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Editor:  Professor Neville Yeomans  
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A/Professor Daniel Stiel, Gastroenterologist
DIGESTIVE HEALTH FOUNDATION

Established in 1990, the Digestive Health Foundation (DHF) is an educational body committed to promoting better health for all Australians by developing education and community health programs to improve awareness and understanding of digestive diseases. Research and education into gastrointestinal disease are essential to contain the effects of these disorders on all Australians.

The DHF is the educational arm of the Gastroenterological Society of Australia, the professional body representing the specialty of gastrointestinal and liver disease in Australia. Members of the Society include physicians, surgeons, scientists and other medical specialties with an interest in GI disorders.

Guidelines for General Practitioners and patient leaflets are available on a range of topics related to GI disorders. Copies are available by contacting the Secretariat at the address below.

GUIDELINES FOR GENERAL PRACTITIONERS

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EXECUTIVE SUMMARY

The third edition of NSAIDs and the Gastrointestinal Tract has been updated to help Australian and NZ clinicians make informed decisions regarding the benefits and risks for an individual patient when choosing an NSAID for long-term (defined as >4 weeks) pain management. Patients who take non-steroidal anti-inflammatory drugs (NSAIDs) may develop serious gastrointestinal (GI) side effects in both the upper and lower GI tract. While the newer classes of NSAIDs (coxibs) have been evaluated in endoscopic ulcer studies and clinical outcome trials, and shown to significantly reduce the risk of upper GI ulcer and complications, they do not eliminate GI complications in at-risk patients. Low-dose aspirin, widely used for cardioprotection, is also not free from GI adverse effects. When low-dose aspirin is taken in combination with a traditional NSAID or a coxib the risk of developing a serious GI event increases significantly. Current evidence on NSAID use suggests a number of factors put patients at higher risk of an NSAID-induced GI adverse event. These include older age, previous history of upper GI symptoms, GI bleeding or an ulcer, co-morbidity, prolonged use, high doses, and concomitant use of drugs like corticosteroids, anti-platelet agents or anticoagulants. If people have at least one of these risk factors, and have to take an NSAID for more than a short period, it is recommended they be prescribed some form of gastroprotection - principally a proton pump inhibitor (PPI) or misoprostol. PPIs are better tolerated and the most effective in the prevention of upper GI events and in at-risk patients. Long-term NSAID therapy can be more complex in patients at high GI risk. Testing for and eradicating H. pylori should be considered in patients starting NSAID therapy and in at risk patients, in conjunction with ongoing gastroprotection. In high risk patients, with low cardiovascular risk, a coxib alone or a traditional NSAID with a PPI may be appropriate. For patients at very high risk of upper GI events, a combination of a coxib plus a PPI may offer the best safety profile. When both GI and cardiovascular risks are high, the optimal strategy is to avoid all NSAID therapy if at all possible. If the NSAID therapy is necessary, and the primary concern is cardiovascular risk, naproxen plus a PPI in patients taking low-dose aspirin is preferred. Close monitoring of GI risk is essential.

RECOMMENDATIONS
APPLICATION STATEMENT

These recommendations have been prepared for the Gastroenterological Society of Australia and every care has been taken in their compilation. The recommendations are intended to be used as a guide only. The Gastroenterological Society of Australia and the compilers of these recommendations shall not be liable to users of these guidelines nor to any other person, firm, company or other body for any loss, direct, indirect or consequential, on whatsoever account for any omission or negligent misstatement contained herein, or by reason of, arising from or in relation to any such user, by any other person, company or body relying or acting upon or purporting to rely or act upon any matter contained therein or arising thereout.

ACKNOWLEDGEMENTS

These guidelines were produced by the Gastroenterological Society of Australia. We would like to acknowledge the contribution of Professor Neville Yeomans and Associate Professor Simone Strasser.

ABBREVIATIONS

CI confidence interval
COX cyclooxygenase
CV cardiovascular
GI gastrointestinal
\(\text{H}_2\text{RA}\) histamine-\(\text{H}_2\)-receptor antagonist
IBD inflammatory bowel disease
NSAID non-steroidal anti-inflammatory agent
OA osteoarthritis
OTC over-the-counter
POB perforation, obstruction or bleeding
PPI proton pump inhibitor
PB perforation, ulceration, and bleeding
RA rheumatoid arthritis
RCT randomised controlled trials
RR relative risk
1 NON-Steroidal ANti-INflammatOrY (NSAID) AGENTS

Chronic pain affects one-in-five adults,\(^1\) limits functioning, and is a significant public health problem in Australia. In 2007, Access Economics estimated there were 3.85 million Australians with arthritis (www.arthritisaustralia.com.au). One study found osteoarthritis, rheumatoid arthritis, and back pain have the largest negative impact on quality of life of any chronic condition (including cancer, chronic respiratory conditions, or heart disease).\(^2\)

Non-steroidal anti-inflammatory agents (NSAIDs) are drugs with analgesic, antipyretic and anti-inflammatory effects - they reduce pain, fever and inflammation. The term “non-steroidal” is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic and non-addictive.

NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. NSAIDs are effective in improving pain and function in patients with arthritis.\(^3\) Research continues into their potential for prevention of specific GI and colorectal cancers, and treatment of other conditions, such as cardiovascular disease.\(^3\)

NSAIDs are generally indicated for the symptomatic relief of the following conditions:\(^4\)

<table>
<thead>
<tr>
<th>Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs are a structurally diverse group of medications that share the ability to inhibit prostaglandin synthetase or cyclooxygenase (COX). While the result of this effect is mainly a reduction in inflammation and peripheral nociceptor sensitisation, there is some evidence NSAIDs have a central analgesic action as well, although the exact mechanism remains unclear.</td>
</tr>
</tbody>
</table>

COX occurs in at least two isoforms (Figure 1): COX-1 (constitutive) mediates formation of prostaglandins responsible for GI mucosal protection from gastric acid and digestive enzymes, haemostasis and renal blood flow; and COX-2 (inducible) catalyses production of prostaglandins that act as inflammatory mediators. COX-2 can also play a homeostatic role (e.g. ulcer healing, maintenance of renal blood flow during stress, prostacyclin production). COX-2 is produced when joints are injured or inflamed. NSAIDs that inhibit COX-2 > COX-1 are referred to as COX-2 preferential or selective agents and some are ‘highly’ selective.

<table>
<thead>
<tr>
<th>Rheumatoid arthritis</th>
<th>Headache and migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td>Postoperative pain</td>
</tr>
<tr>
<td>Inflammatory arthropathies (e.g. ankylosing spondylitis, psoriatic arthritis, reactive arthritis)</td>
<td>Mild-to-moderate pain due to inflammation and tissue injury</td>
</tr>
<tr>
<td>Acute gout</td>
<td>Pyrexia</td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
<td>Renal colic</td>
</tr>
<tr>
<td>Metastatic bone pain</td>
<td>Newborns whose ductus arteriosus is not closed within 24 hours of birth</td>
</tr>
</tbody>
</table>
NSAID Categories

NSAID can be segmented into three broad categories according to action on COX (Table 1):
1) Salicylates (acetylated / non-acetylated)
2) Traditional NSAIDs
3) COX-2 selective inhibitors / coxibs

Salicylates
Aspirin, the oldest drug in the class (pure acetylsalicylic acid[ASA] was first made in 1897), is an NSAID which also irreversibly inhibits platelet aggregation and prolongs bleeding time. This underlies the cardioprotective clinical efficacy of low-dose aspirin and its role in reducing the risk of primary cardiovascular events (but not mortality) and secondary ischaemic heart disease events and mortality. Aspirin has a unique mode of action as it inhibits COX-1 and COX-2 irreversibly by covalent modification (acetylation).

Traditional or Standard NSAIDs
In general, traditional NSAIDs have similar effectiveness in improving pain and function in patients with arthritis. Topical NSAIDs have similar effectiveness as oral NSAIDs in improving pain and function in patients with osteoarthritis of the knee. In general, NSAIDs are more effective than acetaminophen in the management of moderate-to-severe arthritis pain. Traditional NSAIDs, which target both forms of cyclooxygenase, COX-1 and COX-2, are known to have common and serious GI side effects. According to the COX-2 hypothesis, inhibition of COX-2 is the basis for the anti-inflammatory, antipyretic, and analgesic effects of these agents. COX-1 is thought to play an important role in maintaining gastric mucosal integrity and its inhibition is the main mechanism causing adverse GI events.

Naproxen is associated with a lower risk of coronary heart disease events than other traditional NSAIDs. Naproxen at a dose of 500 mg twice daily may not increase the risk of cardiovascular events compared to placebo, while diclofenac and ibuprofen may increase these risks. In addition, naproxen demonstrated a lower risk of cardiovascular events compared with coxibs. There are insufficient data to allow comparisons of the cardiovascular safety of lower doses of naproxen compared with the other NSAIDs.
Table 1. Broad categories of NSAIDs

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Common Brand Names</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salicylates</strong></td>
<td></td>
</tr>
<tr>
<td>acetylsalicylic acid / aspirin (300mg)</td>
<td>Solprin</td>
</tr>
<tr>
<td>low-dose aspirin (100mg)</td>
<td>Astrix; Cartia; Cardiprin 100</td>
</tr>
<tr>
<td>diflunisal</td>
<td>Dolobid</td>
</tr>
<tr>
<td>choline magnesium trisalicylate</td>
<td></td>
</tr>
<tr>
<td><strong>Traditional or nonselective NSAIDs</strong></td>
<td></td>
</tr>
<tr>
<td>Acetates:</td>
<td></td>
</tr>
<tr>
<td>diclofenac</td>
<td>Voltaren; Arthrotec; Diclohexal; Dinac; Fenac</td>
</tr>
<tr>
<td>indomethacin</td>
<td>Indocid; Arthrexin</td>
</tr>
<tr>
<td>sulindac</td>
<td>Aclin; Clinoril</td>
</tr>
<tr>
<td>Propionates:</td>
<td></td>
</tr>
<tr>
<td>flurbiprofen</td>
<td>Ansaid</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>Nurofen; Brufen; Rafen; Act-3; Actiprofen; Bugesic</td>
</tr>
<tr>
<td>ketoprofen</td>
<td>Orudis; Orudis SR; Oruvail SR</td>
</tr>
<tr>
<td>ketorolac trometamol</td>
<td>Toradol</td>
</tr>
<tr>
<td>naproxen</td>
<td>Proxen; Naprosyn; Crysanal; Naprogesic; Aleve; Anaprox; Inza</td>
</tr>
<tr>
<td><strong>Oxicams:</strong></td>
<td></td>
</tr>
<tr>
<td>piroxicam</td>
<td>Candyl; Feldene; Mobilis; Pirohexal; Rosig</td>
</tr>
<tr>
<td>tenoxicam</td>
<td>Ticoltil</td>
</tr>
<tr>
<td>meloxicam</td>
<td>Mobic (slightly COX-2 selective)</td>
</tr>
<tr>
<td><strong>COX-2 Inhibitors/Coxibs</strong></td>
<td></td>
</tr>
<tr>
<td>celecoxib</td>
<td>Celebrex</td>
</tr>
<tr>
<td>valdecoxib</td>
<td>Bextra</td>
</tr>
</tbody>
</table>

Note: The classification of NSAIDs is controversial, often guided by historical development, rather than clinical effect, and can be confusing. Different NSAIDs differ in their COX-2/COX-1 selectivity; however, the measured degree of selectivity can depend on the assay system used. Furthermore, clinical effects are subject to variability from patient to patient. Traditional (sometimes called standard) NSAIDs (e.g. diclofenac, ibuprofen, naproxen) differ considerably in the degree of selectivity. Meloxicam, sometimes termed partially selective and categorised with traditional NSAIDs as non-selective, was included alongside the newer ‘coxibs’ (e.g. rofecoxib, celecoxib, etoricoxib) in the NICE technology appraisal of selective COX-2 inhibitors. Arguably, diclofenac, might also be considered together with this class, as unlike ibuprofen and naproxen, it preferentially inhibits COX-2 to a greater extent than COX-1.

COX-2 Inhibitors/Coxibs

Coxibs, such as rofecoxib and celecoxib, were introduced to decrease the GI morbidity and mortality associated with non-selective NSAIDs. While coxibs have no efficacy advantage and are as effective as traditional NSAIDs in improving pain and function in patients with arthritis, by selectively inhibiting COX-2 they reduce the risk of upper GI ulceration and bleeding by 50-60% compared with traditional NSAIDs. Dyspepsia is still the most common adverse effect of coxib therapy. Furthermore, coxibs reduce but do not eliminate the risk of ulcer complication in ‘high-risk’ individuals. Around 130 patients (500 low-risk or 40 high-risk patients) must be treated with a coxib for one year to prevent one serious GI complication that might have developed with a non-selective NSAID.
Meta-analyses of RCTs have demonstrated an excess risk for serious cardiovascular events associated with coxibs compared with placebo or naproxen, which was predominantly related to an increased risk of myocardial infarction (MI). With coxibs there was an increase from 0.9 to 1.2% events per year, corresponding to a 42% proportional increase in the incidence of a first serious vascular event compared with placebo. This risk appears to increase with dose and persists throughout treatment. The absolute risk increases for an individual patient, depending on their baseline CV risk. Coxibs do not block production of platelet thromboxane (a potent platelet agonist and vasoconstrictor) because platelets do not contain COX-2, but selectively suppress endothelial prostacyclin (an intrinsic vasodilator and platelet inhibitor). This may be the mechanism for increasing the risk of MI, heart failure, stroke and hypertension in comparison with placebo.

The risk with coxibs was similar to that seen with non-naproxen traditional NSAIDs (mostly high-dose diclofenac and ibuprofen). Large scale trials (VIGOR, CLASS, EDGE [part of MEDAL], TARGET and SUCCESS) have raised the hypothesis that increasing degrees of selectivity for COX-2 are associated with augmented CV risk, whereas increasing degrees of selectivity for COX-1 are associated with augmented GI risk. The RR for vascular events for coxibs (combined) was 1.42. Diclofenac (150mg/day), which preferentially inhibits COX-2, rather than COX-1, appears to be associated with a similar excess CV risk to that of coxibs (RR of vascular events vs placebo, 1.63, 6, 21, 22) as does high dose ibuprofen (800mg three times daily).

A 2007 AHA review of the evidence concluded coxibs have important adverse cardiovascular effects. They recommended that in patients with a history of, or at high risk for, cardiovascular disease, coxibs only be used if there are no appropriate alternatives and then only in the lowest dose and for the shortest duration necessary.

### NSAID Usage Patterns

NSAIDs are the most commonly prescribed drugs in the world. One-in-ten take these medications. Globally, an estimated 30 million patients use prescription NSAIDs on a daily basis. An additional 60 million people worldwide use over-the-counter (OTC) NSAIDs. One-third to one-half of these patients are beyond 60 years of age. In the year ending in 2000, 1.2% of the U.S. population ingested NSAIDs daily, 30 billion OTC NSAIDs were purchased, individuals consumed more than 40 billion aspirin tablets and 110 million NSAID prescriptions were written.

In Australia, the rate of NSAIDs prescribed/supplied or advised by GPs peaked in 2001, and has since returned to 5.6 per 100 encounters in 2004-05 following the withdrawal of rofecoxib (Vioxx) and lumiracoxib (Prexige). Of a sample of general practice patients attending with a musculoskeletal condition, one-third (37%) of respondents on NSAIDs were aged between 45 and 64 years, while the age group most likely to be on NSAIDs were respondents aged 65 years and over (27% of those aged over 64 years were taking an NSAID). Amongst patients over 60 years with a past history of ‘arthritis’, 45% were using NSAIDs. Usage is higher in females than males for every age group studied. Over one-third (35.1%) of patients with chronic pain took NSAIDs. Of those on NSAIDs 6.8% had rheumatoid arthritis and 13.0% had taken corticosteroids in the previous 12 months, most for less than one month’s duration. OTC analgesic use is significantly under-reported by patients.

Recent Australian BEACH data, based on over 5500 general practice encounters, show 31% of respondent NSAID users had experienced some adverse GI effects that did not lead to hospitalisation, and 5.7% had been hospitalised with a GI complaint. Using the Standardised Calculator of Risk Events (SCORE) to assess risk of future GI events, two-thirds of respondents had a moderately increased risk of a serious NSAID-associated GI side effects (SCORE > 10). With an aging population and a significant increase in the prevalence of painful degenerative and inflammatory rheumatic conditions, this equates with a high attributable risk for the population.
2 NSAID-INDUCED GASTROINTESTINAL RISK

Although NSAID use is associated with a broad spectrum of adverse reactions - including gastrointestinal (GI) effects, alterations in renal function, effects on blood pressure and cardiovascular events, hepatic injury, skin reactions and haematological abnormalities, many patients require prolonged NSAID therapy for effective analgesia. Non-NSAID analgesics, such as acetaminophen, may not provide sufficient pain relief, and the use of narcotic analgesics can be associated with substantial cognitive side effects.

Spectrum of NSAID-Induced Gastropathy

The GI effects of NSAIDs are cause for concern because of their frequency and potential seriousness.

GI toxic effects induced by NSAIDs are common. Approximately 1 - 2% of NSAID users will develop GI complications yearly. Studies and quantitative systematic reviews, comparing NSAID users against well-matched controls, show NSAIDs to be associated with a 1.5 to 7.2-fold increase in serious adverse GI events across various agents and risk profiles.

GI damage may extend from the oesophagus to the rectum (Table 2), although the acid contact areas of the stomach and duodenum are a more substantial problem.

NSAID-induced GI adverse events range from dyspepsia to ulceration and, most seriously, ulcer complications (haemorrhage, perforation and death). NSAID-related GI adverse events can be classified into three broad categories (Table 3) based on severity and percentages of patients affected.

Nuisance or minor GI side effects are common and affect 10 - 60% of NSAID users. Aspirin, traditional NSAIDs and coxibs increase the risk of upper GI symptoms. NSAID-associated dyspepsia is common and has been reported in up to 25–50% of patients. Dyspepsia is the most common reason for stopping use. However, the presence of dyspepsia does not predict the presence of mucosal lesions in patients taking NSAIDs (see Assessment of GI Risk Factors).

Table 2. Spectrum of NSAID-Induced GI Mucosal Damage

<table>
<thead>
<tr>
<th>Category</th>
<th>Relative Risk (RR)</th>
<th>Percentage of NSAID-users affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper GI Tract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petechial submucosal haemorrhages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erosions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcers (stomach and duodenum)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Acute mucosal lesion &amp; Ulcers)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small Intestine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased permeability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strictures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrous Diaphragms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein-losing enteropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large Intestine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strictures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diverticulitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleed or Perforation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collagenous colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse of IBD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Three Categories of NSAID-Induced GI Toxicity

<table>
<thead>
<tr>
<th>Category</th>
<th>Relative Risk (RR)</th>
<th>Percentage of NSAID-users affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 'Nuisance' symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heartburn, Nausea, Dyspepsia, Flatulence and Abdominal pain</td>
<td>1.5 – 2 fold increase</td>
<td>10 - 60%</td>
</tr>
<tr>
<td>2. Significant mucosal lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcers (asymptomatic /symptomatic)</td>
<td>3 – 8 fold increase</td>
<td>15 - 30%</td>
</tr>
<tr>
<td>3. Serious gastrointestinal complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perforated ulcers</td>
<td>4 – fold increase</td>
<td>1 - 3%</td>
</tr>
<tr>
<td>Catastrophic bleeding</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In the small intestine, an enteropathy characterised by blood, protein loss or both has been demonstrated subclinically in as many as 70% of cases. The intestinal damage may contribute to the iron-deficiency anaemia and hypoalbuminaemia which is evident in some elderly patients who chronically consume NSAIDs, and which is often attributed to underlying disease processes.

Mucosal lesions are also common, with more than half of all patients who take NSAIDs on a regular basis having gastric erosions and 15 - 30% having endoscopically detectable ulcers. The majority of these lesions do not cause significant symptoms. The distinction between erosions and ulcers depends on pathological and endoscopic definitions, with ulcers defined as lesions that penetrate to the level of the submucosa (involving endoscopically evident depth) and erosions defined as lesions confined to the mucosa (without endoscopically appreciable depth). Ulcers may give rise to major bleeding, perforation, or obstruction.

Clinically significant GI events occur in 3 - 4.5% of NSAID users annually. The majority of these events are symptomatic ulcers whereas a smaller percentage (approximately 1-3%) are clinically serious and associated with GI bleeding, perforation, or obstruction. This compares to a background rate of serious GI events of 0.1-0.2% per year in non-exposed people.

Serious NSAID ulcer complications have a significant mortality rate: One study found 10.6% die in hospital and 14.4% within 3 months of the event. The number of deaths associated with NSAID-induced GI damage, as acquired from ARAMIS (the Arthritis, Rheumatism, and Aging Medical Information System), which included postmarketing surveillance of more than 36,000 patients from 17 centres in the USA and Canada, are comparable to mortality statistics for AIDS and other terminal diseases (Figure 3).

Intestinal perforations and strictures have also been reported, and, although the colon is rarely affected, NSAIDs may cause acute colitis. Case-control studies and anecdotal reports have implicated NSAIDs in complicated diverticular disease. Small case series have also suggested that NSAIDs can reactivate inflammatory bowel disease, but direct proof of this association is lacking.

Serious life threatening adverse effects such as ulcer haemorrhage, Stevens-Johnson syndrome or agranulocytosis are rare, with incidences ranging from between one in several hundred to one in many thousands of users.

### Risk Factors for NSAID-Induced GI Complications

The risk of GI events varies widely in relation to the presence of a variety of risk factors. Several studies have shown that the following are the major risk factors for GI events associated with NSAID use (Table 4).

**Figure 3. Deaths Associated with NSAID-induced GI Damage versus Other Causes**

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Number of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukaemia</td>
<td>20,197</td>
</tr>
<tr>
<td>HIV</td>
<td>16,685</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>16,500</td>
</tr>
<tr>
<td>GI</td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>10,503</td>
</tr>
<tr>
<td>Asthma</td>
<td>5,338</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>4,441</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>1,437</td>
</tr>
</tbody>
</table>

Endorsed September 2009
Table 4. Risk factors for NSAID-induced complications

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior history of ulcers</td>
<td>A prior history of complicated ulcers confers the highest relative risk. A history of peptic ulcer disease increased risk 5.9 times, 15.4 times if it was complicated, compared with no history.</td>
</tr>
<tr>
<td>Older Age (&gt; 60-75 years)</td>
<td>The risk of GI adverse effects increases with age in a curvilinear fashion. Compared with patients aged 25–49 years, those aged 60–69 years had 2.4 times the risk, those aged 70–80 years had 4.5 times the risk, and those over 80 years had 9.2 times the risk and carry a risk similar to those with previous ulcer history.</td>
</tr>
<tr>
<td>High NSAID dose</td>
<td>Increasing the dose of NSAIDs is associated with increasing the overall risk ratio. Even increasing NSAID dosage within accepted ranges can triple the risk of ulcer complications. Aiming for the lowest possible dose to control symptoms is desirable.</td>
</tr>
<tr>
<td>Duration of Treatment</td>
<td>Some, but not all, studies have shown risk is greatest during the first 3 months of treatment (12 - 25% of patients develop endoscopic ulcers within 3 months), although the risk continues to increase slowly, but steadily, with continued treatment. Increasing duration of use from 28 days to one year increased risk from 1.54 to 2.2, compared with non-users. The World Health Organization (WHO) consensus statement provides a duration of treatment of 84 days as a threshold for a significant risk of GI effects. Short-term use (5–10 days) of OTC formulations has been shown to be usually safe and well tolerated.</td>
</tr>
<tr>
<td>Multiple NSAID use (including low-dose aspirin)</td>
<td>The concomitant use of NSAID or COX-2 inhibitor with aspirin increases the risk of upper GI bleeding by more than just an additive effect of the drugs. The risk of GI bleeding in patients taking combination of NSAIDs and aspirin is approximately two-fold greater than in patients who take either NSAIDs or aspirin alone, and up to nine times more likely than control groups. This effect is not dose dependent. The risk of GI bleeding is also increased when aspirin is co-prescribed with coxibs compared with coxibs alone. Coxib users also taking aspirin had a four-fold greater relative risk of a POB endpoint (perforation, obstruction or bleeding) than those not taking aspirin. In a pooled subgroup analysis, the benefit of coxibs over NSAIDs that was seen in the overall analysis was attenuated in patients taking aspirin.</td>
</tr>
<tr>
<td>Concomitant corticosteroid use</td>
<td>While corticosteroids do not appear to increase the risk of peptic ulcer disease when used alone, the combined use of corticosteroids with NSAIDs leads to nearly a two-fold increase in the risk of serious GI complications and a greater than 10-fold risk of death when compared to the use of an NSAID alone. Whether steroids are an independent risk factor or an NSAID-specific risk magnifier remains uncertain.</td>
</tr>
<tr>
<td>Concomitant anticoagulant/anti-platelet use</td>
<td>The concomitant use of NSAIDs and oral anticoagulants exacerbates the risk of haemorrhagic peptic ulcer disease by approximately 13-fold, compared with nonusers of either medication, and a 3-fold risk increase over patients on NSAID therapy alone. Recent evidence also has shown that anti-platelet agents, such as clopidogrel, used concomitantly with NSAIDs increase the risk of GI bleeding or serious GI events, especially in patients with a previous history of peptic ulcer disease.</td>
</tr>
<tr>
<td>Concomitant H. pylori infection</td>
<td>One meta-analysis found H. pylori infection in NSAID users was associated with a 3.5-fold increased risk for peptic ulcer disease above the risk associated with NSAID use alone. Both NSAID use and H. pylori independently conferred increased risk of GI bleeding (4.85-fold and 1.79-fold, respectively), and together a synergistic interaction between these two factors, lead to increased incremental risk (6.13-fold). One large randomised controlled trial found treating H. pylori increased the risk for NSAID gastric ulcers.</td>
</tr>
<tr>
<td>Serious co-morbidity or disability</td>
<td>The serious co-morbidities defined in RCTs as influencing the risk of ulcer complications are cardiovascular disease, renal or hepatic impairment and severe disability caused by rheumatoid arthritis.</td>
</tr>
<tr>
<td>Lifestyle factors</td>
<td>Limited data suggest smoking tobacco and alcohol consumption increases the risk of NSAID-related upper GI complications. Based on existing evidence, the level of increased risk is modest.</td>
</tr>
</tbody>
</table>
Certain patient characteristics increase the risk of NSAID-induced GI clinical events. The risk for serious GI complications increases in the following patient groups, necessitating prudent treatment choice:

- Older age
- A history of previous peptic ulcer disease
- Taking corticosteroids
- Taking anticoagulants
- Taking aspirin (including low-dose)
- Taking other anti-platelet drugs

Analysis has identified older age and previous peptic ulcer disease, particularly if complicated, as the strongest predictors of absolute risk. With any one risk factor the risk of a GI event was 2% in one year. Combinations of these risk factors were additive. The one-year risk with combinations of three risk factors increased to approximately 9% and with four it increased to 18%.

Assessment of GI Risk Factors

It is essential to carefully screen patients for risk factors for NSAID-induced GI complications. Symptoms, or the lack thereof, are not good predictors of NSAID complications. Armstrong and Blower found 58% of patients admitted with an NSAID complication had no antecedent GI symptoms. Another review concluded that only 15% of ulcers induced by NSAIDs become clinically apparent and less than half of all ulcer complications present with warning signs. Conversely, as many as 50% of NSAID-using patients with epigastric complaints (e.g. dyspepsia, nausea) have normal mucosa on endoscopic examinations.

Anaemia or hypoalbuminaemia may be a useful marker of NSAID-induced enteropathy in small intestines or blood loss from the bowel. Oral diclofenac 150 mg daily produced anaemia in 10% of about 310 patients in 12 weeks.

### Table 5. Indications for Urgent Endoscopy

**Alarm Signs**

<table>
<thead>
<tr>
<th>National Institute for Clinical Excellence guidelines recommend investigation within 2 weeks, except in acute cases (when it should be sooner)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting blood or blood in faeces (same day referral if significant acute bleeding)</td>
</tr>
<tr>
<td>Difficulty or pain on swallowing</td>
</tr>
<tr>
<td>Unexplained weight loss</td>
</tr>
<tr>
<td>Upper abdominal mass</td>
</tr>
<tr>
<td>Persistent vomiting</td>
</tr>
</tbody>
</table>

**NSAID GI Toxicity Profiles**

All NSAIDs, including low-dose aspirin, increase the risk of serious upper GI complications, but to different degrees. In a meta-analysis of 18 studies, the pooled relative risk (RR) of serious upper GI complications associated with NSAIDs was 3.8.

**Aspirin and Low-dose Aspirin**

Aspirin significantly increases the risk of GI complications, predominantly through an increased risk of peptic ulceration and associated bleeding.

On endoscopic examination, 10-25% of aspirin users will have peptic ulcers. While most aspirin induced ulcers are asymptomatic and of moderate clinical significance, approximately 0.5–2.0% of aspirin users per year will develop serious GI complications of peptic ulcer disease, including haemorrhage, perforation, or severe abdominal pain requiring hospital admission and/or surgical management. The UK-TIA trial demonstrated a statistically significant increase in the occurrence of haematemesis or melena in patients taking 300 mg or 1200 mg of aspirin daily for 1–7 years compared to patients receiving placebo. In the Aspirin Myocardial Infarction Study, patients taking aspirin 500 mg twice daily were more frequently hospitalised for ulcers compared with placebo.
While low-dose aspirin taken daily is cardioprotective, no dose of aspirin appears safe for the GI tract. Doses as small as 10 mg daily can cause sufficient prostaglandin inhibition to affect platelet aggregation and mucosal blood flow, promoting the development of peptic ulceration and bleeding. Across a broad cross section of high and low risk patients taking aspirin 10–325 mg daily, the incidence rate of gastroduodenal ulcers was 7-10%, or one-in-10.94,95 Assuming a linear rate of ulcer development, this translates to an annual ulcer incidence of 28% (mean ulcer duration estimated at 4–5 months).49

Serious ulcer complications are about two- to four-fold higher in patients taking 75–325 mg aspirin daily compared to controls,69,96-99 an absolute risk of around 1% per annum.100 While the risk of GI complications is likely related to the dose provided,91,101 approximately 10% of peptic ulcer related complications and deaths may be attributed to low-dose aspirin (in a country with a low usage of low-dose aspirin at the time of the study).100,102 In very high-risk patients, those with a prior ulcer bleed on aspirin, the annual risk of re-bleeding may be as high as 15%.103 The case-fatality rate for patient admitted to hospital for GI haemorrhage because of peptic ulcer disease is approximately 5-10%;104,105 and is likely higher for patients with CV disease.104

The risk factors for NSAID-induced gastropathy are more likely to be prevalent in patients with CV disease, who tend to be older and more likely to use medications that may put them at risk of developing GI complications.

To minimise the risk of serious ulcer complications in patients with GI risk factors, combining low-dose aspirin with an NSAID (including coxibs) should be avoided.81 Aspirin use increases the risk of GI adverse effects in people taking other NSAIDs.106 As with NSAIDs, consider co-prescribing a gastroprotective agent in patients at high risk of ulcer complications.107

**Traditional NSAIDs**

Upper GI symptoms occur in up to 50% of patients taking traditional NSAIDs,26 and some 5-15% of patients with rheumatoid arthritis discontinue NSAIDs because of dyspepsia.26 The overall odds ratio for serious GI complications with an NSAID has been calculated as 2.74 (95% CI: 2.54–2.97).28 Serious events including upper GI bleeding, perforation and gastric outlet obstruction occur in approximately 1%-1.5% of patients within the first 12 months of treatment with a traditional NSAID.10,11,16,44 When symptomatic ulcers are included this figure rises to more than 5% of patients treated over one year. Patients with rheumatoid arthritis are nearly twice as likely to suffer a serious complication compared to patients with osteoarthritis (table 6).26 The worst GI outcome results in death, but mortality data associated with NSAIDs treatment are scarce.102 One large meta-analysis concluded that 1 in 1200 patients taking NSAIDs for at least 2 months dies from gastroduodenal complications.108

The GI risks are not limited to the upper gastrointestinal tract. GI complications beyond the duodenum may represent 25-50% of all complications associated with NSAIDs.109 These drugs can cause small bowel ulceration, haemorrhage and strictures and can precipitate bleeding from colonic diverticula.109 Increased mucosal permeability and mucosal inflammation are often silent but occur with most NSAIDs.109 Other findings include anaemia, occult blood loss, malabsorption and protein loss. A systematic review reported a consistent increase in lower gastrointestinal injury and clinical events in patients using NSAIDs compared to those not using NSAIDs.110 In addition, data from RCTs have demonstrated that the risk of lower gastrointestinal events is higher with traditional NSAIDs than with coxibs.22,111
### Table 6. GI Complications in Osteoarthritis (OA) versus Rheumatoid Arthritis (RA)

<table>
<thead>
<tr>
<th></th>
<th>OA hospitalisations</th>
<th>RA hospitalisations</th>
<th>RA deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1283</td>
<td>3883</td>
<td>2921</td>
</tr>
<tr>
<td>Person years of observation</td>
<td>3234</td>
<td>19,961</td>
<td>12,224</td>
</tr>
<tr>
<td>Person years taking NSAID</td>
<td>2199</td>
<td>15,638</td>
<td>8471</td>
</tr>
<tr>
<td>Number of GI events</td>
<td>19</td>
<td>228</td>
<td>25</td>
</tr>
<tr>
<td>Number of GI events while taking NSAID</td>
<td>16</td>
<td>205</td>
<td>19</td>
</tr>
<tr>
<td>Rates/year (%) while taking NSAID</td>
<td>0.73</td>
<td>1.31</td>
<td>0.22</td>
</tr>
<tr>
<td>Rates/year (%) while not taking NSAID</td>
<td>0.29</td>
<td>0.19</td>
<td>0.05</td>
</tr>
<tr>
<td>Relative risk while taking NSAID</td>
<td>2.51</td>
<td>6.77</td>
<td>4.21</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; RA, rheumatoid arthritis. Peura and Goldkind Arthritis Research & Therapy 2005 7(Suppl 4):S7

Evidence indicates NSAIDs differ in their GI toxicity; some associated with higher GI risks than others. NSAIDs with increasing inhibitory COX-1 activity appear associated with increasing risks of serious GI complications (Figure 2).

In general, ibuprofen has the lowest risk among NSAIDs (at doses most commonly used over the counter), while diclofenac and naproxen have intermediate risks, and piroxicam and ketorolac carry the greatest risk (Figure 4). It should be noted that the advantage of ‘low risk’ drugs may be lost once their dose is increased. Dosage data shows relative risk increases twofold with high-dose vs. low-dose NSAID therapy. For example, the relative risk for ibuprofen increases at higher doses, i.e. over 1600mg per day, and may be no safer than medium risk agents.

Patients receiving NSAIDs frequently complain of GI symptoms in the absence of ulcers. NSAIDs are associated with a 2-fold increased risk of dyspepsia. Dyspepsia is seen with similar frequency in patients with a normal upper endoscopy (19%), minor endoscopic changes (9%), and in those with ulcers (30%).

However, the presence of dyspepsia does not predict the presence of mucosal lesions in patients taking NSAIDs alone. Only among patients already using gastroprotective agents with NSAIDs is the occurrence of moderate to severe dyspepsia strongly predictive of endoscopic ulcers or multiple erosions.

**COX-2 Inhibitors/Coxibs**

Coxibs have an improved upper GI safety profile, extensively shown in endoscopy and clinical outcomes studies. Two large outcomes trials show high-dose rofecoxib and lumiracoxib were associated with a 50-60% reduction in upper GI complications when compared to traditional NSAIDs.
Figure 4. Comparison by Meta-analysis of the Pooled Relative Risk of Serious Upper GI Complications from Exposure to Individual NSAIDs Compared with Exposure to Ibuprofen

Graph shows pooled relative risk and 95% confidence intervals. This meta-analysis includes only retrospective studies of clinical records which should be representative of clinical practice.
Although the incidence of adverse events with coxibs increased in relation to the presence of risk factors,\textsuperscript{117} the differences from NSAIDs were maintained in subgroups of patients with and without risk factors for ulcer complications,\textsuperscript{118} and across different patient groups.\textsuperscript{10, 11, 16, 19} Coxibs reduce the risk of symptomatic ulcers RR of 0.49 (range 0.38 to 0.62) and serious GI complications RR 0.55 (range 0.38 to 0.80).\textsuperscript{119}

As with standard NSAIDs, individual coxibs may vary in their propensity to cause GI effects, and the effects may vary with dose and duration of treatment although no studies directly compare the GI risk of different coxibs.

The CLASS study did not confirm the benefits of high-dose (800 mg/day) celecoxib versus NSAIDs, probably because of the concomitant use of low-dose aspirin by 22% of patients.\textsuperscript{16} However, a recent meta-analysis confirms that celecoxib at any dose was associated with significantly less clinical ulcers and bleeds than traditional NSAIDs.\textsuperscript{120}

The results of SUCCESS I study,\textsuperscript{19} confirmed the significantly better safety profile of celecoxib (200-400 mg/day) compared with diclofenac and naproxen in 13,274 patients with osteoarthritis. Upper GI complications were seen significantly less in the celecoxib-treated patients (0.1/100 patient years) compared with the traditional NSAIDs (0.8/100 patient years).\textsuperscript{19} Second-generation coxibs, such as lumiracoxib and etoricoxib, have greater selectivity for COX-2 and also show improved GI tolerability compared with traditional NSAIDs in patients suffering from rheumatoid arthritis (RA) or osteoarthritis (OA).\textsuperscript{11, 121, 122}

No clinical trial has specifically evaluated the lower GI tract adverse effects with traditional NSAIDs or coxibs. A study using wireless video capsule endoscopy in healthy volunteers, showed coxibs caused less small-bowel mucosal injury than traditional NSAIDs.\textsuperscript{121} A post hoc analysis of the VIGOR trial revealed a lower incidence of serious lower GI events with rofecoxib when compared to naproxen.\textsuperscript{123} Consistent results were reported from a meta-analysis of lower GI events favouring rofecoxib / etoricoxib over traditional NSAIDs.\textsuperscript{124}

Coxibs appear not to increase mucosal permeability, inflammation or induce anaemia due to occult bleeding.\textsuperscript{125}

Studies with capsule endoscopy compared the incidence of small bowel lesions with NSAIDs plus a proton pump inhibitor (PPI) or celecoxib, and indicated a relative risk ratio favouring celecoxib (RR = 0.29).\textsuperscript{19, 126, 127} Data obtained from different studies have shown celecoxib is associated with a risk reduction and a lower proportion of anaemia than traditional NSAIDs.\textsuperscript{16,119,120}

For dyspepsia symptoms, in patients without ulcerations, coxibs offer little additional benefit to traditional NSAIDs. Patients treated with rofecoxib had a similar incidence of dyspeptic symptoms compared to those treated with diclofenac (28.6% vs 37.1%, P = NS). Further evidence for this can be found in large trials. In the VIGOR trial 3.5% of patients taking rofecoxib experienced upper GI symptoms compared with 4.9% of patients taking naproxen.\textsuperscript{16} In CLASS, 14.4% of patients given celecoxib experienced dyspepsia compared with 16.1% of patients given an NSAID.\textsuperscript{16}

Coxibs provide a comparable gastroprotective effect to that of traditional NSAIDs plus a PPI,\textsuperscript{128} although neither treatment completely eliminates the risk of ulcers in high risk patients (see \textit{Gastroprotectant Co-therapy}).\textsuperscript{129,130}

Concomitant aspirin and coxib treatment carries measurable risk of an adverse upper GI event. In addition to the CLASS study,\textsuperscript{16} evidence from the TARGET and SUCCESS I trial,\textsuperscript{11, 19} one endoscopy study\textsuperscript{128} and epidemiological studies\textsuperscript{122,123} indicate low-dose aspirin increases further the risk of upper GI bleeding and toxicity in NSAID users and attenuates the GI benefits of coxibs. The rate of endoscopic detection of ulcers in patients who took both rofecoxib and low-dose aspirin was similar to that of patients who took ibuprofen.\textsuperscript{131}

The main drawback of coxib therapy comes from the concern that its use is associated with an increased CV risk. Whether this effect is associated only with long-term use, and whether it extends only to coxibs or includes all NSAIDs is yet to be confirmed. A very large RCT is currently comparing chronic use of celecoxib, ibuprofen and naproxen in patients with high cardiovascular risk.\textsuperscript{134} It aims to define the relative cardiovascular safety profile of each agent and provide data to help guide NSAID use for pain management for this population.
3 GASTROPROTECTIVE AND PREVENTION STRATEGIES

Those at increased GI risk should be considered for alternatives to NSAID therapy. If NSAID therapy is required, patients at risk will need prevention strategies including modifications of risk factors or co-therapy of NSAID with a gastroprotective agent.

Target Population for Gastroprotection Strategies

Gastroprotection should be offered to high risk patients, i.e. those with one or more risk factors for NSAID-related GI complications. The National Institute for Clinical Excellence (NICE) suggest any one of the following factors define patients as high risk:6

- Age 65 years or over
- Past history of peptic ulcer disease or serious GI complications
- Concomitant oral steroids or anticoagulants or anti-platelet agents
- Presence of serious co-morbidity, such as cardiovascular disease (CVD), renal or hepatic impairment, diabetes and hypertension.
- Requirement for prolonged use of maximal doses of NSAIDs

Current prevention strategies to reduce serious NSAID-associated GI events are cost-effective in patients with risk factors.135

Appropriate Prescribing & Utilisation Rates

Gastroprotective drugs are greatly underutilised in patients with a risk of NSAID gastropathy. Despite clear guidelines suggesting patients with at least one GI risk factor should receive treatment, approximately 50-75% of patients still do not receive a prescription for a gastroprotective agent.140-142 The same proportion of aspirin users with established CV disease and additional risk factors for GI complications were not prescribed a gastroprotective strategy.143 Even in patients with at least four risk factors associated with NSAID-induced gastropathy, utilisation of gastroprotection was low (35 - 40%)

and 47% still did not use adequate gastroprotection.144 Factors associated with a higher propensity to be prescribed gastroprotection included having two or more risk factors, older age, and history of prior bleeding.139, 145

Limited evidence also suggests many of those who actually receive gastroprotection are non-compliant.146 This is concerning as there is a strong inverse relationship between adherence to gastroprotective agents and the risk of upper GI complications in high-risk NSAID users.146 The risk of an upper GI complication among NSAID users increased 16% for every 10% decrease in adherence.

Targeting Modifiable Risk Factors

Addressing modifiable risk factors should be the first therapeutic option because it can reduce the risk of NSAID-induced GI toxicity (Table 7). Concomitant use of low-dose aspirin, anticoagulants or corticosteroids should be avoided in patients on NSAID therapy. As much as possible, only a single NSAID should be prescribed using the lowest effective dose. Safer NSAIDs should be preferred. Among the traditional NSAIDs, the safest are ibuprofen, naproxen and diclofenac. Lifestyle modifications (diet, alcohol reduction, smoking cessation, weight loss in obese patients) should also be recommended.

Table 7. Modifiable risk factors to target

1. If possible, avoid the use of NSAIDs in patients with previous ulcer bleeding history or taking anticoagulants. Evaluate the use of alternatives (e.g. analgesics, physical therapy)
2. Prescribe the lowest effective dose of NSAIDs
3. Use the drug for the shortest possible period of time
4. Use NSAIDs associated with the lowest relative risk of GI complications
5. If possible avoid the use of two NSAIDs, including low-dose aspirin or anti-platelet agents

Gastroprotectant Co-therapy

The use of pharmacologic agents to prevent NSAID injury has focused on two approaches: inhibition of acid secretion and prostaglandin replacement. These approaches appear to have varying effectiveness in the prevention of NSAID-associated endoscopic ulcers.84, 147/149
Proton Pump Inhibitors (PPIs)

PPIs profoundly block gastric acid secretion by inhibiting the H⁺/K⁺ adenosine tri-phosphatase and are significantly more effective than H₂-receptor antagonists (H₂RAs) for treatment and prevention of acid-related diseases.

Ulcer Healing

PPIs accelerate healing of gastric and duodenal ulcer including those caused by, and in patients who continue, NSAID treatment (Table 8).

Many trials have demonstrated the efficacy of PPIs in healing ulcers caused by NSAID use and their superiority over H₂RAs and misoprostol. Almost all of these trials have used endoscopic criteria for diagnosing the ulcers as well as documenting their healing.

Compared with placebo, PPIs significantly reduced both endoscopic NSAID-associated gastric and duodenal ulcers. Overall, pooled results from five RCTs with omeprazole, lansoprazole or pantoprazole found endoscopic ulcer rates of 14.5% with PPIs vs 35.6% with placebo. NSAID-associated gastric ulcers are more likely to heal when patients receive PPI co-therapy rather than H₂RAs. The ulcer healing rate was also significantly greater with the PPIs (20 mg esomeprazole, 20 mg omeprazole or 15 and 30 mg lansoprazole) than with the H₂RA, ranitidine. Healing of gastric lesions was observed in significantly more patients who received a PPI (80%) than in those who received ranitidine (61%; P < 0.001).

The efficacies of PPIs and misoprostol have been compared in patients with established ulcers and erosions. When compared with misoprostol, there was no difference in treatment success rates in the patients randomised to receive omeprazole. However, when the healing rates for gastric ulcer and duodenal ulcer were considered separately, omeprazole was superior to misoprostol.

Omeprazole also had a significantly better healing rate compared with sucralfate 4g/day (96% vs 78%).

In a literature review of seven clinical trials, after 8 weeks treatment with ranitidine, gastric ulcer healing rates were 50 - 74%, whereas duodenal ulcer healing ranged from 81 - 84%, similar to sucralfate. However, 8-week gastric healing rates were 92% and 88% with esomeprazole 40 mg and 20 mg, respectively. For omeprazole, 8-week healing rates were 87% with omeprazole 40 mg and 84% with omeprazole 20 mg, and for lansoprazole the corresponding values were 73-74% and 66-69% for the 30 mg and 15 mg doses, respectively. Duodenal ulcer healing rates were 92% for omeprazole 20 mg (vs 81% for ranitidine).

Ulcer Prevention

PPI therapy reduces the risk of traditional NSAID associated endoscopic ulcer disease. Omeprazole, lansoprazole and esomeprazole help to protect the stomach and the duodenum during NSAID use (Table 9).

A meta-analysis of RCTs found PPIs, at standard once daily dosing, significantly reduced the risk of endoscopic duodenal ulcers by 81% and gastric ulcers by 60% compared to NSAIDs alone. The overall rate of endoscopic ulcers was 14.5% with PPIs versus 35.6% in the placebo groups. In the MEDAL programme, use of a PPI at baseline was associated with a significantly lower risk of clinical GI events (POB plus symptomatic ulcers) and complicated events (POB).

More recently, esomeprazole showed prevention of GI damage caused by chronic NSAIDs/coxib use in a high-risk population. Published data from two identical, randomised, placebo-controlled trials (VENUS and PLUto) showed remission rates were 79.6% for placebo, 94.7% for esomeprazole 20 mg and 95.3% for 40 mg (both P < 0.001 vs placebo) in the VENUS study and 87.7% for placebo, 94.8% for esomeprazole 20 mg (P = 0.018), and 95.6% for esomeprazole 40 mg (P = 0.007) in PLUto. This shows esomeprazole 20 mg/day as an effective dose for ulcer prevention in long-term NSAID users.
Table 8. PPIs for the Healing of NSAID-Related Gastroduodenal Damage

<table>
<thead>
<tr>
<th>First Author (y)ref</th>
<th>Study Type</th>
<th>Study Population</th>
<th>Study Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein (2007)</td>
<td>Multicenter, randomised, double-blind, double-dummy, parallel-group trial</td>
<td>At least 1 gastric ulcer; need for continuous NSAID therapy</td>
<td>Esomeprazole 40 mg daily (n = 133) vs esomeprazole 20 mg daily (n = 138) vs ranitidine 300 mg daily (n = 139)</td>
</tr>
<tr>
<td>Goldstein (2005)</td>
<td>Multicenter, randomised, double-blind, parallel-group trial</td>
<td>At least 1 gastric ulcer; need for continuous NSAID therapy</td>
<td>Esomeprazole 40 mg daily (n = 129) vs esomeprazole 20 mg daily (n = 138) vs ranitidine 300 mg daily (n = 132)</td>
</tr>
<tr>
<td>Agrawal (2000)</td>
<td>Prospective, double-blind, double-dummy, multicenter, parallel-group study</td>
<td>At least 1 gastric ulcer; need for continuous NSAID therapy</td>
<td>Lansoprazole 30 mg daily (n = 73) vs lansoprazole 15 mg daily (n = 71) vs ranitidine 300 mg daily (n = 70)</td>
</tr>
<tr>
<td>Hawkey [OMNIUM study] (1998)</td>
<td>Randomised, double-blind, international trial</td>
<td>Gastric or duodenal ulcer or &gt;10 erosions in patients needing daily NSAID therapy</td>
<td>Omeprazole 40 mg daily (n = 315) vs omeprazole 20 mg daily (n = 308) vs misoprostol 800 µg daily (n = 298)</td>
</tr>
<tr>
<td>Yeomans [ASTRONAUT study] (1998)</td>
<td>Randomised, controlled, double-blind, international</td>
<td>Gastric or duodenal ulcer or &gt;10 erosions in patients needing daily NSAID therapy</td>
<td>Omeprazole 40 mg daily (n = 187) vs omeprazole 20 mg daily (n = 174) vs ranitidine 300 mg daily (n = 174)</td>
</tr>
<tr>
<td>Massimo Claar (1998)</td>
<td>Randomised, double-blind</td>
<td>Patients on daily NSAIDs (diclofenac, ketoprofen, indomethacin, or naproxen) for OA or RA and with endoscopically proven gastroduodenal ulcer</td>
<td>Omeprazole 40 mg daily (n = 79) vs omeprazole 20 mg daily (n = 77)</td>
</tr>
<tr>
<td>Bianchi Porro (1998)</td>
<td>Randomised, single-blind</td>
<td>Patients with arthritis or arthrosis and NSAID-related gastric or duodenal ulcer</td>
<td>Omeprazole 20 mg daily (n = 50) vs sucralfate 4 g daily (n = 48)</td>
</tr>
<tr>
<td>Bardhan (1994)</td>
<td>Randomised, double-blind, parallel-group, multicenter trial</td>
<td>Endoscopically confirmed gastric ulcer</td>
<td>Lansoprazole 60 mg daily (n = 73) vs lansoprazole 30 mg daily (n = 71) vs ranitidine 300 mg daily (n = 70)</td>
</tr>
</tbody>
</table>

OA, osteoarthritis; RA, rheumatoid arthritis.
<table>
<thead>
<tr>
<th>Duration</th>
<th>Primary End Point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 weeks</td>
<td>Absence of gastric ulcer</td>
<td>Healing rates: esomeprazole 40 mg, 85.7% (79.8–91.7%); esomeprazole 20 mg, 84.8% (78.8–90.8%); ranitidine, 76.3% (69.2–83.3%) (no difference between groups)</td>
</tr>
<tr>
<td>8 weeks</td>
<td>Absence of gastric ulcer</td>
<td>Healing rates: esomeprazole 40 mg, 91.5% (86.7–96.3%); esomeprazole 20 mg, 88.4% (83.1–93.7%); ranitidine, 74.2% (66.8–81.7%) (P &lt; 0.01 compared with both esomeprazole groups)</td>
</tr>
<tr>
<td>8 weeks</td>
<td>Healing of ulcer</td>
<td>Healing rates: compared with ranitidine 300 mg at 53%, lansoprazole 15 mg, 69% (P &lt; 0.05) and lansoprazole 30 mg, 73% (P &lt; 0.01)</td>
</tr>
<tr>
<td>8 weeks</td>
<td>Treatment success (absence of ulcers, up to 5 erosions, and no more than mild dyspepsia); gastric ulcer healing; duodenal ulcer healing</td>
<td>Treatment success: omeprazole 40 mg, 75% (P = 0.24); omeprazole 20 mg, 76% (P = 0.37); and misoprostol, 71% (referent). Gastric ulcer healing: omeprazole 40 mg, 80% (P = 0.14); omeprazole 20 mg, 87% (P = 0.004); and misoprostol, 73% (referent). Duodenal ulcer healing: omeprazole 40 mg, 89% (P &lt; 0.001); omeprazole 20 mg, 93% (P &lt; 0.001); and misoprostol, 77% (referent).</td>
</tr>
<tr>
<td>8 weeks</td>
<td>Treatment success (absence of ulcers, up to 5 erosions, and no more than mild dyspepsia); gastric ulcer healing; duodenal ulcer healing</td>
<td>Treatment success: omeprazole 40 mg, 79% (P &lt; 0.001); omeprazole 20 mg, 80% (P &lt; 0.001); and ranitidine, 63% (referent). Gastric ulcer healing: omeprazole 40 mg, 87% (P &lt; 0.001); omeprazole 20 mg, 84% (P &lt; 0.001); and ranitidine, 64% (referent). Duodenal ulcer healing: omeprazole 40 mg, 88% (P = 0.17); omeprazole 20 mg, 92% (P = 0.03); and ranitidine, 81% (referent).</td>
</tr>
<tr>
<td>8 weeks</td>
<td>Healing of ulcer</td>
<td>Healing rates: omeprazole 40 mg, 88% (79–95%); omeprazole 20 mg, 96.2% (89–99%), P = NS</td>
</tr>
<tr>
<td>8 weeks</td>
<td>Healing of ulcer</td>
<td>Healing rates: omeprazole 96% vs sucralfate 78% (P = 0.01)</td>
</tr>
<tr>
<td>8 weeks</td>
<td>Healing of ulcer</td>
<td>Healing rates: lansoprazole 60 mg, 97.3%; lansoprazole 30 mg, 98.6%; ranitidine 300 mg, 91.4% (P = 0.08)</td>
</tr>
</tbody>
</table>
Study Type
Results
Chronic arthritis patients
Endoscopic ulcers/erosion
Ulcer development

Study population
Primary
Chronic NSAID users

5.4% on placebo vs 1.6% on esomeprazole; 6.2% vs 1.8% by life-table estimates at endoscopic ulcer detection for cases, n = 104 and...
<table>
<thead>
<tr>
<th>Duration</th>
<th>Primary End Point</th>
<th>Results</th>
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<tbody>
<tr>
<td>26 weeks</td>
<td>Ulcer development</td>
<td>5.4% on placebo vs 1.6% on esomeprazole; 6.2% vs 1.8% by life-table estimates at 6 months (RRR, 71%; P &lt; 0.001)</td>
</tr>
<tr>
<td>6 months</td>
<td>Ulcer development</td>
<td>Ulcer development: 20.4% on placebo, 5.3% on esomeprazole 20 mg (P &lt; 0.001) and 4.7% on esomeprazole 40 mg (P &lt; 0.001)</td>
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<tr>
<td>6 months</td>
<td>Ulcer development</td>
<td>Ulcer development: 12.3% on placebo, 5.2% on esomeprazole 20 mg (P = 0.018) and 4.4% on esomeprazole 40 mg (P = 0.007)</td>
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<tr>
<td>6 months</td>
<td>Ulcer development</td>
<td>Ulcer development: 16.5% on placebo, 0.9% on esomeprazole 20 mg (P &lt; 0.001) and 4.1% on esomeprazole 40 mg (P = 0.002)</td>
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<tr>
<td>6 months</td>
<td>Endoscopic ulcers/erosion or moderate-severe</td>
<td>Probability of remaining free of the end points: 0.78 for omeprazole vs 0.53 for placebo, P = 0.004</td>
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<tr>
<td></td>
<td>dyspeptic symptoms</td>
<td></td>
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<tr>
<td>3 weeks</td>
<td>Endoscopic findings</td>
<td>Gastric ulcer-free: 100% in omeprazole groups vs 88% in placebo group (P &lt; 0.01); no difference in duodenal ulcer rate or dyspepsia rate</td>
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<tr>
<td>3 months</td>
<td>Endoscopic ulcers</td>
<td>4.7% for omeprazole vs 16.7% for placebo</td>
</tr>
<tr>
<td>At least 7 days</td>
<td>Endoscopic ulcer</td>
<td>Acute group: OR, 0.70 (95% CI, 0.24–2.04), ARR, 36.6%; chronic group: OR, 0.32 (95% CI, 0.15–0.67), ARR, 34.6%</td>
</tr>
<tr>
<td>26 months</td>
<td>NSAID-related complications requiring</td>
<td>Concomitant PPI therapy associated with reduced risk for NSAID-related complications</td>
</tr>
<tr>
<td></td>
<td>hospitalisation</td>
<td>(adjusted OR, 0.33 (95% CI, 0.17–0.67, P = .002)</td>
</tr>
<tr>
<td>n/a</td>
<td>PUB</td>
<td>For NSAID-related PUB: adjusted RR, 0.33 (95% CI, 0.27–0.39) and for aspirin users (all doses): adjusted RR, 0.30 (95% CI, 0.20–0.44)</td>
</tr>
<tr>
<td>n/a</td>
<td>Dyspepsia (epigastric pain, dyspepsia, nausea)</td>
<td>ARR, 9%; RRR, 66% with NSAID + PPI vs NSAIDs; ARR, 3.7%; RRR, 12% with coxibs vs NSAIDs. Conclusion: NSAID + PPI better for dyspepsia reduction</td>
</tr>
<tr>
<td>Variable</td>
<td>Endoscopic ulcer detection</td>
<td>For duodenal ulcer: PPI vs placebo: RR, 0.19 (95% CI, 0.09–0.37), P &lt; .001; for gastric ulcer: PPI vs placebo: RR, 0.40 (95% CI, 0.32–0.51), P &lt; .001</td>
</tr>
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</table>
The ASTERIX trial, primary prevention of gastroduodenal ulcers in patients requiring daily LDA for secondary cardiovascular prevention, showed 1.6% on esomeprazole 20 mg/day developed endoscopically detected ulcers versus 5.4% in the placebo group at 26 weeks.181 The corresponding life-table estimates at 6 months were 6.2% versus 1.8%.

In a cohort study of acute (7–30 days) NSAID users the odds ratio of having an ulcer was 0.70 (95% CI, 0.24–2.04), with an absolute risk reduction of 36.6% in patients who took a PPI vs those who did not.162 In chronic NSAID users (>30 days) the odds ratio was 0.32 (95% CI, 0.15–0.67), with an absolute risk reduction of 34.6%. The prevalence of H. pylori infection was similar in the two cohorts.

Secondary Prevention
Secondary prevention, or prevention of repeat gastroduodenal damage in patients who have already had such damage, is of utmost importance as this is the group at highest risk of further injury such as perforation and bleeding with continued NSAID use. After healing of an ulcer, maintenance PPI therapy for 6 months was more effective at preventing recurrent ulcer bleeding than H. pylori eradication therapy given for 1 week among patients taking naproxen who had prior NSAID-associated ulcer bleeding (absolute risk reduction 14.4%, 95% CI: 4.4–24.4).14 Thus, a PPI will be required in patients who have had a prior GI complication even after successful eradication of H. pylori infection, if they require continued NSAID therapy.3

A decade ago, the OMNIUM trial demonstrated maintenance treatment with omeprazole 20 mg/day (remission in 61%) reduced ulcer recurrence compared with both misoprostol 400 μg/day (remission in 48%, P = 0.001) and placebo (remission in 27%, P < 0.001). Patients on omeprazole had fewer adverse events than those receiving misoprostol.41 At the same time, the ASTRONAUT trial showed superiority of omeprazole 20 mg/day over ranitidine 300 mg/day in maintaining remission (72% vs 59%, P = 0.004).151

PPIs were superior to misoprostol in preventing recurrence of NSAID-induced endoscopic duodenal ulcers, and comparable to misoprostol in preventing the recurrence of NSAID-induced endoscopic gastric ulcers. A prospective, double blind, active and placebo controlled study170 compared the efficacy of lansoprazole (15 mg or 30 mg/day) and misoprostol (200 μg four times daily) in the prevention of ulcer recurrence among H. pylori-negative high-risk patients with a history of endoscopically detectable gastric ulcers. After 12 weeks of therapy, 93% of patients in the misoprostol group were free from gastric ulcers, compared with 80% and 82% in the lansoprazole 15 mg and 30 mg groups. Significantly more patients in the misoprostol groups reported treatment related adverse events and withdrew from the study. When withdrawal from the study was considered as a treatment failure, lansoprazole and misoprostol were clinically equivalent.

Aspirin with PPI co-therapy
PPIs appear to mitigate against the risk of peptic ulcer disease in aspirin users.171 They are also effective in reducing the risk of aspirin-related GI complications in patients with a history of previous aspirin-related GI bleeding.150, 172

Treatment with esomeprazole 20 mg/day significantly reduced (~70%) the risk of gastroduodenal ulcer formation in predominantly H. pylori-negative patients, aged over 60 years without pre-existing gastroduodenal ulcers, who received low-dose aspirin treatment for secondary prevention of cardiovascular events. Esomeprazole prevented or resolved minor esophageal lesions and reduced the frequency of upper gastrointestinal symptoms.161
Co-prescription of PPIs (omeprazole or lansoprazole) at standard doses has been shown to decrease the risk of recurrent GI haemorrhage by up to 90%.[84, 103, 149] After controlling for confounding covariates, patients who received placebo were at a 9.6-fold increased risk for recurrent ulcers.[103] In a study comparing clopidogrel to omeprazole in the same setting, 8.6% of patients developed recurrent bleeding on clopidogrel, compared with only 0.7% on aspirin plus esomeprazole.[172] The use of PPIs in the high-risk patient taking low-dose aspirin seems to be an appropriate therapeutic approach.

**NSAIDs/PPI Combination vs Coxibs**

The available evidence indicates both types of therapy, either NSAID/PPI co-therapy or a coxib, are equivalent in effectiveness.[129, 173] While the incidence of complications was high in both groups (>5% in 6 months), in selected high-risk patients there was a similar incidence of GI complications and ulcers with a numerical difference in favour of coxib therapy.[129, 130] For dyspepsia there was a numerical difference in favour of the PPI and NSAID therapy. Data from the VENUS and PLUTO studies did not show any advantage with double- vs. single-dose PPIs for the prevention of endoscopic ulcers.[160]

Among patients with a prior ulcer bleed, treatment with a traditional NSAID plus PPI or a coxib is still associated with a clinically important risk of recurrent ulcer bleed, after 6 months of therapy. Two small RCTs found no significant difference in the rate of recurrent bleeding or ulcer complications (about 4–6%) with a coxib alone versus a traditional NSAID plus PPI.[129, 174, 175] The relatively small numbers do not exclude a small benefit of one strategy over the other. Although the rates of recurrent bleeding may have been lower than those seen with traditional NSAIDs alone, this was not assessed in these studies and the risk was not eliminated with either of these strategies. Patients with prior ulcer bleeding require close monitoring and alternative strategies including discontinuation of the NSAID when possible or use of a coxib plus PPI could be considered.

A large ongoing trial (CONDOR) comparing the GI adverse events between celecoxib alone and diclofenac plus omeprazole in patients with arthritis at high risk of GI adverse effects will potentially provide further data.[176]

**Coxib with PPI Co-therapy**

From the limited studies available, for patients with prior gastrointestinal bleeding the combination of a coxib and a PPI reduces the risk of upper gastrointestinal bleeding from that of coxibs alone.

One RCT found a significantly lower rate of recurrent upper GI ulcer bleeding with a coxib plus a PPI (0%) compared to the coxib alone (8.9%) over 1 year (P < 0.001).[177]

Use of a COX-2 inhibitor plus a PPI is also supported by two RCTs using endoscopic ulcers as the primary outcome. Pooled analysis of the data from the VENUS and PLUTO studies in high-risk patients showed that among patients taking coxibs (n = 400), the use of concomitant PPI therapy was associated with significantly lower rates of endoscopic ulcers compared with placebo.[160] A subgroup analysis of the MEDAL programme suggested a lower incidence of clinical GI events among patients taking a coxib plus a PPI compared with a coxib alone; however, statistical analysis was not performed.

Two case-control studies[132, 178] report a coxib/PPI combination is associated with a reduction in the risk associated with traditional NSAID use and a greater risk reduction than the combination of a traditional NSAIDs and PPI. An observational study suggests patients using a PPI/celecoxib combination have an additional 25% risk reduction compared to patients taking the coxib alone.[133]

Based on the limited data available, the combination of a coxib with a PPI may offer the best GI safety profile in patients at very high GI risk.[3, 8, 179, 180] The combination appears cost effective.[135]
**Histamine$_2$ Receptor Antagonists (H$_2$RAs)**

Among NSAID users, H$_2$RAs are the most commonly used over-the-counter gastroprotective agents. Like PPIs, they suppress gastric acid secretion from parietal cells.

**Ulcer Healing**

The gastric ulcer healing rates associated with the use of H$_2$RAs in patients continuing to take NSAIDs, most assessed at 4 weeks, ranged from 30% to 67%. After 8 weeks one-quarter to one-half of patients still had unhealed ulcers. Duodenal ulcer healing rates were generally higher. H$_2$RAs heal a greater proportion of duodenal, but not gastric, ulcers when the patient discontinues NSAID use. NSAID-associated gastric ulcers are more likely to heal when patients receive concomitant treatment with a PPI rather than ranitidine. H$_2$RAs have shown to be inferior to PPIs at reducing the risk of GI bleeding.

**Prevention of Relapse**

Traditional doses of H$_2$RAs reduced the incidence of duodenal ulcers but not gastric ulcers, and did not significantly reduce the risk of symptomatic ulcers among NSAID users. Double doses of H$_2$RAs demonstrated greater effectiveness at preventing chronic NSAID related endoscopic gastric and duodenal ulcers. There is insufficient evidence to support the use of H$_2$RAs for the prevention of upper gastrointestinal bleeding. There was no evidence of efficacy for histamine receptor antagonists protecting against lower bowel injury. In addition, the ARAMIS cohort found H$_2$RAs may increase the risk for subsequent serious GI complications.

Currently, there is insufficient evidence to support the use of double doses of H$_2$RAs in high-risk NSAID users. Like PPIs, long-term clinical outcome studies are not available.

**Misoprostol**

NSAID use depletes gastric prostaglandin production, which appears central to the development of ulcers. Misoprostol, a synthetic analogue of prostaglandin $E_1$, enhances mucosal blood flow and stimulates secretion of mucus and bicarbonate in the upper GI tract, protecting the mucosa from chemical damage.

**Ulcer Healing**

Misoprostol is effective in the treatment of patients with established NSAID associated gastric and duodenal erosions and ulcers. Comparative studies suggest that PPIs are substantially more effective in these patients.

**Prevention of Relapse**

At the recommended dose, Misoprostol has demonstrated efficacy in several studies versus placebo in both the primary and secondary prevention of NSAID-induced endoscopic ulcers and NSAID-associated serious GI complications (e.g. bleeding, perforation, obstruction).

The Misoprostol Ulcer Complications Outcomes Safety Assessment (MUCOSA) trial showed full-dose misoprostol (200 $\mu$g four times daily) reduced the risk of NSAID-induced ulcer complications by 40% compared to NSAIDs alone. Meta-analysis confirmed misoprostol reduced the risk of gastric ulcer by 74% and duodenal ulcer by 53%, compared with placebo. Misoprostol was shown to be equivalent to lansoprazole and superior to ranitidine 150 mg b.d.

Misoprostol efficacy is significantly related to the frequency of dosing. Ulcers develop more frequently in patients who received lower daily doses. Half-dose misoprostol (200 $\mu$g twice daily) does not prevent recurrent ulcer complications in high-risk patients with arthritis and a history of ulcer bleeding. At this dose omeprazole was more effective for the prevention of recurrent endoscopic duodenal ulcers, but equivalent for secondary prevention of gastric ulcers.

**Tolerability**

Misoprostol is limited by its dose-related side-effect profile, with 1 in 14 patients prematurely discontinuing therapy because of GI events such as abdominal cramps, nausea and diarrhea. Misoprostol also has abortifacient activity, and is contraindicated in pregnant patients. The need for multiple daily doses also renders this drug unpopular. PPI therapy is better tolerated than misoprostol.
Antacids and Sucralfate

In short-term prevention studies, antacids at high-doses provide some protection against NSAID-related lesions when given prior to treatment. As for long-term prophylaxis, no clinical effect was observed. Antacids are significantly less effective than H2RAs.

Sucralfate forms an ulcer adherent complex at duodenal ulcer sites, protecting the ulcer and promoting healing. It may also inhibit pepsin activity in gastric fluid. Sucralfate is effective in the treatment of NSAID-induced duodenal ulcers, when the NSAID is stopped, but not effective in the treatment or prevention of NSAID-related gastric ulcers.81 Misoprostol is superior for the prevention of NSAID-uclers, and ulceration rates in the sucralfate group were equivalent to placebo rates. Sucralfate proved similar to ranitidine, but significantly less effective than omeprazole at treating mucosal lesions.189

Use of these agents is not recommended because of the availability of superior therapeutic options.

Eradication of Helicobacter pylori (H. pylori)

H. pylori and NSAIDs are the major causes of gastroduodenal ulcers. Peptic ulcers are more prevalent among H. pylori-positive compared to H. pylori-negative patients irrespective of NSAID use (OR, 4.03) and more prevalent among NSAID users than non-users irrespective of H. pylori status (OR, 3.10).106 Peptic-ulcer disease is rare in H. pylori negative non-NSAID takers.

Eradication therapy is one of the mainstays of treatment in ulcer patients with H. pylori infection. H. pylori eradication reduces the risk of upper gastrointestinal endoscopic ulcers in patients starting traditional NSAIDs and reduces the risk of upper gastrointestinal complications in patients already taking aspirin.3 A strategy of test and treat for all patients taking NSAIDs would not be justified based on the prevalence of H. pylori, however, it may be useful for patients at high GI risk before starting a traditional NSAID plus a PPI or coxib plus a PPI.3

RCTs have shown that H. pylori eradication in naive NSAID users is associated with a significant reduction of the incidence of endoscopic ulcers in patients starting NSAIDs.191-193 However, the benefit is less evident, or absent, in patients already on long-term NSAIDs or in those who had an ulcer history or history of ulcer complications, where co-therapy with a PPI seems necessary.88, 84, 193, 194

Another recent RCT showed H. pylori eradication therapy in patients on long-term NSAID treatment had no beneficial effect on the occurrence of ulcers, erosions, or dyspepsia followed for 12 months.194

Post-hoc analysis of the VIGOR study suggested that the GI benefit of coxib therapy is greater in patients without H. pylori infection than in those with the infection.63

In patients already taking an NSAID, H. pylori eradication appears to be less effective than PPI therapy in reducing the risk of peptic ulcer recurrence or ulcer bleeding. RCTs demonstrated maintenance PPI therapy was superior to H. pylori eradication alone in primary or secondary prevention of endoscopic ulcers among NSAID users.84, 193, 195, 196 While an inadequate rate of successful H. pylori eradication may have reduced the apparent efficacy of this strategy, it does not appear to be sufficient to prevent NSAID-induced ulcers among patients at high-risk and is less effective than PPI therapy.

H. pylori eradication prior to starting aspirin was shown to significantly reduce the risk of endoscopic ulcers compared to placebo in a small RCT.197

Among patients already treated with aspirin, one RCT found H. pylori eradication was as effective as PPI therapy in preventing recurrent bleeding, the rate of recurrence at six months was 1.9% with H. pylori eradication compared to 0.9% with PPI.84 In another RCT, the risk of recurrent ulcer complications at 12 months was 14.8% in patients taking placebo compared to 1.6% in patients receiving PPI therapy after H. pylori eradication and healing of an ulcer.103

For patients with a history of an ulcer complication who require subsequent therapy with an NSAID or aspirin, H. pylori eradication alone may not be a sufficient risk reduction strategy. Co-therapy with a PPI in such patients at high risk for recurrence of an ulcer complication has been recommended.198
**NSAID-Induced Dyspepsia**

Patients receiving NSAIDs frequently complain of GI symptoms in the absence of ulcers. Many NSAIDs may cause dyspeptic symptoms (such as epigastric discomfort and fullness, upper abdominal pain, nausea, and bloating), especially at high doses. Dyspepsia is a common adverse event of NSAID therapy and is the most common reason for drug discontinuation.\(^{83, 114}\)

Discontinuing NSAID use or lowering NSAID dose may be associated with resolution or a decrease in dyspepsia symptoms, and anecdotal reports suggest that NSAID-associated dyspepsia may resolve with a different NSAID. However, many patients will not be able to discontinue their current NSAID or lower its dose. For these patients, antisecretory agents may be most appropriate.

Antisecretory drugs, especially PPIs, reduce the incidence of dyspepsia and GI symptoms associated with NSAIDs and coxibs.\(^{48-50}\) Two multinational, randomised controlled trials evaluated the efficacy of PPIs for the relief of NSAID-related symptoms (NASA1 and SPACE1).\(^{50}\) The patients had a chronic condition requiring an NSAID, coxin, high-dose aspirin (>325 mg/day), or a combination of these for longer than 7 months, had no ulcers or erosive esophagitis at baseline, and were _H. pylori_-negative. Both trials demonstrated significant improvement with esomeprazole 20 and 40 mg/day compared with placebo. This benefit was also seen when data were pooled for coxibs alone.

A meta-analysis to compare the rates of dyspepsia for coxibs versus the NSAID/PPI combination in high-risk patients with arthritis showed that the NSAID/PPI combination affords greater risk reduction for dyspepsia than coxibs when compared with the common baseline of NSAIDs.\(^{169}\)

Sucralfate may also reduce dyspeptic symptoms.\(^{199, 200}\) In studies with endoscopic ulcer as the endpoint, acid suppression with traditional-dose H₂RA did not provide clear cut control of NSAID-induced GI symptoms compared to placebo.\(^{201}\) This is in contrast to assessing symptoms alone, which demonstrate efficacy for cimetidine and antacids compared to placebo for the prevention of NSAID-related dyspepsia.\(^{202, 203}\)

Misoprostol does not reduce the frequency of NSAID-induced dyspepsia.\(^{48, 185}\) Approximately 10% of patients with NSAID-induced dyspepsia will not find relief with any available antisecretory drugs.\(^{173}\)

The presence of moderate to severe dyspepsia among patients using an NSAID and a gastroprotective agent is a strong predictor of endoscopic ulcer (Note: The absence of these symptoms does not rule out endoscopic lesions among these patients).\(^{204}\) NSAID-using patients with continued dyspepsia despite use of cimetidine had a 31-fold increased probability of ulcers (P < 0.01).\(^{205}\) The data are supported by similar trials examining the efficacy of ranitidine, omeprazole and misoprostol.

The algorithm in Figure 5 describes the flow of potential therapeutic alternatives in patients who develop dyspepsia during NSAID therapy.

**Very High Risk Patients**

Long-term NSAID therapy can be more complex in patients with high gastrointestinal risk. Testing for and eradicating _H. pylori_ in patients at high risk of NSAID-related GI bleeding should be considered but will be insufficient without ongoing gastroprotection.

If cardiovascular risk is low, a coxin alone or a traditional NSAID with a PPI appear to offer similar protection from recurrent gastrointestinal bleeding, but this protection is incomplete. Therefore, for patients at very high risk of upper gastrointestinal events, a combination of a coxin plus a PPI may offer the best gastrointestinal safety profile.

When both gastrointestinal and cardiovascular risks are high, the optimal strategy is to avoid NSAID and coxin therapy if at all possible. If anti-inflammatory analgesics are required, the choice of therapy depends on the relative importance of GI and CV risks of individual patients,\(^{206}\) recognising that these patients are probably taking aspirin for their cardiovascular risk.
If gastrointestinal risk is the primary concern, a coxib (such as 200 mg celecoxib twice daily) plus a PPI (such as 20 mg esomeprazole twice daily) is recommended. This combination probably offers the best GI protection for very high risk patients. If the primary concern is cardiovascular risk (e.g., recent myocardial infarction), naproxen plus a PPI in patients on aspirin would be preferred. Naproxen may be the preferred NSAID because it does not appear to be associated with excess cardiovascular risk. However, gastrointestinal risk should be closely monitored, as this strategy carries a higher gastrointestinal risk than a coxib plus a PPI in patients on aspirin.

Patients at very high risk, including those with multiple risk factors and those who develop NSAID-related GI complications despite use of a gastroprotective strategy, can be offered two simultaneous gastroprotective medications.

Figure 5. Management of Dyspepsia Associated with NSAID Use

(a) Management of NSAID-associated dyspepsia in patients with no risk factors

<table>
<thead>
<tr>
<th>Presence of dyspepsia soon after NSAID use?</th>
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<tr>
<td>Options:</td>
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<tr>
<td>1. No NSAID</td>
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<td>2. Add a PPI</td>
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<td>3. Change to a coxib</td>
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<tr>
<td>4. Reduce dose</td>
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<tr>
<td>5. Change time of use</td>
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<td>Persistence of symptoms?</td>
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<td>ENDOSCOPY</td>
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(b) Management of NSAID-associated dyspepsia in patients with presence of risk factors

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<thead>
<tr>
<th>NSAID + PPI</th>
<th>Dyspepsia?</th>
<th>Coxib + PPI</th>
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<table>
<thead>
<tr>
<th>COXIB</th>
<th>Dyspepsia?</th>
<th>Coxib + PPI</th>
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<tr>
<td>Try low-dose NSAID/coxib</td>
<td>NO NSAID/COXIB</td>
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</table>
**Recommendations**

The best therapeutic strategy in the individual patient who needs NSAIDs must be based on consideration of the benefits and risks. The benefits derived from the reduction of pain, inflammation and improvement in quality of life (and those derived from the prevention of CV events with low-dose aspirin) must be balanced against the potential GI and now CV adverse events derived from traditional NSAID or coxib use. From a cost-benefit perspective, prevention strategies should be focused on patients with GI risk factors, which must now be modified by the presence/absence of CV risk factors.

**Levels of Evidence**

**Level I:** At least one properly conducted randomised controlled trial, systematic review, or meta-analysis.

**Level II:** Other comparison trials, non-randomised, cohort, case-control, or epidemiologic studies, and preferably more than one study.

**Level III:** Expert opinion or consensus statements.

**Burden of NSAID-induced Gastropathy**

- NSAIDs are effective in improving pain and function in patients with arthritis (Level I).
- In general, NSAIDs have similar effectiveness in improving pain and function in patients with arthritis (Level I).
- Aspirin and traditional NSAIDs increase the risk of upper gastrointestinal complications (Level I) and increase the risk of small and large bowel bleeding and other complications (Level II).
- Coxibs increase the risk of upper gastrointestinal ulcers and complications but to a lesser extent than traditional NSAIDs (Level I).
- In Australia over one-third of people using NSAIDs are aged between 45 and 64 years, while the age group most likely to use NSAIDs were aged 65 years and over.

**Risk Factors**

- Past history of peptic-ulcer disease, older age, concomitant use of aspirin, corticosteroids, anticoagulants or anti-platelet agents are associated with an increased risk of serious GI events among NSAID users (Level I).
- The strongest predictor of absolute risk is age and previous peptic ulcer disease, particularly if complicated (Level I).
- This risk is greatest during the first 3 months of treatment, although the risk continues to increase slowly, but steadily, with continued treatment (Level II).
- The risk of gastrointestinal bleeding with traditional NSAIDs and/or aspirin is increased in patients infected with *H. pylori* (Level II).
- Symptoms, or the lack thereof, are not good predictors of NSAID complications (Level II).
- Anaemia or hypoalbuminaemia may be a useful marker of NSAID-induced enteropathy in small intestines or blood loss from the bowel (Level II).

**NSAID Initiation**

(see NSAID pain management algorithm)

- All NSAIDs, including low-dose aspirin, increase the risk of serious upper GI complications, but to different degrees (Level I). Compared to traditional NSAIDs, coxibs are associated with a lower risk of upper gastrointestinal bleeding (Level I).
- NSAIDs should be prescribed with the lowest effective dose and for the shortest duration (Level II).
- Appropriate therapy to provide good pain relief, should aim to preserve GI mucosa and minimise cardiovascular risks.
- Coxibs increase the risk of coronary heart disease events (Level I).
- Non-naproxen traditional NSAIDs increase the risk of coronary heart disease events (Level II).
- Naproxen is associated with a lower risk of coronary heart disease events than other traditional NSAIDs and coxibs (Level II).
- The GI benefit of coxibs is largely lost with the addition of aspirin. Concomitant cardioprotective aspirin (≤ 325 mg once daily) may increase GI toxicity (Level I).
Gastroprotection

- Patients with a moderately increased risk of GI complications should be offered a gastroprotective strategy (Level I).
- High-risk is defined as two or more of the following factors; older age, past history of peptic ulcer disease especially if serious GI complications, concomitant oral steroids or anticoagulants, presence of serious comorbidity (such as cardiovascular disease (CVD), renal or hepatic impairment, diabetes and hypertension) or requirement for prolonged use of maximal doses of NSAIDs (Level II).
- Targeting modifiable risk-factors should be the first step (Level II).
- PPI therapy reduces the risk of traditional NSAID associated endoscopic ulcer disease, but there is less evidence for a reduction in bleeding events (Level II). PPI therapy also reduces upper gastrointestinal symptoms associated with coxibs and traditional NSAIDs (Level II).
- Among patients with a prior ulcer bleed, treatment with a coxib or a traditional NSAID plus PPI is still associated with a clinically important risk of recurrent ulcer bleed (Level II).
- In patients with prior gastrointestinal bleeding, the combination of a PPI and a coxib reduces the risk of upper gastrointestinal bleeding from that of coxib alone (Level II).
- High-dose misoprostol reduces the risk of upper gastrointestinal ulcer complications from traditional NSAIDs (Level II).
- PPI therapy is better tolerated than misoprostol (Level I).
- There is insufficient evidence to support the use of H$_2$RAs for the prevention of upper gastrointestinal bleeding (Level III).
- Patients at very high risk for recurrent ulcer bleeding who need NSAIDs should at least receive combination treatment with a coxib and a PPI. This combination probably offers the best GI protection for very high risk patients (Level II).
- Alternatively, patients at very high risk, including those with multiple risk factors and those who develop NSAID-related GI complications despite use of a gastroprotective strategy, can be offered two simultaneous gastroprotective medications (Level III).
- Patients at high GI risk and high cardiovascular risk should, whenever possible, avoid all treatments in this category (Level I). If therapy is required, Naproxen plus a PPI in patients on aspirin is preferred. GI risk should be closely monitored.

H. pylori Testing and Eradication

- Eradication therapy is one of the mainstays of treatment in ulcer patients with H. pylori infection.
- H. pylori eradication reduces the risk of upper gastrointestinal endoscopic ulcers in patients starting NSAID therapy (Level II).
- Eradication of H. pylori does not appear to reduce the frequency of endoscopic ulcers in chronic NSAID users, and appears to be less effective than PPI therapy in reducing the risk of peptic ulcer recurrence or ulcer bleeding (Level II).

H. pylori eradication reduces the risk of upper gastrointestinal complications in patients already taking aspirin (Level III).

- A strategy of test and treat for all patients taking NSAIDs would not be justified based on the prevalence of H. pylori, however, it may be useful for patients at high GI risk before starting a traditional NSAID plus a PPI or coxib plus a PPI (Level III).
5 ALGORITHM NSAID BASED-PAIN MANAGEMENT

An algorithm for decision making in pain management based on the evidence reviewed and an understanding of the mechanisms of action of this class of drugs has been proposed by Chan (2006) and Ong et al. (2007) (Figure 6).

Figure 6. Evidence-based NSAID Pain Management Algorithm

<table>
<thead>
<tr>
<th>Cardiovascular risk</th>
<th>Gastrointestinal risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Low</td>
<td>NSAID</td>
</tr>
<tr>
<td>No aspirin</td>
<td></td>
</tr>
<tr>
<td>High*</td>
<td>NSAID (Naproxen®) + PPI (mdoprostol suitable)</td>
</tr>
<tr>
<td>Low dose aspirin</td>
<td></td>
</tr>
</tbody>
</table>

*Gastrointestinal risk is arbitrarily defined as low (no risk factors), moderate (presence one or two risk factors), or high (more than two risk factors, previous ulcer complications, or concomitant use of corticosteroids or anticoagulants). All patients with a history of ulcers who require NSAIDs should be tested for H. pylori and if infection is present, eradication therapy should be given. High cardiovascular risk is arbitrarily defined as the requirement for low-dose aspirin for primary cardiovascular event prevention (calculated 10-year cardiovascular risk >10%) or secondary prevention of serious cardiovascular events. Naproxen is the preferred NSAID in patients with a high CV risk. Although Chan and Ong recommended against the use of either an NSAID or coxib in this dual high risk situation, the clinician will need to make individualised assessments of risk versus benefit when need for anti-inflammatory therapy is high (NB The algorithm below (Figure 7) recommends naproxen + PPI).

Figure 7. Algorithm for the Use of Long-term NSAID Therapy and Gastroprotective Agents (According to a Patient’s GI and CV risk)

ASA = aspirin  
*NSAID = traditional NSAID  
COX-2 inhibitor = coxibs

* In high-risk patients, a COX-2 inhibitor and a traditional NSAID + PPI show similar reductions of rebleeding rates, but these reductions may be incomplete.  
† In general, most patients on aspirin + naproxen would need the addition of a PPI. However, for some patients at very low GI risk, naproxen alone may be appropriate.
6 REFERENCES


