A GUIDE TO

deprescribing

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CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES

NON STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

KEY POINTS

- **NSAIDs may be useful for short-term relief of pain due to inflammatory causes.**
- **The gastrointestinal bleeding risk from NSAIDs is increased by the concomitant use of gastrointestinal irritants and reduced by concomitant use of acid reduction therapy.**
- **The use of a PPI with a non-selective NSAID reduces the risk of GI bleeding to a rate similar to that of celecoxib without a PPI.**
- **H pylori eradication in patients taking NSAIDs, eradication almost halves the rate of peptic ulceration.**
- **In the studies available, the risk of cardiovascular adverse events with NSAIDs is lowest with naproxen, while the risk of gastrointestinal adverse effects is lowest with celecoxib.**

CONTEXT

This guide considers the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

RECOMMENDED DEPRESCRIBING STRATEGY

- Dose reduction or cessation may be considered for all patients taking NSAIDs whose symptoms are under control and are relatively stable.
- Some patients may find intermittent use of NSAIDs as effective as continuous use.
- Maximise non-pharmacological treatments for example, heat packs, massage, exercise, physiotherapy.
- Maximise the use of alternative analgesics such as 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 PPIs.
- Cessation should be considered in patients who develop gastrointestinal side effects or anaemia. Elderly patients may present with subtle symptoms such as unexplained loss of weight, anorexia etc.

	LOW GI RISK	MODERATE GI RISK	HIGH GI RISK*
Low CV Risk	Lowest effective dose of an effective NSAID	Low dose Celecoxib or Diclofenac + PPI	Celecoxib + PPI
High CV Risk	Low dose Celecoxib or Naproxen + PPI	Naproxen + PPI	Avoid if possible Low dose Celecoxib + PPI

Table 5: Suggested options for NSAIDs according to GI and CV risk (Information from references [8,9,10,18,19,35]) *Patients taking an antiplatelet agent should be considered at high GI risk when an NSAID is used as well.

BENEFIT VERSUS HARM

Favours Continuing Medication ← → **Favours Deprescribing Medication**

Main Benefits
- Short term relief of inflammatory pain

Main Harms
- Gastrointestinal bleeding, renal failure and cardiac issues

Increased Benefit
- Short term use for pain from an inflammatory cause
- Acute short term pain from injury

Reduced Harms
- Concurrent use of proton pump inhibitor
- H Pylori eradication

Decreased Benefits
- Chronic pain without inflammatory component
- Mono-articular arthritis which may be managed with local strategies.

Increased Harms
- Concurrent use of diuretics and/or angiotensin inhibing agents
- Presence of renal dysfunction
- Prior gastrointestinal bleeding
- Concurrent use of gastric irritants (e.g. corticosteroids, anticoagulants, antiplatelets, alcohol)
- Presence of H Pylori

BACKGROUND

The use of NSAIDs in Australia is escalating because of increasing musculoskeletal problems in the community (probably related to ageing and obesity). In addition, there is a strong impact of direct to consumer advertising of non-prescription NSAIDs which are available in pharmacies and supermarkets.

NSAIDs are a chemically diverse group of prostaglandin inhibitors that have a wide range of pharmacological effects in addition to their primary anti-inflammatory actions. These include impact on the platelets, gastric protective lining, renal vasculature and other vascular smooth muscle.

The reduction of prostaglandin synthesis is based on their inhibition of the activity of the cyclooxygenase (COX) enzymes COX-1 and COX-2. These two COX isoforms have differing functions and inhibition of the different isoforms results in different therapeutic actions and side effects. Inhibition of COX-1 can impact on platelet function, gastrointestinal acid protection and renal vasculature, while inhibition of COX-2 can reduce 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**)[1] and so their relative likelihood of certain side-effects varies (see later).

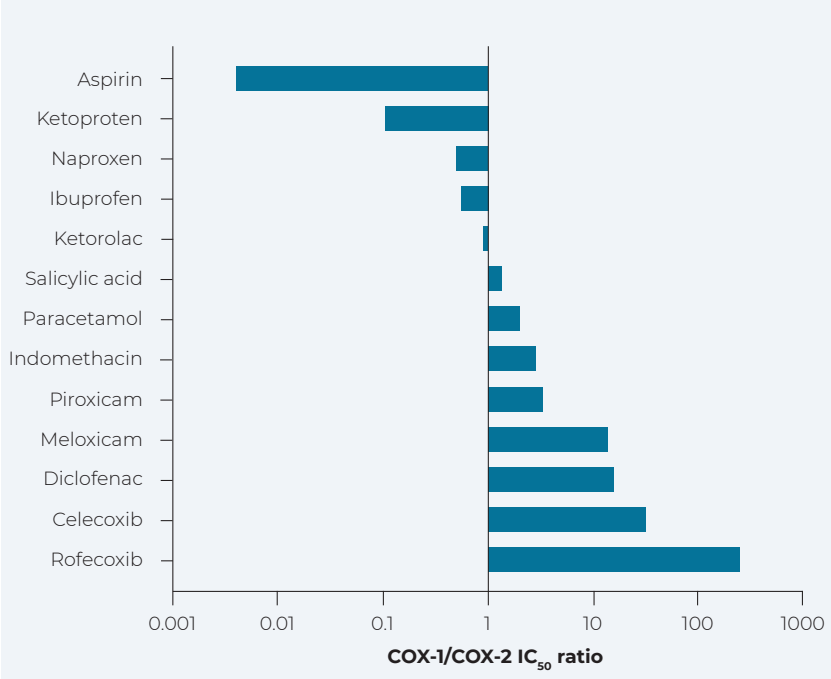

Figure 1: Selectivity of NSAIDs for COX-1 and COX-2[1]

EFFICACY

NSAIDs have a long history of clinical use since aspirin, paracetamol and phenacetin were serendipitously discovered more than 100 years ago.[2]

Currently available NSAIDs include a range of agents with efficacy for the relief of inflammatory pain caused by different arthropathies.

A network meta-analysis of the use of NSAIDs in patients with osteoarthritis or rheumatoid arthritis compared multiple NSAIDs to others.[3] The authors 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.[3] A more recent network meta-analysis focussed on knee and hip osteoarthritis and reviewed 74 studies.[4] They found that diclofenac 150mg daily was slightly more effective than other regimens and that celecoxib 100mg was sightly less effective (in terms of likelihood of achieving a clinically significant change in pain scores).

Other than these two regimens, they found comparable efficacy for all of the following:

- Ibuprofen 1200mg and 2400mg daily
- Naproxen 750mg and 1000mg daily
- Diclofenac 75 mg and 150mg daily
- Celecoxib 200mg and 400mg daily

A guideline from the NSAID Consensus Group in Europe summarised comparable effectiveness in arthritis: [5]

- Different doses of celecoxib (100, 200, and 400 mg / day) were all comparable to naproxen (1,000 mg/day), and superior to placebo, in a 12-week study in patients with RA.
- Celecoxib (200 mg/day) was as effective as diclofenac (150 mg/day) in the long-term management of RA.
- Celecoxib (200 mg/day) was as effective as naproxen 1,000 mg/day in patients with knee OA.

They concluded, **"all these studies clearly show that nonselective-NSAIDs and COX-2 selective inhibitors have comparable efficacy, apparent in functioning and disability, as well as in pain."**

The relative lack of differences in efficacy of NSAIDs means that choices of agents are often based on gastrointestinal, cardiovascular and other adverse effect risk profiles as well as patient preferences and prescriber familiarity.[6,7]

ADVERSE EFFECTS

The majority of adverse effects of NSAIDs are directly related to their inhibition of synthesis of various prostanoids, resulting in their significant haemodynamic, gastrointestinal, cardiovascular and renal effects. The selectivity of the NSAID for COX-1 (inhibition is responsible for gastric adverse effects) and COX-2 (inhibition is responsible for platelet mediated adverse effects such as myocardial infarction) influences the nature and frequency of adverse effects (see **Figure 2**).

HAEMODYNAMIC AND RENAL EFFECTS OF NSAIDS

The use of all NSAIDs has been associated with dose-dependent renal side effects of various types. These include a reduction in glomerular filtration, acute and chronic renal failure, renal papillary necrosis and acute interstitial nephritis. Many of these side effects are short-term and reversible upon NSAID withdrawal.[8]

In addition, the changes in fluid distribution and vascular tone impact on the incidence of and degree of control of hypertension and heart failure. Renal side-effects are relatively rare in healthy, well hydrated patients. However, in patients with other risk factors and/or on other drugs such as diuretics and angiotensin inhibitors, chronic use of NSAIDs may result in end-stage chronic renal disease.

Along with **renal insufficiency, diabetes, heart failure and older age are risk factors for increased haemodynamic effect of NSAIDs.**

GASTROINTESTINAL BLEEDING RISK

While many NSAIDs have a direct (topical) irritant effect on the gastric mucosa, the primary mechanism for gastroduodenal toxicity is via inhibition of COX-1 dependent prostaglandins, which protect the mucosal lining from injury by luminal acid. The majority of mucosal injury is superficial, with endoscopically proven ulceration in up to 30% of patients.[9,10,11]

The relative risk of gastrointestinal complications is influenced by a number of factors including type and duration of NSAID, concurrent medication and patient factors. Combining these factors together, it is possible to classify patients as being at high, moderate or low risk of gastrointestinal complications (see **Table 1**).[12,13,14] In 2-4% of patients who chronically use NSAIDs, peptic ulcer complications (perforation, haemorrhage and/or death) may occur.[15]

It should be noted that damage to the lower gastrointestinal tract is now recognised in a large number of patients taking NSAIDs. This may result in lower GI bleeding (small intestine or colonic) without overt symptoms. With the increased use of mitigation strategies, which are largely only effective for upper GI problems, (see below) there is a trend towards fewer upper GI problems and a greater number of lower GI problems causing hospitalisation.[16]

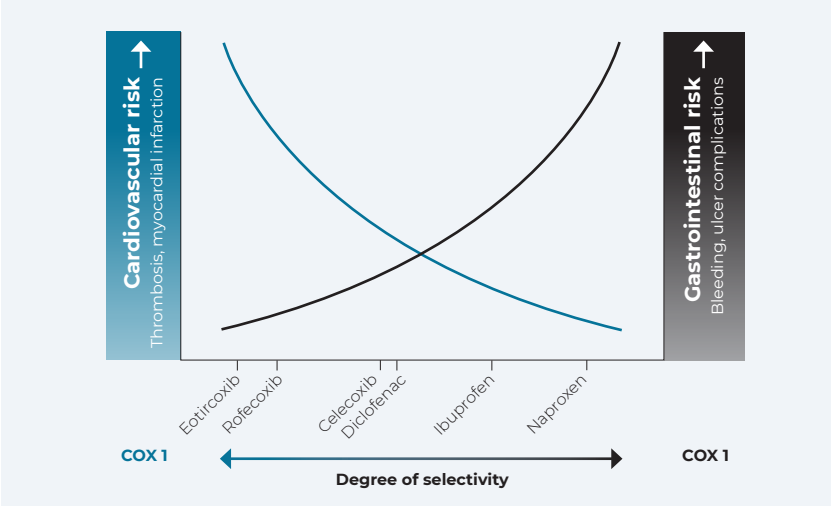

Figure 2: Impact of COX-1/COX-2 specificity on adverse effects of NSAIDs

RISK FACTORS	
■ Age > 65 years ■ High Dose NSAID ■ Concurrent use of aspirin, SSRIs, corticosteroids ■ or anticoagulants	HIGH RISK history of complicated Peptic Ulcer Disease or more than 2 risk factors
POSSIBLE ADDITIONAL RISK FACTORS	**MODERATE RISK**
■ alcohol overuse, ■ smoking ■ GORD ■ H Pylori ■ serious comorbid medical conditions	history of uncomplicated ulcer or 1-2 risk factors
	LOW RISK
	No risk factors

Table 1: Risk factors and risk classification of gastrointestinal bleeding with NSAIDs (adapted from [12,13,14])

Non-Selective versus Selective NSAIDs

Based on pharmacological features, it would be expected that a higher level of COX-2 specificity would have less gastrointestinal toxicity.

Masclee et al undertook a review of the medications being taken by 114,835 patients with diagnosed upper gastrointestinal bleeding.[17] They found that only 9.9% of patients with bleeding did not have any medications that could be implicated. Non-selective NSAIDs were present in 32.6% of cases (increased relative risk 4.3) and COX-2 inhibitors in 22.5% of cases (increased relative risk 2.9).[17]

A 2013 meta-analysis of predominantly individual participant data from randomized trials compared nonselective NSAIDs or COX-2 inhibitors with either placebo or another nonselective NSAID or COX-2 inhibitors.[18] The analysis utilized data from over 300,000 participants in over 750 trials. As compared with placebo, all NSAID regimens increased upper gastrointestinal complications including upper gastrointestinal perforation, obstruction, or bleeding. They found that all NSAID regimens increase upper gastrointestinal complications (1.8 fold for coxibs, 1.9 fold for diclofenac, 4 fold for ibuprofen and 4.2 fold for naproxen).[18]

Dose of NSAID and Duration of NSAID Use

The use of high daily doses of individual NSAIDs was associated with approximately a 2-3 fold increase in relative risk for upper gastrointestinal complications compared with low or medium doses.[19]

Administration of NSAIDs for a short period of time (less than a week) in healthy individuals is unlikely to result in any significant gastric pathology. While the majority of gastrointestinal issues occur in the first three months of treatment, longer duration of therapy is associated with an increased risk of problems.

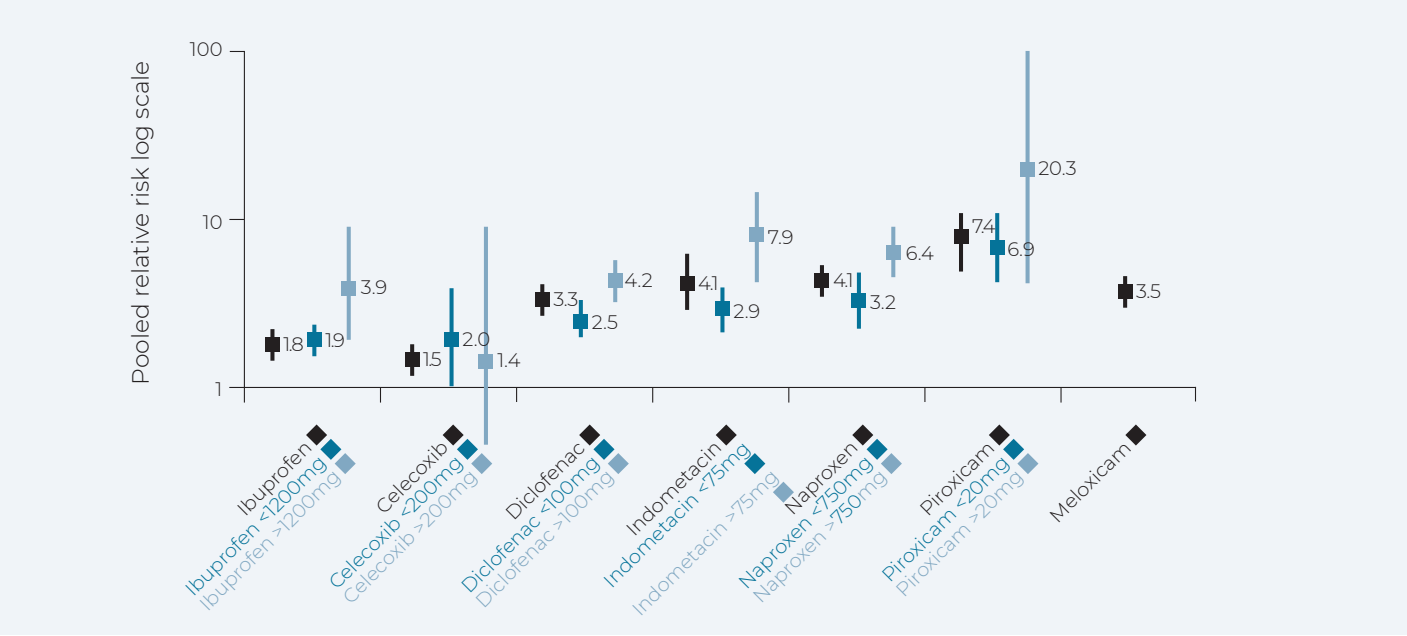

Table 2: High vs Low Dose NSAIDs and relative risk of upper GI complications (adapted from 19)

Concurrent Medications

The gastrointestinal bleeding risk from NSAIDs is increased by the concomitant use of gastrointestinal irritants and reduced by concomitant use of acid reduction therapy (see **Figure 3**).

Of interest, although COX-2 inhibitors were less likely to be associated with gastrointestinal bleeding than non-selective NSAIDs, there was no appreciable difference between the COX-2 inhibitor/low dose aspirin and non-specific NSAID/low dose aspirin combinations.

Patient Factors

Older patients and patients with a prior history of peptic ulcer disease are at greater risk of bleeding from the use of NSAIDs.[20,21]

Mitigation of NSAID-Induced Gastrointestinal Bleeding Risk

Reducing the risk of NSAID-induced GI complications can be achieved by combinations of:

- targeting modifiable risk factors
- adding gastro-protective agents
- testing for (and treating if necessary) Helicobacter pylori infection.

Risk factors that may be modifiable include alcohol and some other medication use, smoking and the dose and duration of the NSAID being used.

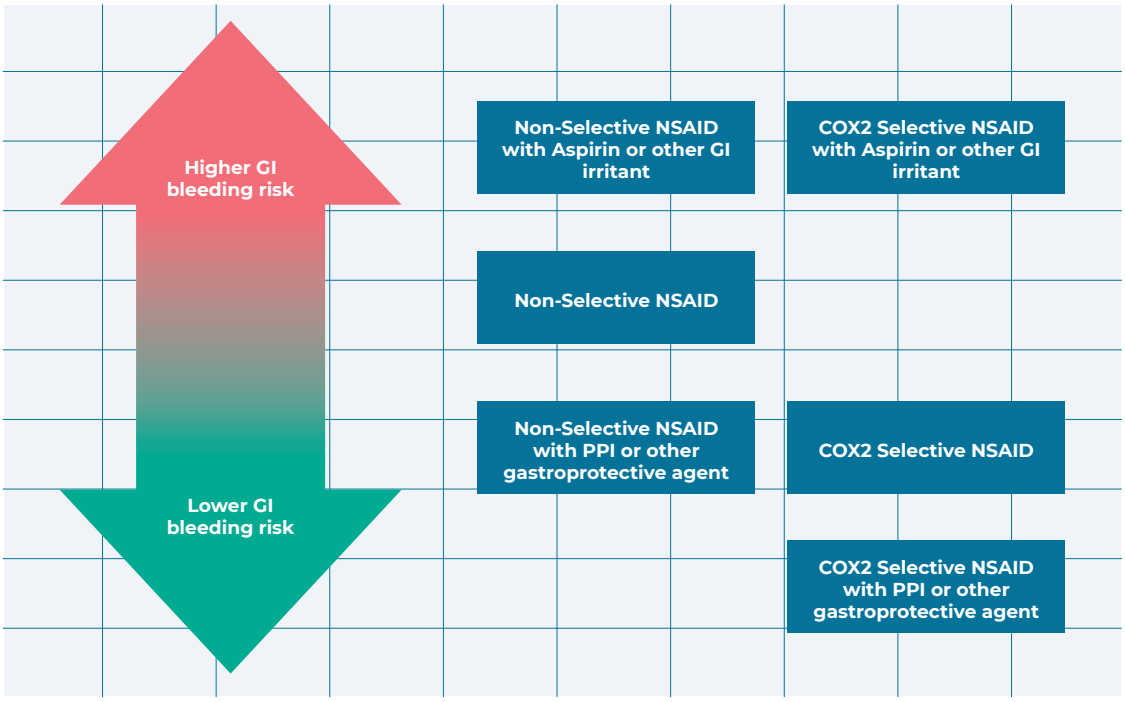

Figure 3: Relative gastrointestinal bleeding risk from long-term use of NSAIDs

Multiple studies have evaluated co-therapy with anti-secretory agents for the prevention of upper GI events in patients requiring NSAIDs.[22,23,24] A number of studies compared the rate of recurrent GI complications caused by a non-selective NSAID taken with a proton pump inhibitor with that caused by celecoxib.[22,23,25] Recurrent GI bleeding occurred in approximately 5% of patients over a 6 month follow-up, regardless of which regimen was used. Thus, the use of a PPI in combination with a non-selective NSAID reduces the risk of GI bleeding to that comparable to celecoxib.

The use of celecoxib in combination with a PPI was tested in a study of patients after recovery from non selective NSAID induced gastrointestinal bleeding.[26] At 13 months after randomisation to either celecoxib 200mg bd or celecoxib 200mg bd plus 20mg esomeprazole 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."**[26]

It has long been established that the presence of H pylori infection in patients taking NSAIDs increases the risk of peptic ulcer and of ulcer bleeding.[27,28] A meta-analysis shows that the risk of gastropathy was increased 3.5 fold and the risk of GI bleeding increase 6 fold in patients taking NSAIDs who were infected with H pylori compared to those that were not.[29]

A meta-analysis of H pylori eradication in patients taking NSAIDs, eradication almost halved the rate of peptic ulceration from 11.8% to 6.3% (ARR 5.5% NNT 18).[30]

CARDIOVASCULAR EVENTS

In addition to their propensity to cause and contribute to heart failure and hypertension, NSAIDs appear to increase the risk of myocardial infarction. This increase is thought to be due to their complex effects on thromboxane and prostacyclin combined with other effects on sodium and water retention and vascular endothelial growth factor.[31,32]

In 2005, rofecoxib (Vioxx®) was removed from the market as a result of an increase in myocardial infarction incidence. This was based on the finding of 20 myocardial infarctions over 2698 person years of follow-up in the rofecoxib arm of the VIGOR study compared to 4 infarcts from 2699 person years for the naproxen arm (ARI 0.6% per year, NNH 166).[33]

The most recent analysis of the vascular effects of NSAIDs was conducted by the Coxib and traditional NSAID Trialists' (CNT) collaboration.[18] They found an increased rate of major coronary events with coxibs (~75% increase), diclofenac (~70% increase) and ibuprofen (~120% increase), but not with naproxen.[18] Absolute risks were quantified for coxibs as an annual increase in risk of 0.4% (NNH 250). This is consistent with a recent review that indicated a NNH of 303 for coxibs associated with major vascular events.[31]

The impact of underlying cardiovascular risk was examined in a review by McGettigan and Henry.[34] They found that there was no difference in the increased relative risk for rofecoxib, celecoxib, naproxen, diclofenac or ibuprofen. However, as the increase in risk caused by the NSAID is consistent, the absolute risk increase in high cardiovascular risk patients would be greater. In the CNT collaboration analysis, estimates were made on the absolute excess risk of vascular events for patients with low and high cardiovascular risk. Ibuprofen, diclofenac and celecoxib (but not naproxen) all increased the risk considerably in patients with elevated cardiovascular risk (see **Table 4**). As can be seen patients with a high cardiovascular risk (in their analysis 10% over 5 years) can have a relatively marked increase in vascular events with numbers needed to harm as low as 83 over 1 year. These effects would be expected to be even more significant in patients whose cardiovascular risk was higher than 10%.

McGettigan and Henry also examined the impact of dose and found that high doses were associated with a significantly greater risk of cardiovascular events for all of the agents other than naproxen.[34]

		5 YEAR CARDIOVASCULAR RISK			
		2.5%		10%	
DRUGS		ESTIMATED ANNUAL VASCULAR EVENTS/1000	NNH (PER YEAR)	ESTIMATED ANNUAL EXCESS VASCULAR EVENTS/1000	NNH (PER YEAR)
Ibuprofen	Fatal (NNH)	0.6	1667	3	333
	Non-Fatal	2	500	9	111
	Total	**2.6**	**385**	**12**	**83**
Diclofenac	Fatal (NNH)	0.4	2500	2	500
	Non-Fatal	2	500	8	125
	Total	**2.4**	**416**	**10**	**100**
Coxib	Fatal (NNH)	0.5	2000	2	500
	Non-Fatal	2	500	7	143
	Total	**2.5**	**400**	**9**	**111**
Naproxen	Fatal (NNH)	0		0	
	Non-Fatal	0		-1	
	Total	**0**		**-1**	

Table 4: Absolute risk of vascular events caused by NSAIDs for patients with different levels of cardiovascular risk[34]

DISCONTINUATION SYNDROMES

Generally, there is no tapering required when deprescribing NSAIDs for osteoarthritis. Where there is an underlying inflammatory condition (e.g. rheumatoid arthritis) there may be an increase in pain after cessation. This may be attenuated by slow dose reduction.

FACTORS TO CONSIDER

Deprescribing of NSAIDs may involve dose reduction, reduction of duration of therapy or a change to a more appropriate NSAID based on the individual patient's gastrointestinal and cardiovascular risk factors.

IN FAVOUR OF DEPRESCRIBING

- NSAIDs are useful for symptom management and it may be reasonable to reduce the dose or cease agents when symptoms have been under control and stable for some time. Maximising other medications with a less severe side effect profile (especially paracetamol) and utilisation of non-pharmacological options should be considered in all patients as a way of minimising NSAID dose and duration.
- Localised arthritic pain often responds well to topical NSAID therapy or corticosteroid injections, both of which have less 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 possible. Where use is imperative, the lowest dose that achieves symptom control should be used for the shortest period possible, with appropriate gastroprotection.

AGAINST DEPRESCRIBING

- NSAIDs can be an effective analgesic and anti-inflammatory. Short term treatment for acute inflammatory processes may be beneficial in selected patients with minimal risk.
- Patients with chronic inflammatory conditions (e.g. rheumatoid arthritis) may require long-term therapy with ongoing monitoring and co-therapy to minimise adverse effects.

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RESOURCES

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AUTHORSHIP

This guide was updated by Dr Peter Tenni and Dr David Dunbabin from a document developed in consultation with the Deprescribing Reference Group.

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