A GUIDE TO

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CONSULTANT PHARMACY SERVICES

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

KEY POINTS

NSAIDs are useful for relief of pain, especially when due to inflammation or tissue injury.

Non-selective NSAIDs (e.g. naproxen) have a higher rate of gastrointestinal adverse effects but may be safer from a cardiovascular perspective, whereas COX-2 selective agents (e.g. celecoxib) have a lower risk of gastrointestinal adverse effects but may cause more cardiovascular events.

The gastrointestinal bleeding risk from NSAIDs is increased by the concomitant use of gastrointestinal irritants and reduced by concomitant use of a PPI. GI risk is lowest with the combination of a COX-2 selective NSAID + PPI.

Risk of myocardial infarction is highest within 7 days of commencing an NSAID and short-term use should therefore not be assumed to be safe.

Multiple patient factors increase the risks associated with NSAID therapy with older patients and those with a history of peptic ulcer disease particularly at risk.

Frequent review of the appropriateness of NSAID therapy should be conducted in all patients with the aim to use the lowest effective dose for the shortest duration possible.

Topical NSAIDs are a similarly effective and safer option than oral NSAIDs in the management of certain types of pain, in particular knee and hand OA.

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CONTEXT

This guide considers the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for the management of pain and inflammation.

BENEFIT VERSUS HARM

	Favours Continuing Medication	Favours Deprescribing Medication
Main Benefits Relief from pain and inflammation. Facilitation of function and activity.	**Increased Benefit** • Pain from an inflammatory cause • Acute short-term pain from injury	**Decreased Benefits** • Neuropathic or nociplastic pain • Mono-articular arthritis which may be managed with local strategies
Main Harms GI bleeding, kidney injury, CVD and heart failure.	**Reduced Harms** • Concurrent use of proton pump inhibitor • H. pylori eradication	**Increased Harms** • Presence of renal dysfunction • Heart failure • Previous ACS or high absolute CV risk • Presence of bleeding risk factors • Concurrent use of gastric irritants (e.g. systemic corticosteroids, anticoagulants, antiplatelets, alcohol) • Concurrent use of diuretics and/or ACE inhibitors/ARBs • Presence of H. pylori

RECOMMENDED DEPRESCRIBING STRATEGY

- Dose reduction or cessation may be considered for many patients taking NSAIDs whose symptoms have improved.
- Some patients may find intermittent use of NSAIDs as effective as continuous use.
- Maximise non-pharmacological treatments (heat packs, massage, exercise, physiotherapy etc.).
- Maximise the use of alternative analgesics (e.g. paracetamol or topical NSAIDs).
- Estimation of cardiac and gastrointestinal bleeding risk for individual patients may guide the selection of the most appropriate NSAID and dose (with or without a PPI).
- Cessation should be considered in patients who develop gastrointestinal side effects or anaemia. Older patients may present with subtle symptoms such as unexplained loss of weight, anorexia etc.

BACKGROUND

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in Australia for their anti-inflammatory and analgesic properties. Over 6 million prescriptions for NSAIDs were dispensed in the year to June 2021.[1] In addition, there is ongoing direct-to-consumer advertising of non-prescription NSAIDs which are available 'over the counter' in pharmacies and supermarkets. Following the recent up-scheduling of paracetamol/codeine combinations and new limitations on opioid prescribing for chronic pain, use of NSAIDs appears likely to remain widespread.

NSAIDs are a chemically diverse group of drugs which work by inhibiting cyclooxygenase (COX) enzymes. In addition to providing a therapeutic analgesic and anti-inflammatory effect, COX inhibition leads to a wide range of secondary pharmacodynamic effects on platelet aggregation and coagulation, the gastric mucosa, renal vasculature, and other vascular smooth muscle. These effects are predominantly due to reduced production of various prostaglandins, thromboxanes, and prostacyclins.

Two main COX isoforms are involved in the pharmacology of NSAIDs: COX-1 and COX-2. These two isoforms have different functions and the varying levels of inhibition afforded by different NSAIDs results in the differing therapeutic and adverse effect profiles of each of these agents. At the basic level, inhibition of COX-1 impacts on platelet function, gastrointestinal mucosa and renal vasculature, while inhibition of COX-2, which is upregulated in response to inflammation and tissue damage[2], reduces inflammation, pain and fever. While all NSAIDs have some impact on both COX-1 and COX-2, some are more selective for COX-2 than others (see **Figure 1**) and so their relative likelihood of certain side effects varies (see later).

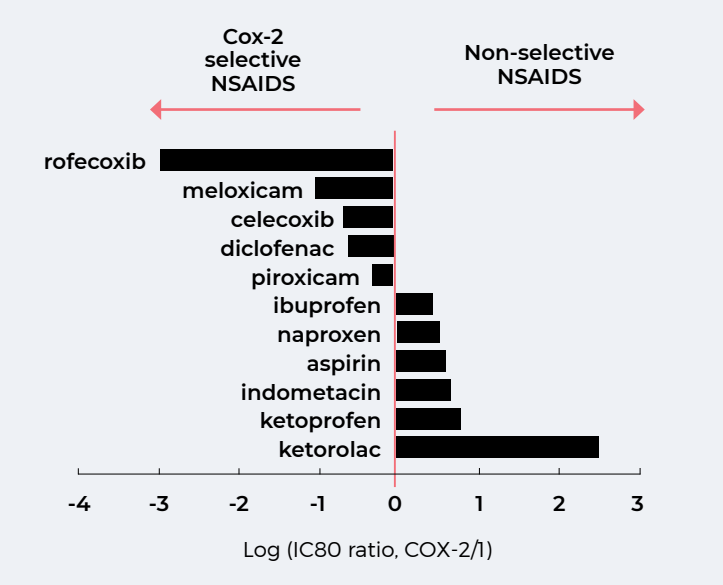

Figure 1: Relative COX selectivity of nonsteroidal anti-inflammatory drugs displayed by the concentration of the drugs (IC80) required to inhibit COX-1 and COX-2 activity by 80%. Adapted from reference 2.

EFFICACY

ORAL NSAIDs

NSAIDs have been used in clinical practice for over 100 years.[3] Currently available NSAIDs are widely used for their analgesic, anti-inflammatory, and antipyretic actions.

A recent network meta-analysis by da Costa et al. examining analgesia regimens for knee and hip osteoarthritis (OA) included 68 studies focused on NSAIDs. The effect of most full dose NSAID regimens was either greater than or close to the threshold for minimal clinically important effect on pain, and greater than the effect of either paracetamol or opioids. They found that the probability of a clinically important benefit to pain being achieved was 99.9% for diclofenac 150mg/day, 68.1% for naproxen 1000mg/day, 42.1% for ibuprofen 1200mg/day, and 20.0% for celecoxib 200mg/day. While diclofenac 150mg/day appeared to be one of the more effective oral regimens, it also had a higher rate of adverse events associated with its use (Figure 2).[4]

Another network meta-analysis examining the use of NSAIDs in patients with rheumatoid arthritis (RA) as well as those with OA found that diclofenac, celecoxib, naproxen and ibuprofen were all significantly better than placebo in terms of pain relief after 6 and 12 weeks of use. Agents were similar in efficacy with a range of benefit from ~9-13 points on a 1-100 visual analogue pain scale.[5]

The similarity in efficacy between the NSAIDs means that choice of agent is often based on gastrointestinal, cardiovascular and other adverse effect risk profiles as well as patient preference and prescriber familiarity.[6,7]

TOPICAL NSAIDs

Several NSAIDs are available in topical preparations with diclofenac gel the most widely used in Australia. The meta-analysis by da Costa et al. also included topical NSAIDs (see **Figure 2**). They found topical diclofenac (administered via a plaster) to be one of the most efficacious treatments (studies looked at knee OA only). The probability of a clinically important benefit to pain being achieved was 92.3% for topical diclofenac compared with 99.9% for oral diclofenac (150mg/day). The rate of dropout due to adverse effects was also lower with topical diclofenac compared with oral diclofenac.[4]

The Osteoarthritis Research Society International (OARSI) conducted a meta-analysis in 2020 which concluded that *"Topical NSAIDs are more effective than acetaminophen (paracetamol) but not oral NSAIDs for function improvement in people with knee osteoarthritis. Topical NSAIDs are safer than acetaminophen (paracetamol) or oral NSAIDS in trials and real-world data"*.

The 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of hand, hip, and hand OA strongly recommends the use of topical NSAIDs for management of knee OA and conditionally recommends their use for hand OA (due to a lower quality of evidence and difficulties associated with frequent application to the hands that are often subject to washing etc.). They further recommend that topical NSAIDs should be considered prior to oral NSAIDs for these indications given the benefit of lower systemic exposure to the drug.[8]

There is limited data available to compare specific topical formulations, however, a 2017 Cochrane review found that diclofenac administered in a gel, as is most common in Australia, is likely the most effective for acute pain, and is similarly effective to other diclofenac topical formulations for the management of chronic pain.[9]

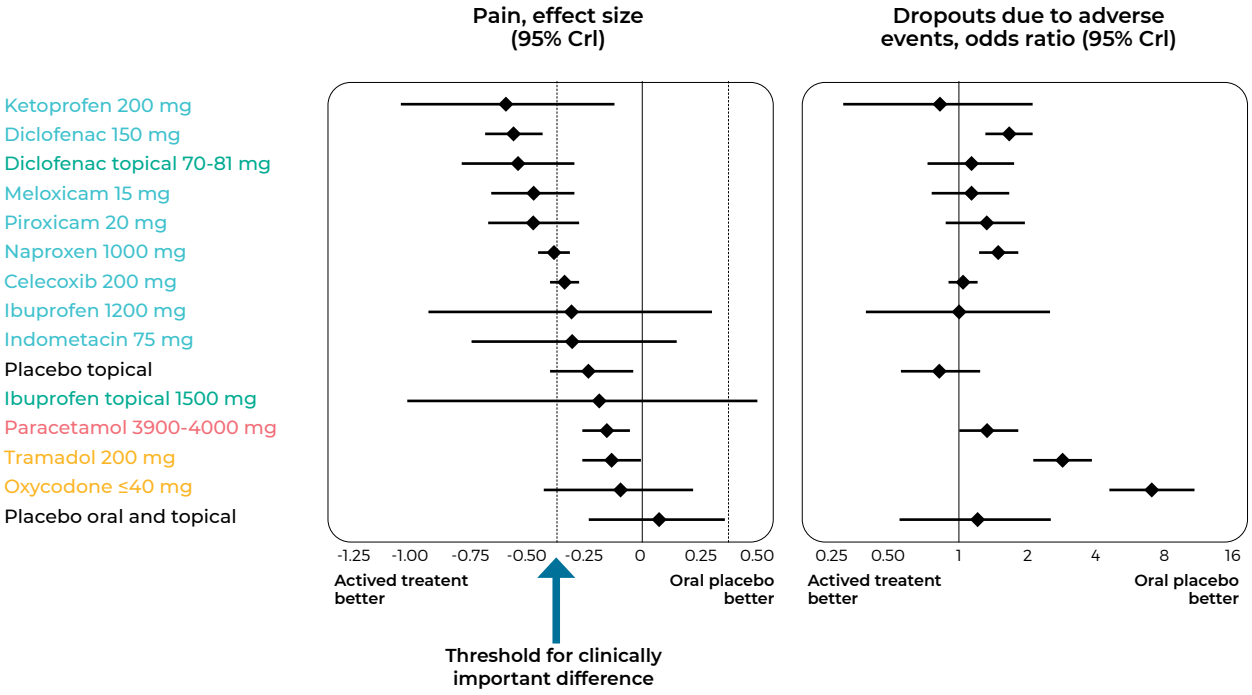

Figure 2: Results from a network meta-analysis comparing various analgesic regimens in the treatment of hip and knee OA. Adapted from reference 4.

ADVERSE EFFECTS

Most of the haemodynamic, gastrointestinal (GI), cardiovascular, and renal adverse effects associated with oral NSAIDs are directly related to the reduction in COX enzyme-mediated synthesis of biologically important prostanoids.

Frequency of adverse effects vary, among other factors, on the level of COX-1 vs COX-2 inhibition. The general relationship between level of selectivity and relative risk of GI and CV events is summarised in **Figure 3**.

Topical NSAIDs have a much lower rate of adverse effects than oral NSAIDs with adverse effects generally limited to local irritation from cutaneous application.

GASTROINTESTINAL BLEEDING RISK

While a few oral NSAIDs have a direct irritant effect on the gastrointestinal mucosa, the primary mechanism behind gastroduodenal NSAID toxicity is inhibition of the COX-1 produced prostaglandins involved in mucosal protection. NSAID induced mucosal injury is common, with endoscopically proven ulceration in up to 30% of those taking regular oral NSAIDs, and can occur quickly, with increased rates of mucosal damage apparent within two weeks of NSAID commencement.[12-15] Most NSAID induced mucosal damage is superficial, but in 2-4% of patients who chronically use NSAIDs, peptic ulcer complications (perforation, haemorrhage and/or death) may occur.[16]

The relative risk of GI complications is influenced by a number of factors including type and dose of NSAID, concurrent medication and patient factors. Older patients and patients with a prior history of peptic ulcer disease are at greater risk of gastrointestinal complications.[17-18] Risk is further increased by the concomitant use of certain medications including antiplatelet agents, anticoagulants, systemic corticosteroids, and SSRIs.[19]

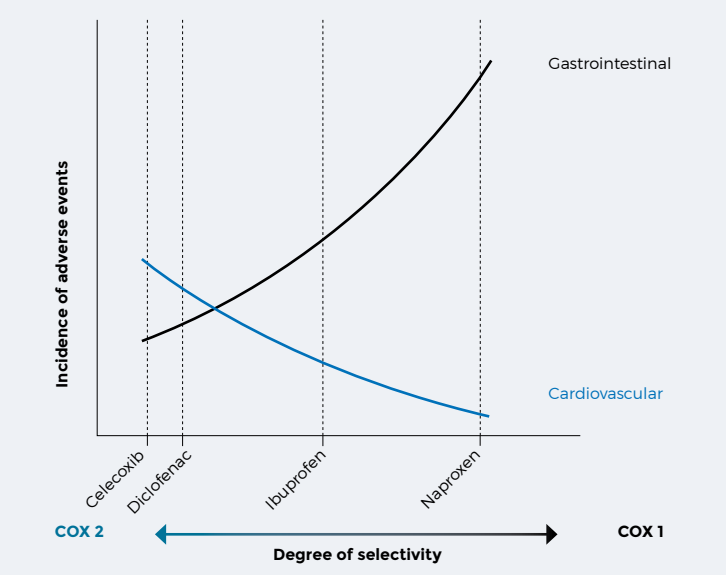

Figure 3: The impact of COX selectivity on the incidence of excess GI and CV events. Adapted from references 10 and 11.

Combining these factors together, patients may be categorised as being at high, moderate, or low risk of gastrointestinal complications (see **Table 1**).

It should be noted that as well as upper GI damage, NSAIDs may cause lower GI damage. This may result in bleeding in the small intestine or colon, sometimes without overt symptoms. With the increased use of mitigation strategies such as co-prescription of proton pump inhibitors (PPIs), which are largely effective only for upper GI problems (see below), there is a trend towards fewer upper GI problems and more lower GI problems causing hospitalisation.[20]

Non-Selective versus COX-2 selective NSAIDs

As COX-1 is responsible for production of prostaglandins involved in GI mucosal protection, NSAIDs which have a high affinity for COX-1 (non-selective NSAIDs) tend to have a high incidence of GI adverse effects, whereas NSAIDs with lower affinity for COX-1 (COX-2 selective NSAIDs) have a lower incidence of GI adverse effects.

This difference was demonstrated in a 2013 meta-analysis of predominantly individual participant data from randomised trials comparing several NSAIDs. The analysis utilised data from over 300,000 participants in over 750 trials. As compared with placebo, all NSAID regimens increased upper GI complications including upper GI perforation, obstruction, or bleeding, however the risk ratios were 1.81 for coxibs (doses studied were mostly high), 1.89 for diclofenac (mostly 150mg/day), 3.97 for ibuprofen (2400mg/day) and 4.22 for naproxen (mostly 1000mg/day) (see Table 2 for estimated NNH).[11]

Another review by Masclee et al examined the medications being taken by 114,835 patients with diagnosed upper gastrointestinal bleeding. Non-selective NSAIDs were present in 32.6% of cases (increased relative risk 4.3) compared with COX-2 selective NSAIDs in only 22.5% of cases (increased relative risk 2.9).[19]

Importantly, in addition to a lower rate of upper GI complications, COX-2 selective NSAIDs also appear to cause fewer lower GI complications than non-selective NSAIDs. This makes the combination of COX-2 selective NSAID plus PPI (for upper GI protection) the preferred option in patients with elevated GI bleed risk.[21]

Stratifying risk of NSAID associated upper GI toxicity		
Note: *H. Pylori* is an independent risk factor and should be treated prior to NSAID initiation		
Low Risk	**Moderate Risk**	**High Risk**
No risk factors	1 - 2 Risk factors (High risk if both *)	3+ Risk factors (or 2 if both *) OR History of complicated ulcer
Risk Factors		
Age >65 years		
NSAID used at high dose		
* Concurrent use of antiplatelet agent, anticoagulant, systemic corticosteroid, or SSRI		
* History of uncomplicated ulcer		

Table 1: Example of a risk stratification tool for GI risk associated with NSAID therapy. Adapted from reference 18.

Dose of NSAID

A meta-analysis by Castellsague et al. of observational data concluded that, compared with low or medium doses, the use of high daily doses of NSAIDs is associated with approximately a 2-3 fold increase in relative risk for upper GI complications. Relative risks for the individual NSAIDs included in the study are shown in **Figure 4**.[22]

MITIGATION OF NSAID-INDUCED GASTROINTESTINAL BLEEDING RISK

Helicobacter pylori

It has long been established that both *Helicobacter Pylori (H. pylori)* colonisation, and NSAID use are independent risk factors for the development of peptic ulcer disease (PUD) and ulcer bleeding.[23,24] A meta-analysis of observational data published in 2002 suggests these risks are also additive. The authors found that NSAID users were 19.4 times more likely than non-users to

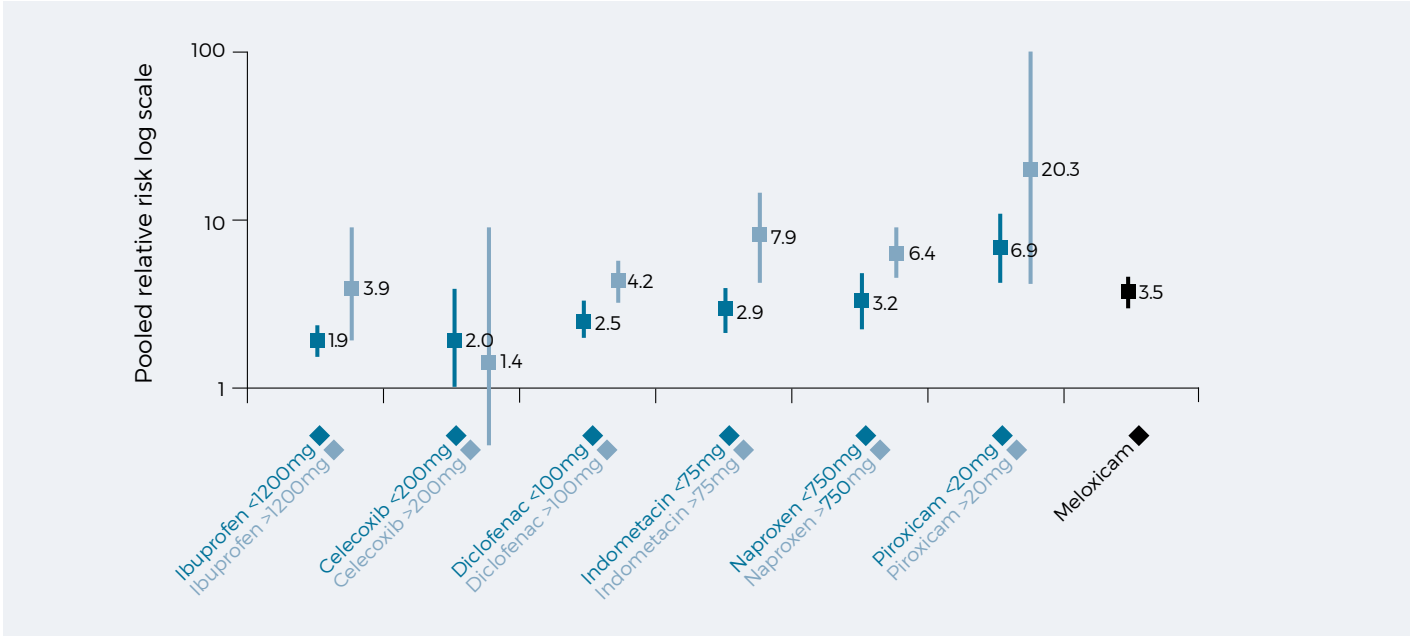

Figure 4: High vs Low Dose NSAIDs and Relative Risk of Upper GI Complications. Adapted from reference 22.

develop PUD and those who were also colonised with *H. pylori* were a further 3.5 times more likely to develop PUD. This means that compared to people without either risk factor, NSAID users who were colonised with *H. pylori* were 61.1 times more likely to develop PUD. These people were also 6.1 times more likely to experience peptic ulcer bleeding than those without either risk factor.[25]

Another meta-analysis by Tang et al. found that eradication of *H. pylori* in patients taking NSAIDs almost halved the rate of peptic ulceration from 11.8% to 6.3% (ARR 5.5% NNT 18).[26]

Australian guidelines advise testing for the prescence of *H. pylori* prior to initiating NSAID therapy in anyone with a history of PUD, or at elevated risk of NSAID associated GI bleeding, and prescribing eradication therapy if detected.[27] International guidelines have suggested an even more liberal approach to testing, citing evidence that *H. pylori* eradication is the most cost effective strategy for primary prevention of PUD in people >50 years old.[18]

Proton Pump Inhibitor Therapy

The value of PPI therapy for prevention of NSAID associated upper GI complications has been demonstrated in numerous studies. A 2016 meta-analysis by Yuan et al. combined data from 125,053 study participants in order to compare the risks of GI toxicity between different types of NSAIDs with and without acid suppressive therapy.[28]

They found that the probability of an ulcer being identified at endoscopy in patients prescribed a COX-2 selective NSAID + PPI was 0.51%, a COX-2 selective NSAID alone 4.00%, a non-selective NSAID + PPI 3.72%, and a non-selective NSAID alone 15.87%. Results were similar across the other analyses in the study, ulcer complications: 0.04%, 0.13%, 0.15%, and 0.53% respectively, and symptomatic ulcer N/A, 0.08%, 0.08%, and 0.70% respectively.[28] The authors concluded that COX-2 selective NSAIDs plus PPI therapy was associated with the lowest event probability followed by selective COX-2 inhibitors alone, then non-selective NSAIDs plus PPI therapy, and lastly non-selective NSAID therapy alone.

The use of celecoxib in combination with a PPI has also been tested in a study of high risk patients recovery from non-selective NSAID induced gastrointestinal bleeding.[29] At 13 months after randomisation to either celecoxib 200mg BD or celecoxib 200mg BD plus a PPI, the recurrent ulcer bleeding rates were 12/136 (8.9%) without a PPI and 0/137 (0%) with a PPI. Not surprisingly, these authors concluded, "Patients at very high risk for recurrent ulcer bleeding who need anti-inflammatory analgesics should receive combination treatment with a COX 2 inhibitor and a PPI."[29]

Although COX-2 selective agents are less likely to be associated with GI complications than non-selective NSAIDs, risk associated with the combination of COX-2 selective NSAID plus low dose aspirin appears to be similar to that of non-selective NSAIDs.[30]

Risks of GI complications associated with various combinations of NSAIDs, PPIs and gastro-irritants are shown in **Figure 5**.

RENAL AND HAEMODYNAMIC EFFECTS OF NSAIDs

The use of all NSAIDs has been associated with dose-dependent renal side effects. These include a reduction in glomerular filtration, acute and chronic renal failure, renal papillary necrosis and acute interstitial nephritis. In addition, blockade of prostaglandin production in the kidney leads to salt/fluid retention, increased vascular tone, and thus impairment of hypertension and heart failure control. Many of these side effects are short-term and reversible upon NSAID withdrawal and rarely cause issues in healthy, well hydrated patients.[31] However, in patients with other risk factors and/or on other drugs such as diuretics, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers, use of NSAIDs may result in acute kidney injury, worsen chronic renal disease, or trigger decompensation of heart failure.

Along with renal insufficiency, diabetes, heart failure, and older age are risk factors for NSAID induced haemodynamic adverse effects.

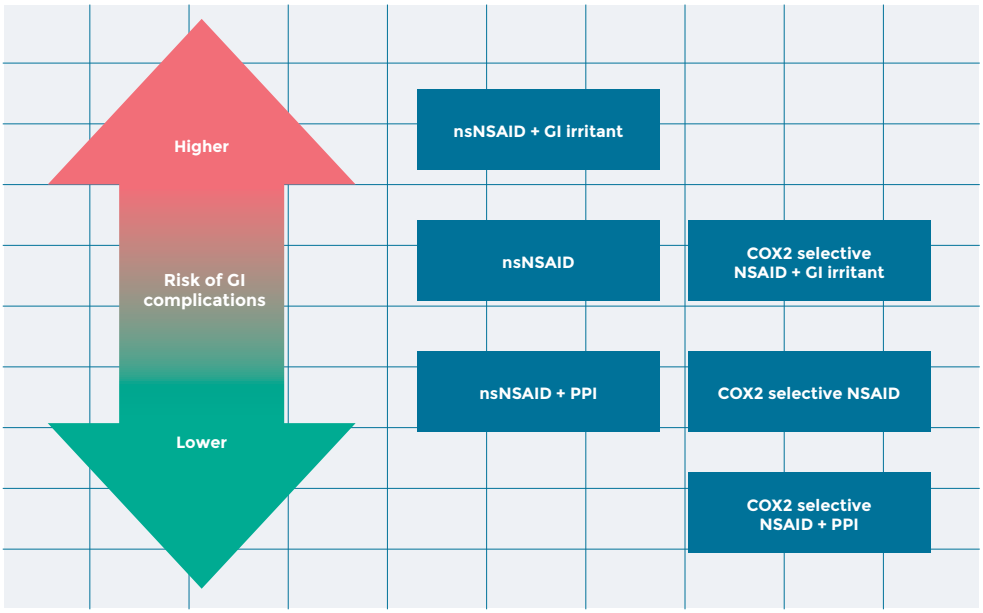

Figure 5: Relative risk of GI complications from NSAIDs.[18, 19, 21, 28, 30]

nsNSAID = non-selective NSAID

CARDIOVASCULAR ADVERSE EFFECTS

Myocardial Infarction

NSAIDs increase the risk of myocardial infarction due to their complex effects on certain prostanoids, on sodium and water retention, and on vascular endothelial growth factor.[32,33]

In contrast to GI safety, COX-2 selective agents appear to carry a higher risk of cardiovascular events compared with non-selective agents.[11] This is thought to be due mainly to the inhibition of COX-2 produced prostacyclin (prostacyclin inhibits platelet aggregation), coupled with continuation of COX-1 mediated thromboxane production (thromboxane encourages platelet aggregation), resulting in an overall increase in tendency for platelets to aggregate.[2] In 2005 one of the most COX-2 selective agents, rofecoxib (Vioxx®), was removed from the market due to the finding of a high myocardial infarction risk compared with naproxen (ARI 0.6% per year, NNH 166).[34]

The most recent analysis of randomised data examining the vascular effects of NSAIDs was conducted by the Coxib and traditional NSAID Trialists' (CNT) collaboration.[11] Compared to placebo, they found an increased rate of major coronary events with coxibs (~75% increase), diclofenac (~70% increase) and high dose ibuprofen (~120% increase), but no increase with naproxen.[11] Estimated annual excess vascular events were calculated for both low and high cardiovascular risk patients (2.5% and 10% 5-year CV risk respectively). Excess events ranged from 0 to 2 per 1000 patient years in the low CV risk group to -1 to 9 per 1000 in the high-risk group (see Table 2). It should be noted that most of the ibuprofen data came from trials which used 800mg three times daily; double the dose most often used in contemporary practice.[11] The difference in event incidence between low and high cardiovascular risk patients in this study is substantial and should encourage a cautious approach to the use of NSAIDs in high CV risk individuals, particularly considering that 5-year CV risk is much higher than 10% in many patients.

More recent observational data has challenged the view that non-selective NSAIDs such as naproxen are safe in regard to myocardial infarction. A Bayesian meta-analysis published in 2017 found an increased incidence of myocardial infarction for all NSAIDs within 7 days of commencement. Odds ratios were 1.24 for celecoxib, 1.48 for ibuprofen, 1.50 for diclofenac, 1.53 for naproxen, and 1.58 for rofecoxib.[35] Interestingly, this meta-analysis also suggests that risk of myocardial infarction is highest within the first 7 days of therapy.[35] Short term use of NSAIDs should therefore not be assumed to be safe from a cardiovascular perspective. This study also concluded that higher doses were associated with higher risk, regardless of the NSAID used.

Taken together, the available data suggests all NSAIDs are likely to increase risk of myocardial infarction to some degree. Due to favourable results in randomised controlled trials, naproxen remains the preferred agent when cardiovascular risk is high but this needs to be contrasted against the much higher rate of GI adverse effects.

Heart Failure

Randomised controlled trials and observational studies have shown an increase in the incidence of new-onset heart failure and heart failure exacerbation in NSAID takers.[36,37] A meta-analysis published in 2008 by Scott et al. examined randomised controlled trial data comparing NSAIDs to placebo and reported an increased risk of heart failure in patients taking NSAIDs (OR 2.31). The population studied does not appear to have been at particularly high risk of heart failure with incidence of heart failure only 0.18% in the placebo group. Incidence was 0.47% in the NSAID group, showing an absolute risk increase of 0.29% or a NNH of 348.[37] Risk appears to be increased by age and the presence of pre-existing heart failure. The same study was unable to determine a difference in outcomes between non-selective and COX-2 selective NSAIDs suggesting that this is a class effect.

A more recent nested case-control study of European population-based healthcare data suggested incidence may differ slightly between NSAIDs with odds ratios of hospitalisation for heart failure of 1.19 for diclofenac, 1.18 for ibuprofen, 1.16 for naproxen, but no significant association with celecoxib.[38]

Atrial Fibrillation

Multiple observational studies have found an association between the use of NSAIDs and the incidence of atrial fibrillation. A meta-analysis published in 2014 found NSAIDs increased the risk for AF by 12%. The risk seemed highest among new NSAID users in whom incidence was increased by 53%. Risk was apparent for both COX-2 selective and non-selective NSAIDs.[39]

	Cardiovascular events				Upper GI complications			
Baseline risk	2.5% (per 5-years)		10% (per 5-years)		0.2% (per year)		0.5% (per year)	
	Estimated annual excess events/1000	NNH (per year)	Estimated annual excess events/1000	NNH (per year)	Estimated annual excess events/1000	NNH (per year)	Estimated annual excess events/1000	NNH (per year)
Coxib	2	500	7	143	2	500	4	250
Diclofenac	2	500	8	125	2	500	4	250
Ibuprofen	2	500	9	111	6	167	15	67
Naproxen	0	-	-1	-	6	167	16	63

Table 2: Incidence of excess cardiovascular and gastrointestinal events by NSAID for patients with different levels of baseline risk. Adapted from reference 11.

SUGGESTED OPTIONS FOR NSAID USE

Taking into account the risk of vascular and gastrointestinal harm, it is possible to offer recommendations regarding NSAID choice in certain clinical situations, as per the table below.

		Gastrointestinal Risk		
		Low	**Moderate**	**High**
Cardiovascular Risk	**Low**	Any NSAID	COX-2 selective NSAID OR Other NSAID + PPI	Celecoxib + PPI
	High	Naproxen OR Ibuprofen ≤1200mg/day	Ibuprofen ≤1200mg/day + PPI	**Avoid NSAID if possible** OR Low dose celecoxib +PPI

Table 3: Suggested options for NSAIDs according to GI and CV risk (Adapted from references[18, 21, 40-42]). A higher CV or bleed risk may be acceptable to some patients where quality of life is significantly improved by effective analgesia. In all cases systemic NSAIDs should be used at the lowest effective dose. PPI therapy should be considered in all patients with moderate to high GI bleed risk.

FACTORS TO CONSIDER

Chronic pain strongly and negatively impacts quality of life and is associated with poorer outcomes across multiple health domains. Normal daily functions such as sleep, mobility, food preparation, and self-care can become significantly impaired by chronic pain.[21] A relatively high risk of NSAID induced adverse event may therefore be acceptable for some patients where quality of life is improved by effective analgesia. Patients or decision makers should be involved in the decision-making process.

It is possible that alternate analgesic options will be required following NSAID discontinuation, and this should be considered prior to deprescribing, as some alternatives (e.g. opioids) may have a less favourable risk/benefit profile in some patients.

Dose reduction, change of administration route, or change to a more appropriate NSAID based on the patient's individual gastrointestinal and cardiovascular risk status may be more appropriate than complete cessation of NSAID therapy.

IN FAVOUR OF DEPRESCRIBING

Pain and inflammation often change over time and may even resolve completely. It may therefore be reasonable to reduce the dose or cease oral NSAIDs when symptoms have been under control and stable for some time. Maximising other medications with a more favourable side effect profile (especially paracetamol or topical NSAIDs) and utilising non-pharmacological options should be considered in all patients as a way of minimising oral NSAID dose and duration.

Localised arthritic pain often responds well to topical NSAID therapy or steroid injections, both of which have a lower incidence of systemic adverse effects than oral NSAIDs.

All NSAIDs should be avoided for patients at high risk of gastrointestinal adverse effects (particularly with past peptic ulcer disease) if at all possible. Where use is imperative, the lowest dose that achieves symptom control should be used for the shortest period possible, and use of a COX-2 selective NSAID with PPI prophylaxis is most appropriate.

While absolute incidence of NSAID associated cardiovascular events is lower than GI events, patients with high baseline cardiovascular risk or heart failure should avoid oral NSAID therapy if possible.

AGAINST DEPRESCRIBING

NSAIDs can provide effective analgesia and anti-inflammatory effects. Benefits on pain and function may be significant and can outweigh risks in many patients.

Patients with chronic inflammatory conditions (e.g. rheumatoid arthritis) may require long term oral NSAID therapy (though opportunities to optimise DMARD therapy should be considered before accepting the need for long term oral NSAIDs).

DISCONTINUATION SYNDROMES

Generally, tapering is not required when deprescribing NSAIDs, however, gradual reduction may help to reassure the patient during the deprescribing process. Stepping down the dose prior to cessation also helps to establish the lowest effective dose if therapy continuation does become necessary.

Medication overuse headache from frequent intermittent use of NSAIDs (and other analgesics) is a common issue estimated to affect around 1% of the general population.[43] Withdrawal headaches following cessation of analgesia in this setting are common and may persist for several months.

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