 100%. • Culture: sensitivity, 70–80%; specificity, 100%. • Histology: sensitivity, >95%; specificity, 100%.
Stool Antigen Test	• Sensitivity: 91–98%; specificity: 94–99%. • Although inconvenient, the results are accurate. • Useful for confirming eradication.
Serologic ELISA	• Sensitivity: 85%; specificity: 79%. • Only useful for preliminary testing. • Cannot be used to confirm eradication.
Urea Breath Test	• Specificity: 91–98%; sensitivity: 95–100%. • Useful for confirming eradication. • PPI medicine needs to be stopped two weeks before testing.
Urine-based ELISA & Rapid Urine Test	• 70–96% sensitivity; 77–85% specificity. • Not a reliable indicator of eradication.

PPI, proton pump inhibitor; ELISA, enzyme-linked immunosorbent assay.

accurate diagnosis, primarily focusing on NSAID usage and past PUD episodes [57]. If the initial clinical presentation points to PUD, the patient should be examined for any warning signs. Alarming symptoms, such as anemia, hematemesis, melena, anorexia, and vomiting, are typically linked to PUD-related complications [46]. In order to diagnose PUD accurately, certain tests may also be used (Table 2, Ref. [46]).

Long-term usage of NSAIDS frequently results in subepithelial hemorrhage, mucosal erosions, and ulceration [3]. Esophagogastroduodenoscopy (EGD), also known as upper endoscopy, is the gold standard test for diagnosis since it can detect these endoscopic abnormalities [47]. As it is highly sensitive and extremely precise at determining the existence of mucosal ulcers both in the stomach and the duodenum, it is the standard technique for diagnosing PUD [55]. Despite the fact that an EGD can be recommended to any patient with epigastric discomfort since it is neither time-consuming nor cost-effective, individuals over the age of 55 or who exhibit complications are often strongly urged to do so [46]. In order to rule out any malignant lesions present, patients with NSAID-induced PUD may also be advised to have a biopsy along with an EGD [58].

In the paper "Clinical features of gastroduodenal injury associated with long-term low-dose aspirin therapy" by Iwamoto J *et al.* [59], it was shown that even individuals with no signs of PUD had ulcers or erosions on EGD, showing the significance of EGD in NSAID users. In another study by Iwasaki H *et al.* [60] in Japan, the majority of the patients with PUD were also diagnosed using EGD.

Prevention and Treatment of NSAID-induced Peptic Ulcer

The prevalence of upper GI injuries related to NSAIDs has been rising due to their extensive usage in the primary and secondary prevention of cardiovascular and cerebrovascular diseases. These injuries encompass gastric mucosal erosions, peptic ulcers, and bleeding. Several strategies are currently accessible to mitigate GI harms associated with NSAIDs, including prescribing COX-2 inhibitors and co-prescribing gastro-protective agents such as PPIs, misoprostol, and H2RAs [61].

Role of PPIs

Ever since Omeprazole was introduced in 1989, PPIs have consistently emerged as the primary treatment option for acid-related disorders. PPIs have repeatedly demonstrated higher patient tolerance, outstanding safety, and altogether a superior capacity to reduce acid in comparison to older drugs which include H2RAs, synthetic prostaglandin analogs, and anticholinergics [61]. According to a meta-analysis, PPIs reduced the risk of upper GI ulcers linked to low-dose aspirin (OR = 0.16; 95% CI: 0.12–0.23) and bleeding (OR = 0.27; 95% CI: 0.16–0.43). PPIs were evaluated for their ability to prevent upper GI damage caused by low-dose aspirin, which is an NSAID, in comparison to a control group that took a placebo, a cytoprotective drug, or an H2RA [62]. PPIs exert their superior biochemical effect by directly inhibiting the acid pump itself. Unlike H2RAs, PPIs can reliably maintain intragastric pH above 4 for a duration of 15 to 21 hours daily, whereas H2RAs achieve this for only 8 hours [63]. Aside from their extended duration of action, PPIs also exhibit superior effectiveness in terms of controlling postprandial and nocturnal intragastric pH, which holds clinical significance for certain patients [64]. The long-term effectiveness of PPIs remains consistent without requiring dose escalation, while H2RAs may exhibit tachyphylaxis, potentially occurring as quickly as 3 to 5 days of regular use [65].

The class of heterocyclic chemical compounds known as benzimidazole, which has both pyridine and benzimidazole components joined by a methylsulfinyl group, is the source of all PPIs now in use. PPIs come in a variety of forms, including enteric-coated tablets, gelatin capsules, and coated granules that can be dissolved in water to create a solution. For immediate action in hospitalized patients, intravenous formulations are also offered. PPIs enter the bloodstream after ingestion and build up in the acidic secretory canaliculi of the activated gastric parietal cells. The PPIs undergo acid-catalyzed breaking of a chiral sulfoxide bond in this acidic environment, with the exception of esomeprazole and dexlansoprazole, which are non-chiral. Active sulfenic acid and/or sulfonamide molecules are produced as a result of this cleavage. Subsequently, these compounds form covalent bonds with cysteine residues on the H+/K+ ATPase, effectively inhibiting acid secretion until new pumps can be synthesized, which can take up to 36 hours [66]. For PPIs to bind, active canaliculi expression of H+/K+ ATPase must be present, which happens after a meal. One meal does not activate all of the parietal cells or all of its proton pumps. Only about two-thirds of proton pumps are completely inhibited by a single dose of PPI, leaving up to one-third of pumps untouched. With successive meals, previously inactive enzymes are drawn into the secretory canaliculi, which causes proton exchange to rise once more but this happens at a slower rate. Pre-prandial dosing is essential due to the short serum half-life. This physiology explains why PPIs' pharmacologic efficacy has been increasing over the course of many treatment days [66].

Furthermore, PPI usage might protect against cancer in Barrett's esophagus, since PPIs heal the chronic esophageal inflammation of reflux esophagitis, which is a risk factor for the development of malignancy [67]. While PPIs are extensively utilized, concerns regarding potential drug interactions persist [68]. PPIs are expensive and long-term use can result in adverse effects which include osteoporosis, fractures, community-acquired pneumonia, and diarrhea linked with Clostridium difficile. A warning about the potential risk of hip, wrist, and spine fractures when used at high doses (more than once daily) or for a long period of time (more than one year) was added to PPI product labels by the U.S. Food and Drug Administration (FDA) in 2010 [69]. A meta-analysis of eight observational studies revealed that individuals who use PPIs had a greater risk of developing pneumonia [70]. Furthermore, prolonged and high-dose usage of PPIs is believed to impact the absorption of calcium, magnesium, and vitamin B12. This is because stomach acid plays a role in aiding the assimilation and ionization of less soluble forms of dietary calcium, as well as the release of vitamin B12 that is bound to food [71]. Moreover, they can have an impact on the metabolism of other medications that are metabolized by the cytochrome P450 (CYP) system. For example, PPIs have been known to slow down the clearance of drugs such as warfarin, diazepam, and phenytoin. There has been significant concern regarding the potential of PPIs to diminish the antiplatelet effects of clopidogrel, as both medications are metabolized by the CYP2C19 enzyme [68]. As a result, the FDA has issued a warning label regarding this matter [72].

Role of H2RAs

Due to concerns surrounding the long-term safety of PPIs, healthcare professionals are actively seeking alternative gastro-protective agents. One such alternative is the use of H2RAs, which have been widely employed as gastro-protective agents. A phase III, randomized, double-blind and placebo-controlled trial was conducted to investigate the effects of famotidine, a H2RA, in preventing peptic ulcer and esophagitis in patients who were on low-dose aspirin [73]. H2RAs are considered cost-effective options

as conventional anti-secretory medications. It was emphasized in the 2010 expert consensus agreement that was updated by the American College of Gastroenterology (ACG), American College of Cardiology Foundation (ACCF), and American Heart Association (AHA), that GI hazards related to antiplatelet medication and NSAID usage should be minimized. According to the revised document, H2RAs are a viable and reasonable alternative to PPIs for preventing and treating GI injury caused by low-dose aspirin (LDA) therapy [74].

The mechanism of action of H2RAs involves the competitive inhibition of histamine type-2 receptors on parietal cells, leading to the inhibition of acid secretion. This results in a reduction of both basal and stimulated gastric acid secretion. Furthermore, H2RAs also contribute to a decrease in pepsin secretion, thereby reducing peptic activity. While H2RAs have shown efficacy in reducing the risk of NSAID-induced duodenal injury, further confirmation is required regarding their therapeutic effect on NSAID-induced gastric ulcers [75]. Therefore, H2RAs have not always been advised for preventative therapy in NSAID users due to their limited ability to appreciably lower the rate of gastric ulcers caused by the use of NSAID when provided in conventional doses. H2RAs and the prevention and treatment of gastric ulcers, however, appear to be related in a dose-response manner [76]. Standard doses of H2RAs have thus shown efficacy in lowering the risk of duodenal ulcers linked with NSAID usage, but they might not have the same level of efficacy in preventing gastric ulcers associated with NSAID use. On the other hand, high-dose H2RAs have been shown to be effective in preventing both chronic duodenal and gastric ulcers related to NSAID use.

H2RAs, whether used alone or in combination with NSAIDs, present certain advantages in terms of gastroprotection compared to other strategies. H2RAs are efficiently absorbed when taken orally, their absorption is minimally affected by concurrent antacid use, and food does not impact their absorption. This eliminates the requirement for dosing based on meals, which is often necessary with PPIs, particularly in the treatment of gastroesophageal reflux disease (GERD) [76]. Furthermore, unlike PPIs, the available data suggest that there are no significant interactions between H2RAs and medications, except for cimetidine and clopidogrel [77].

To summarize, PPIs are widely recognized as the preferred and efficacious prophylactic agents [78]. Based on the available evidence, a study demonstrated that the combination of selective COX-2 inhibitors with PPIs was the most effective strategy for prophylaxis. This was followed by the use of selective COX-2 inhibitors alone, and then nonselective NSAIDs with PPIs. Nonselective NSAIDs with H2RAs ranked the lowest in terms of effectiveness (Fig. 4, Ref. [79]). Additionally, another meta-analysis indicated that H2RAs were found to be less effective in preventing GIB and ulcer formation associated with LDA use, suggesting the preferential usage of PPIs in cases of intolerance [80].

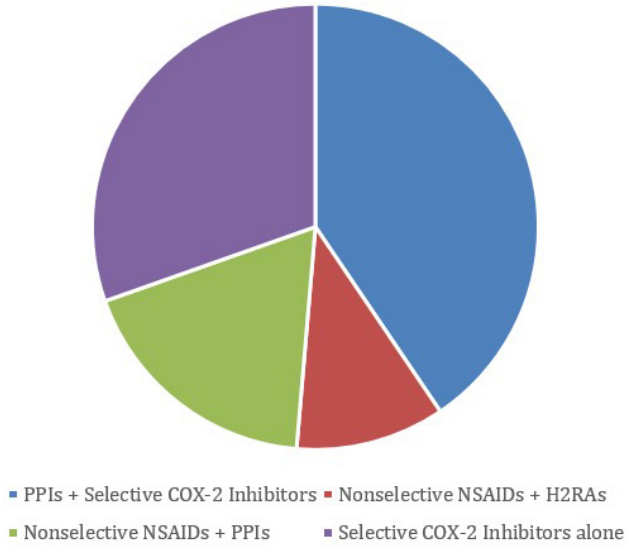

Fig. 4. Overview of the effectiveness of common treatment strategies used to prevent gastric ulcers in patients taking NSAIDs [79]. COX, Cyclo-oxygenase; H2RAs, H2 receptor antagonists.

This review lacks comprehensive information on the studies mentioned, including details such as sample sizes, inclusion criteria, and treatment duration. It does not address potential biases, such as publication bias or funding bias, that may have influenced the results of the reviewed studies. Although the present review briefly mentions some adverse effects of long-term PPI use, such as osteoporosis, fractures, and infections, it does not provide a thorough analysis of the safety profile of PPIs and H2RAs. Furthermore, the review focuses on PPIs and H2RAs as preventive strategies for NSAID-induced ulcers, and does not explore other interventions and approaches such as misoprostol, sucralfate, and selective COX-2 inhibitors, which can be used in combination with or as alternatives to these medications.

Conclusion

This article reviews the evidence for a link between chronic NSAIDs usage and peptic ulcers, in addition to highlighting the pathogenesis, clinical manifestations, and management options. With this information, physicians can more carefully assess the benefits versus risks of NSAIDs and are able to provide alternatives with minimum side effects. Prescribing the lowest effective dosage of NSAIDs for the shortest interval can avoid toxicity in patients without risk factors. In summary, the highest risk of developing gastric ulcers includes alcoholism, previous history of peptic ulcers, anticoagulant use, smoking, *H. pylori* infection,

renal failure, etc. PPIs, Misoprostol, sucralfate and a broad range of selective COX-2 inhibitors can be used as an alternative whilst having easier-to-manage adverse effects compared to NSAID-induced toxicity. Finally, further research should be conducted to provide a more structured protocol to manage NSAID-induced ulcers.

Availability of Data and Materials

Not applicable.

Author Contributions

HIs, AS, HIm, SA, MF, MK, GMAM, TI and RI collected and analyzed the literature. HIs and RI were involved in conceptualizing the article and its formatting. HIm, AS, SA, MF, MK and GMAM wrote the manuscript. HIs and TI were involved in editing the preliminary drafts of the manuscript. RI, HIs and TI were involved in reviewing the final manuscript. HIs and TI were involved in the supervision of the whole process. AS worked on the introduction and background part of our article. HIm and MF made their valuable contribution covering the risk factors and pathogenesis. MK, GMAM and SA covered the article's clinical signs and symptoms and treatment segment. All authors contributed significantly to editorial changes of important content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors follow ICMJE guidelines.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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