Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of drugs that are widely used to alleviate the symptoms associated with conditions in which an inflammatory component is present, e.g. osteoarthritis and rheumatoid arthritis, as well as several instances of somatic pain. In addition to NSAIDs, low-dose aspirin (acetylsalicylic acid or ASA) is used for the primary and secondary prophylaxis of both cerebrovascular and cardiovascular events. It is also well-recognised that NSAIDs have severe gastrointestinal side-effects, ranging from dyspepsia to gastroduodenal ulcers and bleeding. These agents are prescribed and used frequently in all age groups, but especially in the elderly population. Up to 70% of the elderly take NSAIDs on a weekly basis. Only a small proportion of patients using these agents develop gastrointestinal toxicity. However, due to the large numbers of patients using them, this still places a significant burden on the healthcare system.

Numerous factors may increase the risk of upper gastrointestinal complications, including ulceration. In a resource-limited country like South Africa, in which a significant number of patients are seen at primary healthcare level (including community pharmacies), it is important to note that additional risk factors for early identification of gastrointestinal events or toxicity exist. These risk factors have been included in a suggested checklist for the pharmacist, and can be used per patient, per visit (see Table I).

### NSAID-induced gastropathy

The following important aspects form the basis of our current understanding of NSAID-induced gastropathy:

- The use of NSAIDs is an important cause of upper-gastrointestinal adverse events.
- NSAIDs-induced gastrointestinal toxicity can also involve the lower-gastrointestinal tract.
- The coxibs, or cyclooxygenase-2 (COX-2) enzyme-selective NSAIDs, e.g. celecoxib, are also associated with an increased risk of upper-gastrointestinal adverse outcomes.
- Parenteral NSAIDs are also associated with a significantly increased risk of lower-gastrointestinal toxicity.
- According to a recent study, when comparing celecoxib with non-selective NSAIDs, the risk of developing lower-gastrointestinal toxicities appears to be equal.

### Pathophysiology of NSAID gastric damage and other toxicities

The NSAIDs, including aspirin, cause gastric mucosal damage in two specific ways (refer to Figure 1), namely:

- Systemic inhibition of endogenous mucosal prostaglandin synthesis.
- Direct or topical irritation of the gastric epithelium.
Systemic inhibition of endogenous mucosal prostaglandin synthesis is the result of their inhibition of the COX enzyme. COX is the rate-limiting enzyme in the conversion of arachidonic acid to prostaglandins (PGs), and is inhibited by the NSAIDs. Two COX isoforms have been identified, namely COX-1 and COX-2 (refer to Table II).

**Table I: Risk assessment for gastrointestinal events**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>Visit 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of multiple NSAIDs (including OTC NSAIDs and aspirin)</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Dosage (higher dosages increase the risk)</td>
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<tr>
<td>Month of NSAID use</td>
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<td></td>
<td></td>
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<tr>
<td>Prior ulcer complications</td>
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<td></td>
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<tr>
<td>Advanced age (especially over 65 years)</td>
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<tr>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Concomitant use of corticosteroids, e.g., prednisone</td>
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<tr>
<td>Concomitant use of selective serotonin-reuptake inhibitors, e.g., fluoxetine</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant use of anticoagulants, e.g., warfarin, and antiplatelet agents</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

* It is interesting to note that the greatest risk of gastrointestinal complications occurring exists during the first few months of treatment,

† Rheumatoid arthritis, appears to independently increase the risk of adverse gastrointestinal events,

¥ Selective serotonin-reuptake inhibitors, when used alone or in combination with NSAIDs, substantially increase the risk of upper gastrointestinal haemorrhage

**Mechanisms of action**

- Taking an NSAID
  - Cyclo-oxygenase-2 inhibition
  - NO production
  - PMN activation
  - Formation of oxygen radicals

- Inflammation
  - Inflammation

- Topical irritation
  - Detrimental physiological effects

- Epithelial damage
  - Protection of the gastrointestinal mucosa

**Figure 1: Pathogenesis of gastric damage induced by nonsteroidal anti-inflammatory drugs (including aspirin)**
Angiogenesis is important for the repair of gastrointestinal ulcer risks. The use of clopidogrel and other medicines that impair platelet homeostasis reduces the benefit of the ulcer-sparing abilities, and increases the bleeding associated with PU may be due to the erosion of the ulcer into an artery. Depending on the site of the bleeding, it may be occult, or present as black-coloured stools (melena), or the patient may vomit blood (hematemesis). When attempting to diagnose peptic ulcer disease, specific tests have to be requested to enable an accurate diagnosis. A gastroscopic examination is performed, which can also be used to perform biopsies. Invasive diagnostic measures include or exclude this diagnosis. Gastric acid secretory studies have to be requested to enable an accurate diagnosis. A patient presenting with a bleeding ulcer will need to undergo a haematocrit (Hct) and haemoglobin (Hb) test as part of their work-up, to determine the extent of the bleeding. When there is a concern that there may be concomitant infection with Helicobacter pylori, specific tests will have to be conducted to include or exclude this diagnosis. Gastric acid secretory studies may have to be performed.

**Diagnosis of NSAID-induced gastropathy**

When attempting to diagnose peptic ulcer disease, specific tests have to be requested to enable an accurate diagnosis. A patient presenting with a bleeding ulcer will need to undergo a haematocrit (Hct) and haemoglobin (Hb) test as part of their work-up, to determine the extent of the bleeding. When there is a concern that there may be concomitant infection with Helicobacter pylori, specific tests will have to be conducted to include or exclude this diagnosis. Gastric acid secretory studies may have to be performed.

**Signs and symptoms associated with NSAID-induced peptic ulceration**

The clinical manifestations of peptic ulceration (PU) may depend on the severity thereof. With NSAID-induced ulcers, upper-gastrointestinal bleeding, perforation, and obstruction, may be some of the most serious, life-threatening complications. The bleeding associated with PU may be due to the erosion of the ulcer into an artery. Depending on the site of the bleeding, it may be occult, or present as black-coloured stools (melena), or the patient may vomit blood (hematemesis).

Table III highlights the common signs and symptoms of peptic ulceration.

<table>
<thead>
<tr>
<th>Functions</th>
<th>COX-1</th>
<th>COX-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location (where they are normally found)</td>
<td>Mostly found in body tissue, which includes the stomach, kidneys, intestines and platelets.</td>
<td>Undetectable in most tissues during normal physiological conditions, but is particularly expressed in inflammatory conditions and arthritis.</td>
</tr>
</tbody>
</table>

The side-effects associated with the NSAIDs are due to the non-selective inhibition of COX-1, while their anti-inflammatory properties are due to the inhibition of COX-2. Non-selective or traditional NSAIDs, e.g. NSAIDs such as ibuprofen and diclofenac, inhibit COX-1 and COX-2, whereas the selective COX-2 inhibitors, e.g. celecoxib, are highly-selective inhibitors of the COX-2 isozyme.

So why is COX-2 associated with adverse gastrointestinal outcomes? The original hypothesis was that selective COX-2 inhibitors would spare COX-1-mediated PGs, and only inhibit the production of COX-2-mediated PGs involved in the inflammatory process. However, COX-2 is involved in the mucosal defence and repair, and it seems that both the COX-isosforms are responsible for the physiological processes of tissue injury. In animal studies, where COX-1 was selectively inhibited, it did not seem that the inhibition resulted in significant gastric damage. In other studies, where selective COX-2 inhibitors were compared to NSAIDs in relation to gastric complications, they produced severe gastrointestinal complications less frequently than NSAIDs, but when compared to placebo, clinically significant gastrointestinal injuries appeared more frequently than in the control group.

The addition of aspirin to a selective COX-2 regimen further reduces the benefit of the ulcer-sparing abilities, and increases the ulcer risks. The use of clopidogrel and other medicines that impair angiogenesis do not cause ulcers, but rather prevent the healing of gastric erosions that may lead to ulceration and bleeding. Angiogenesis is important for the repair of gastrointestinal mucosal disruptions. Furthermore, following the administration of NSAIDs, leukocytes (mostly neutrophils) tend to adhere to the vascular endothelium of the gastric microcirculation. This seems to be a critical event in the formation of gastric ulcers. When this step was inhibited in laboratory animals, it seemed as though gastric ulcers were prevented.

However, the neutrophil adhesion in the vascular endothelium contributes to NSAID-induced gastropathy in two ways:

- Physical obstruction of capillary flow.
- Release of tissue-damaging proteases and oxygen-derived free radicals, once neutrophils have been activated.

The inhibition of COX-2 induces neutrophil adherence when NSAIDs are administered. Therefore, when a selective COX-2 inhibitor is administered, it may spare much of the total PG synthesis by the mucosa. It also triggers the key event in the pathogenesis of NSAID-induced gastropathy.

The topical irritant properties associated with NSAIDs are mostly linked with the more acidic NSAIDs, such as aspirin. This is due to their ability to decrease the hydrophobicity of the mucous gel layer in the gastric mucosa. Aspirin is the most damaging of all the NSAIDs, although most of them have topical irritant effects. Other formulations of the NSAIDs, e.g. prodrugs, parenteral formulations, rectal preparations, and enteric-coated aspirin, may be associated with less acute topical gastric mucosal injury, but may still be involved with varying degrees of gastrointestinal toxicity, due to their systemic inhibition of endogenous PGs.

Cardiovascular-related toxicity, due to the administration of COX-2 inhibitors, led to the withdrawal of the bestseller in this class, namely rofecoxib, from the global market. However, cardiovascular toxicity has now been linked to non-selective NSAIDs as well, with the possible exclusion of naproxen. The cardiovascular toxicity associated with COX-2 inhibitors may be due to the inhibition of the synthesis of prostacyclin (PGI2), which may have anti-thrombotic properties, while sparing thromboxane A2 (TXA2), a prothrombotic substance. PGE2 is the PG that is primarily associated with inflammation. If this PG could be selectively inhibited, it may prove to be an option for the reduction of inflammation, without the associated cardiac risk profile.
Using a non-selective COX-2 inhibitor, instead of a non-selective NSAID, does not completely eliminate ulcers and complications for at-risk patients, but may reduce the risk, provided that the patient’s cardiovascular profile has been taken into consideration.

When selecting a gastroprotective strategy, the patient should be evaluated holistically, by taking into account the cardiovascular risks and concomitant antiplatelet therapy.

### Principles of reducing risk

When identifying and reducing the risk of NSAID-induced gastrointestinal ulcers, the following therapeutic principles may be used:

- **Co-therapy with the NSAID and a proton-pump inhibitor (PPI), or misoprostol, reduces the ulcer risk and associated complications in high-risk patients.**
- **Using a non-selective COX-2 inhibitor, instead of a non-selective NSAID, does not completely eliminate ulcers and complications for at-risk patients, but may reduce the risk, provided that the patient’s cardiovascular profile has been taken into consideration.**
- **When selecting a gastroprotective strategy, the patient should be evaluated holistically, by taking into account the cardiovascular risks and concomitant antiplatelet therapy.**

### Identifying a risk profile for patients

The risk may be reduced by substituting the NSAID with a non-NSAID analgesic, such as paracetamol. This may not necessarily be feasible, especially in a patient with a severe debilitating inflammatory condition, such as arthritis. Figure 2 presents a possible algorithm for the management of vulnerable patients on long-term NSAIDs, and those who also have cardiovascular risks.

It illustrates the following basic principles:

- When a patient requires long-term NSAID therapy, the need for the NSAID should be reviewed, and alternative treatment approaches sought.
- If no other alternative exists, the NSAID should be used at the lowest possible effective dosage, for the shortest possible time.
- If the patient is going to be on long-term NSAID-therapy, a gastrointestinal and cardiovascular risk profile should be completed using the patient’s history, physical examination, and laboratory investigations, as needed.
- The lowest effective dose of aspirin should be initiated in patients with an increased cardiovascular risk.
- Naproxen may be used in patients with a low gastrointestinal risk and a high cardiovascular risk, because it has the lowest cardiovascular risk profile in the group.
- If a patient needs naproxen and aspirin, the addition of a gastroprotective agent, such as a PPI, should be considered.
- Testing for *Helicobacter pylori* in patients with a high-risk of NSAID-related gastrointestinal bleeding should be considered.
- A coxib and a PPI may offer good gastrointestinal protection in a patient with a very high risk of an upper-gastrointestinal event.
- When a patient has both a high gastrointestinal and cardiovascular risk profile, then NSAIDs should be avoided. If this is not possible, then the physician should prioritise the cardiovascular and the gastrointestinal risks. If the gastrointestinal risk is the primary concern, a COX-2 inhibitor plus a PPI, should be given. If the cardiovascular risk is the primary concern, then naproxen and a PPI should be considered, especially if the patient is already on aspirin.

### Pharmacotherapeutic strategies for the prevention and treatment of NSAID-induced ulcers

#### General

| Table III: Clinical presentation of peptic ulceration or peptic ulcer disease 

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Mild epigastric pain, or it may present with acute, life-threatening, upper-gastrointestinal complications</td>
</tr>
<tr>
<td>Signs</td>
<td>Weight-loss with nausea, vomiting and anorexia. Complications including bleeding ulcer, perforation, penetration, or obstruction.</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Abdominal pain. Nocturnal pain presenting between midnight and 03.00, waking the patient from sleep. Heartburn, belching and bloating that accompany the pain. Nausea, vomiting and anorexia, which are usually associated with a gastric ulcer, rather than a duodenal ulcer. May be seasonal, and may occur more frequently in the spring or autumn. Episodes may present in clusters that may last for weeks, and then the patient may go into remission for weeks to months, or even years.</td>
</tr>
</tbody>
</table>

More invasive tests will need to be performed to confirm the diagnosis, but also to determine the extent of the gastric involvement.

These could include the following:

- **Fibre-optic upper endoscopy:** This confirms up to 90% of peptic ulcers, and can allow the treating physician to directly inspect the lesions, take a biopsy, and visualise superficial erosions, as well as envisage active bleeding sites.
- **Radiography, with barium, can also be carried out to detect and diagnose peptic ulcers. Some authors view this as the procedure of choice for suspected peptic ulcers.**

The diagnosis should be made using the patient’s clinical picture, and the clinical laboratory tests, where available.

### Other treatment options

#### Misoprostol

Ulcer prophylaxis may be achieved by using misoprostol when the patient has to remain on NSAID therapy. Misoprostol is a synthetic prostaglandin E1-analogue, which replaces the cytoprotective PGs that are depleted by the NSAIDs from the gastrointestinal mucosa. Its efficacy in preventing ulcers in patients using NSAIDs has been demonstrated in various studies, where the efficacy has been proven above the use of placebo.

Although the use of misoprostol has been demonstrated to reduce the risk of gastrointestinal events, it has been proved to have its own spectrum of side-effects. Side-effects associated with the use of misoprostol include abdominal pain, nausea, and diarrhoea, and it should be avoided in women of childbearing potential.

The side-effect profile, and frequent dosing needed with misoprostol, makes compliance to therapy increasingly difficult. Comparative studies have shown that the PPIs may be more effective in patients with NSAID-induced gastric ulcers. Head-to-head studies comparing PPIs to either low- or high-dose
misoprostol found no significant difference between PPIs and misoprostol in the prevention of endoscopic ulcers. However, the PPIs proved to be superior in the prevention of duodenal ulcers.

Fixed-dose combinations of misoprostol and diclofenac (Arthrotec®) have shown a less-frequent association with endoscopically-diagnosed ulcers. The incidence of side-effects with misoprostol is dose-dependent. However, reducing the dose will reduce both side-effects and efficacy.

Sucralfate
Sucralfate is a basic aluminium salt of sucrose octasulfate, which forms an adherent complex at duodenal ulcer sites. It may be beneficial to use when treating NSAID-induced duodenal ulcers, provided that the causative NSAID has been stopped. Sucralfate has not been shown to be effective in the prevention of NSAID-related gastric ulcers. Its routine use for this purpose is not recommended, due to the availability of superior therapeutic options.

$H_2$-receptor antagonists (cimetidine, ranitidine, famotidine and nizatidine)
These agents act by competitively inhibiting the action of histamine at the $H_2$-receptor site on the gastric parietal cell, and thereby modulating the gastric pH. Standard dosages of the $H_2$-receptor antagonists may be effective in reducing NSAID-induced duodenal ulcers, but not gastric ulcers (the ulcer type most frequently associated with NSAIDs).

When given at high doses, the $H_2$-receptor antagonists, e.g. famotidine 20 or 40 mg twice daily, may reduce the incidence of gastric and duodenal ulceration. Having stated that, it is not recommended that these agents are used routinely in asymptomatic patients receiving NSAIDs, since this may mask dyspeptic symptoms associated with mucosal injury. PPIs have proven to be superior in healing gastroduodenal ulcers in patients using NSAIDs, and are better in preventing ulcer recurrence.

PPIs (omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole)
These agents bind irreversibly to the proton pump (H⁺-K⁺-ATPase), inhibiting basal and stimulated gastric-acid secretion. They are administered as prodrugs that are activated in the acidic environment of the parietal cells. Lansoprazole has been proven to protect and heal the gastric mucosa after gastric damage induced by a NSAID via a novel mechanism of action, which uses anti-apoptotic action mediated through regulating factors involved in mitochondrial and Fas-mediated death pathways of apoptosis. In addition to inhibiting acid secretion, lansoprazole also seems to offer gastroprotection through inhibition of apoptosis, and

ASA = American Society of Anesthesiologists, CV = cardiovascular, GI = gastrointestinal, PPI = proton-pump inhibitor.

Figure 2: Algorithm for the use of NSAIDs in high-risk patients, i.e. those with gastrointestinal and cardiovascular risks
stimulation of cell survival and proliferation.\textsuperscript{3,7} After three to four days of therapy, the degree of acid suppression increases, as more of the proton pumps are inhibited. They act only on actively-secreting proton pumps, and should be taken 30-60 minutes prior to having a meal.

The PPIs are available in various dosage forms and formulations, which include delayed-release, enteric-coated dosages that have pH-sensitive granules in a gelatin capsule, rapidly disintegrating capsules, and delayed-release enteric-coated tablets. Similar healing times are seen in five of the PPIs, omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole, with similar maintenance times for ulcer healing and symptom relief, when used at the recommended dosages.\textsuperscript{3,7}

In conclusion, the PPIs, especially when used as co-therapy to NSAIDs, reduce the risk of NSAID-induced gastric and duodenal ulcers, and are better tolerated than misoprostol. All of the PPIs are equally effective when used at standard dosages, and they reduce the risk of NSAID-related ulcer bleeding.\textsuperscript{3,7,9} Chronic use of PPI therapy may be associated with an increased risk of infection and nutritional deficiencies, as gastric acid plays a role in the defence against bacterial colonisation and nutrient absorption.\textsuperscript{3,7} Patients should be carefully monitored when using chronic therapy with the PPIs.\textsuperscript{3,7,9}

**COX-2 inhibitors (celecoxib and rofecoxib)**

As a result of concerns regarding their cardiovascular safety, and recent information on their related gastrointestinal toxicity, the use of coxibs should be evaluated, and the risks vs. the benefits for each patient carefully weighed up. Celecoxib is no longer considered to be a selective COX-2 inhibitor, as it carries the same gastrointestinal warnings as the non-selective NSAIDs.\textsuperscript{3,7}

There seems to be a dosage-dependent correlation with cardiovascular toxicity for celecoxib.\textsuperscript{3,7} The increase in the cardiovascular toxicity appears to relate to the dosage and the duration of use.\textsuperscript{3,7} When using these agents, they should be given at the lowest possible dosage, for the shortest possible duration.\textsuperscript{3,7}

The gastric side-effects of the COX-2 inhibitors appear to be similar to those of the non-selective NSAIDs, namely dyspepsia, abdominal pain, fluid retention, hypertension, and renal toxicity.\textsuperscript{3,7}

**New approaches: gaseous mediator-releasing NSAIDs**

As discussed in the section on pathophysiology, the hypothesis exists that the deficiency of PGs in the gastrointestinal mucosa can lead to ulceration. This has opened up new opportunities for drug development.\textsuperscript{1} Some of these were developed in the 1980s for use in the prophylaxis of NSAID-induced gastrointestinal injury. Unfortunately, some were associated with adverse effects, such as diarrhoea and abdominal pain.\textsuperscript{1} Other endogenous mediators that may produce PG-like effects, such as mucosal defence, have brought about the development of novel NSAIDs that can slowly release “gastroprotective” substances.\textsuperscript{1,10}

Endogenous gaseous mediators, such as nitric oxide (NO) and hydrogen sulphide (H$_2$S), exhibit many PG-like effects in the gastrointestinal tract.\textsuperscript{1} NO is already known for its vasodilatory mechanism of action. However, it can also inhibit leukocyte adherence to the vascular endothelium.\textsuperscript{1,10} Administration of these agents increases the resistance of the gastric mucosa to injury by the NSAIDs, or other noxious substances.\textsuperscript{1,10} This presents an opportunity to “couple” NO and H$_2$S with the NSAIDs, and may prevent, or even compensate for, the inhibition of gastric PG-synthesis. NO and H$_2$S also has anti-inflammatory properties, thereby boosting the anti-inflammatory properties of the NSAIDs in question.\textsuperscript{1,10}

**Conclusion**

The use of NSAIDs is an important cause of gastropathy. It was always thought that only the non-selective NSAIDs were the causative agents, but the selective COX-2 inhibitors have now also been shown to be associated with untoward gastrointestinal side-effects. NSAID-related ulcers require an individualised assessment of a patient’s current disease state and medication use. More importantly, the patient should be assessed for his or her risk of gastrointestinal and cardiovascular toxicities. If the patient needs to continue on the NSAID, then an appropriate regimen should be sought, with the best possible efficacy, and lowest possible number of side-effects. New advances have been made in designing novel anti-inflammatory drugs, with reduced toxicity. Coupling of NSAID-mieties that slowly release gastroprotective gaseous mediators, such as NO and H$_2$S, appears to be a promising new approach to reduce the toxicity of these agents.

**References**