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PrescQIPP Community Interest Company

Non-steroidal anti-inflammatory drugs (NSAIDs)

Over £74 million is spent annually on all non-steroidal anti-inflammatory drugs (NSAIDs), including cyclo-oxygenase-2 (COX-2) inhibitors in England and Wales (NHSBSA Dec19-Feb20).

This bulletin reviews NSAIDs and offers guidance and implementation support resources for organisations considering reviewing NSAIDs as a medicine optimisation or medicine safety project.

Recommendations

- Regularly review the appropriateness of NSAID prescribing, especially in people who are at higher risk of gastrointestinal (GI), cardiovascular and renal morbidity and mortality, e.g. older people.[1] Consider switching to a lower risk NSAID or stopping treatment where appropriate.
- Consider alternatives, such as a topical NSAID, or physiotherapy or a different analgesic such as paracetamol or an opioid before prescribing NSAIDs.[1] Be aware that repeated opioid use can lead to dependence and tolerance. If pain relief is not seen within two to four weeks of an opioid being initiated, then the patient is unlikely to gain benefit in the long term.[2]
- Ensure that the patient understands that it is unusual for any analgesic to completely eliminate chronic pain. The focus of treatment is on reducing a person's pain and improving their quality of life.[2]
- Choose the NSAID with the lowest cardiovascular, renal and/or GI risk, depending upon the individual patient's risk factors. If more than one product is suitable for an individual patient, choose the product with the lowest acquisition cost.[3]
- Do not prescribe NSAIDs where contraindicated. Only prescribe NSAIDs in patients at risk of renal impairment/failure (particularly the elderly) where use is unavoidable.[1]
- When an NSAID is needed then prescribe the lowest dose for the shortest duration, e.g. ibuprofen (≤1200mg daily in divided doses) or naproxen (≤1000mg daily in divided doses).[1,3] These are associated with a lower cardiovascular risk than other NSAIDs.[4]
- Be aware that COX-2 inhibitors, diclofenac (150mg daily) and ibuprofen (2.4g daily) are associated with an increased risk of thrombotic events. The increased risk for diclofenac is similar to that of licensed doses of etoricoxib.[4]
- Co-prescribe a PPI with the lowest acquisition cost, lansoprazole or omeprazole capsules, (generic esomeprazole 20mg capsules and pantoprazole 20mg tablets are alternatives if omeprazole or lansoprazole are unsuitable) for NSAID gastroprotection in patients:[1]
    - With osteoarthritis and rheumatoid arthritis
    - Who are elderly
    - With low back pain, axial spondyloarthritis, psoriatic arthritis and other peripheral spondyloarthritides
    - Who are at high or moderate risk of GI adverse events

Recommendations

- Consider prescribing ibuprofen or naproxen in preference to mefenamic acid in the treatment of menorrhagia.[5] Although only mefenamic acid is specifically licensed for menorrhagia, there are concerns that it is more likely to cause seizures in overdose, and it has a lo w therapeutic window which increases the risk of accidental overdose.[5]
- Adopt measures to minimise NSAID risk such as using treatment alternatives, NSAID choice, addressing factors which put patients at higher risk of adverse events, regularly monitoring and reviewing treatment, empowering patients to KNOW, CHECK, ASK about their medicines and deprescribing NSAIDs through shared decision making.

Background

NSAID analgesic effect is normally seen within one week, whereas the anti-inflammatory effects are seen within three weeks.[4] 60% of patients will respond to any individual NSAID, but there is a wide variation in response and so more than one NSAID may need to be tried in an individual patient.[4] Patients should understand that it is unusual for any analgesic to completely eliminate chronic pain. The focus of treatment is on improving their quality of life and reducing their pain.[2] In menorrhagia NSAIDs can be taken for as long as they are beneficial.[5]

All NSAIDs (including selective COX-2 inhibitors) have been associated with serious GI toxicity, a small increased risk of thrombotic events (e.g. myocardial infarction (MI) and stroke) and rarely precipitating renal failure.[4,6,7] The appropriateness of NSAID prescribing should be reviewed on a routine basis, especially in people who are at higher risk of GI, renal and cardiovascular morbidity and mortality, e.g. older people.[6] Alternatives to NSAIDs include a topical NSAID, physiotherapy or a different analgesic such as paracetamol or an opioid.[1] However, repeated opioid use can lead to dependence and tolerance. If pain relief is not seen within two to four weeks of initiating an opioid, then the patient is unlikely to gain benefit in the long term.[2]

If an NSAID is prescribed, this should be used at the lowest effective dose for the shortest possible duration.[1] Ibuprofen (1200mg or less per day) or naproxen (1000mg or less per day) are preferred choices for safety reasons.[1]

National guidance

The National Institute for Health and Care Excellence (NICE) guidance which include NSAIDs in their treatment recommendations include:

- CG177 Osteoarthritis: care and management[3]
- NG100 Rheumatoid arthritis in adults: management[8]
- NG59 Low back pain and sciatica in over 16s: assessment and management[9]
- NG65 Spondyloarthritis in over 16s: disease and management[10]
- NG73 Endometriosis: diagnosis and management[11]
- NG88 Heavy menstrual bleeding: assessment and management[12]

NICE CG177, osteoarthritis care and management in adults advises the following:[3]

- Recommend exercise as a core treatment, to improve muscle strength and general aerobic fitness.
- Consider paracetamol and/or topical NSAIDs before oral NSAIDs, COX-2 inhibitors or opioids.
- The Guideline Development Group (GDG) highlighted reduced effectiveness of paracetamol in the management of osteoarthritis compared with previous opinion. They advise taking this into account in routine prescribing until the planned full review of evidence on the pharmacological management of osteoarthritis is published (expected publication 25 August 2021).[3]

- Use oral NSAIDs or COX-2 inhibitors at the lowest effective dose for the shortest possible duration.
- When offering treatment with an oral NSAID/COX-2 inhibitor, the first choice should be either a standard NSAID or COX-2 inhibitor (other than etoricoxib 60mg). In either case, co-prescribe with a PPI choosing the one with the lowest acquisition cost.
- All NSAIDs/COX-2 inhibitors have analgesic effects of a similar magnitude but vary in their potential GI, liver and cardio-renal toxicity; therefore, when choosing the agent and dose, take into account individual risk factors, including age. When prescribing these drugs, consideration should be given to appropriate assessment and/or ongoing monitoring of these risk factors.
- If a person with osteoarthritis needs to take low-dose aspirin, healthcare professionals should consider other treatments before adding an NSAID (with a PPI) if pain relief is ineffective or insufficient.[3]

NICE NG100 Rheumatoid arthritis in adults: management recommends that NSAIDs are considered when control of pain or stiffness is inadequate.[8] Take account of potential GI, liver and cardio-renal toxicity, and the person's risk factors, including age and pregnancy. When treating symptoms of RA with oral NSAIDs:

- Offer the lowest effective dose for the shortest possible time,
- Offer a proton pump inhibitor (PPI), and
- Review risk factors for adverse events regularly.[8]

If a person with RA needs to take low-dose aspirin, healthcare professionals should consider other treatments before adding an NSAID (with a PPI) if pain relief is ineffective or insufficient.[8]

NG59 Low back pain and sciatica in over 16s: assessment and management recommends non-pharmacological interventions such as:[9]

- Self-management by providing people with advice and information, tailored to their needs and capabilities, to help them self-manage their low back pain with or without sciatica at all steps of the treatment pathway including:
  - » Information on the nature of low back pain and sciatica
  - » Encouragement to continue with normal activities
- Consider a group exercise programme (biomechanical, aerobic, mind–body or a combination of approaches) within the NHS for people with a specific episode or flare-up of low back pain with or without sciatica, taking people's specific needs, preferences and capabilities into account when choosing the type of exercise.
- Consider manual therapies (spinal manipulation, mobilisation or soft tissue techniques such as massage) for managing low back pain with or without sciatica, but only as part of a treatment package including exercise, with or without psychological therapy.
- Consider psychological therapies using a cognitive behavioural approach for managing low back pain with or without sciatica but only as part of a treatment package including exercise, with or without manual therapy (spinal manipulation, mobilisation or soft tissue techniques such as massage).
- Consider a combined physical and psychological programme, incorporating a cognitive behavioural approach (preferably in a group context that takes into account a person's specific needs and capabilities), for people with persistent low back pain or sciatica:
  - » When they have significant psychosocial obstacles to recovery (for example, avoiding normal activities based on inappropriate beliefs about their condition) or
  - » When previous treatments have not been effective.
- Promote and facilitate return to work or normal activities of daily living for people with low back pain with or without sciatica.

NSAIDs are included as pharmacological interventions to consider for managing low back pain. Recommendations include:[9]

- Consider oral NSAIDs for managing low back pain, taking into account potential differences in GI, liver and cardio-renal toxicity, and the person's risk factors, including age.
- When prescribing oral NSAIDs for low back pain, think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment.
- Prescribe oral NSAIDs for low back pain at the lowest effective dose for the shortest possible period of time.

When NSAIDs are not considered suitable for the individual patient:[9]

- Consider weak opioids (with or without paracetamol) for managing acute low back pain only if an NSAID is contraindicated, not tolerated or has been ineffective.
- Do not routinely offer opioids for managing acute low back pain and do not offer opioids for managing chronic low back pain.
- Do not offer paracetamol alone, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, tricyclic antidepressants or anticonvulsants for managing low back pain.

NG65 Spondyloarthritis in over 16s: disease and management recommends that people are provided with explanations and information about pharmacological and non-pharmacological treatment options, including possible side effects.[10]

Non-pharmacological management of spondyloarthritis include:[10]

- Referral to a specialist physiotherapist to start an individualised, structured exercise programme.
- Consider hydrotherapy as an adjunctive therapy to manage pain and maintain or improve function.
- Consider a referral to a specialist therapist (such as a physiotherapist, occupational therapist, hand therapist, orthotist or podiatrist) for people with spondyloarthritis who have difficulties with any of their everyday activities.

NSAIDs are included as pharmacological interventions to offer in axial spondyloarthritis:[10]

- Offer NSAIDs at the lowest effective dose to people with pain associated with axial spondyloarthritis, and think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment.
- If an NSAID taken at the maximum tolerated dose for two to four weeks does not provide adequate pain relief, consider switching to another NSAID.

NSAIDs are also included as pharmacological interventions to consider in the treatment of psoriatic arthritis and other peripheral spondyloarthritides:[10]

- Consider NSAIDs as an adjunct to standard disease modifying anti-rheumatic drugs (DMARDs) or biological DMARDs to manage symptoms.
- Use oral NSAIDs at the lowest effective dose for the shortest possible period of time, and think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment.
- If NSAIDs do not provide adequate relief from symptoms, consider steroid injections (local or intramuscular) or short-term oral steroid therapy as an adjunct to standard DMARDs or biological DMARDs to manage symptoms.

NG73 Endometriosis: diagnosis and management recommends that the benefits and risks of analgesics are discussed, taking into account any comorbidities and the woman's preferences.[11] NSAIDs are included as an analgesic option:

- Consider a short trial (e.g. three months) of paracetamol or NSAID alone or in combination for first-line management of endometriosis-related pain.

NG88 Heavy menstrual bleeding: assessment and management recommends NSAIDs are considered for the treatment of women with menorrhagia with no identified pathology, fibroids less than 3cm in diameter, or suspected or diagnosed adenomyosis when a levonorgestrel-releasing intrauterine system is declined or not suitable.[12] NSAIDs are listed as options alongside tranexamic acid and hormonal therapy including combined hormonal contraception and cyclical oral progestogens. Note that this is an off-label use for NSAIDs.

NSAIDs are offered as an option in the treatment of women with fibroids of 3cm or more in diameter if pharmacological treatment is needed while investigations and definitive treatment are being organised and as a treatment option. Alternative pharmacological treatment options include tranexamic acid, ulipristal acetate, levonorgestrel-releasing intrauterine system, combined hormonal contraception, and cyclical oral progestogens.

The NICE CKS for menorrhagia provides guidance on the choice of NSAID:[5]

- The choice of NSAID includes ibuprofen, naproxen, or mefenamic acid.
  - » Only mefenamic acid is specifically licensed for menorrhagia. There are concerns that it is more likely to cause seizures in overdose, and it has a low therapeutic window which increases the risk of accidental overdose.
- The following doses are recommended:
  - » Ibuprofen - 400 mg three or four times daily.
  - » Mefenamic acid - 500 mg three times daily.
  - » Naproxen - 500 mg as the first dose, then 250 mg every 6–8 hours.
- Advise the woman:
  - » To start the NSAID on the first day of bleeding and to continue until bleeding stops or reduces to satisfactory levels.
  - » That NSAIDs can be taken for as long as they are beneficial.

The NICE CKS for NSAIDs - prescribing issues, advises the following when initiating NSAIDs:[1]

- Prescribe NSAIDs at the lowest effective dose for the shortest possible duration.
- When prescribing NSAIDs, take into account the person's individual risk factors for adverse effects and consider if:
  - » An alternative to an NSAID may be suitable, for example:
    - A topical NSAID.
    - Physiotherapy, or referral for consideration of surgery.
    - A different oral analgesic (such as paracetamol, or an opioid).
  - » The person has any contraindications to oral NSAIDs.
  - » There are any potentially hazardous drug interactions.
  - » The person is already using an NSAID - for example, ibuprofen or aspirin purchased over-the-counter.
  - » Gastroprotection is indicated. For example, because the person is:
    - At increased risk of GI adverse effects (for example, people that require long-term treatment).
    - Experiencing dyspepsia from standard NSAIDs.

- More frequent review and monitoring for adverse effects is required - for example, for people who are:
    - At risk of multiple adverse effects (for example, the elderly, people with comorbidities).
    - Taking drugs which may interact with an NSAID.
    - At increased risk of GI or cardiovascular or renal adverse effects.

NSAID adverse events: Pharmacology and evidence

Pharmacology

NSAIDs act peripherally and centrally but the peripheral action predominates. NSAIDs work by reversibly inhibiting cyclo-oxygenase (COX) enzymes. The two main types of COX enzymes are COX-1 and COX-2. COX-1 produces prostaglandins that help maintain gastric mucosal integrity and platelet-initiated blood clotting. COX-2 is produced in response to inflammatory cytokines and is thought to be responsible for the anti-inflammatory action of NSAIDs. NSAIDs vary in how selective they are for inhibiting COX-1 and COX-2 pathways. There is no absolute selectivity for either of the COX enzymes as even highly selective COX-2 inhibitors will inhibit COX-1 at high enough concentrations.[1]

- Nonselective NSAIDs include ibuprofen (1200mg or less per day), naproxen, indometacin and mefenamic acid.
- Nonselective NSAIDs thought to have a preference for COX-2 are diclofenac, etodolac, ibuprofen (2.4g daily), meloxicam and nabumetone.
- COX-2 specific NSAIDs are celecoxib and etoricoxib.[1]

NSAID GI adverse events

COX-1 inhibition is thought to be responsible for GI toxicity. COX-2 inhibitors selectively inhibit COX-2 and have a reduced risk for GI toxicity.[1]

All NSAIDs are associated with serious GI toxicity.[4] A large meta-analysis by the Coxib and traditional NSAID Trialists (CNT) Collaboration found that both non-selective NSAIDs and selective inhibitors of COX-2 increase upper GI complications - see table 1.[13]

Table 1 – Comparison of upper GI complications with non-selective NSAIDs and selective inhibitors of COX-2

	Rate Ratio (RR)	95% confidence interval (CI)	P value
COX-2 inhibitors	1.81	1.17 - 2.81	p=0.0070
Diclofenac	1.89	1.16 - 3.09	p=0.0106
Ibuprofen	3.97	2.22 - 7.10	p<0.0001
Naproxen	4.22	2.71 - 6.56	p<0.0001

COX-2 inhibitors are associated with a reduction in the risk of GI symptoms and complications compared with non-selective NSAIDs, but they do not eliminate the risk of GI adverse events.[1]

Evidence on the relative safety of non-selective NSAIDs indicates differences in the risks of serious upper GI adverse effects:[4]

- Highest risk non-selective NSAIDs, e.g. piroxicam, ketoprofen, and ketorolac trometamol
- Intermediate risk non-selective NSAIDs, e.g. indometacin, diclofenac, naproxen, high dose ibuprofen
- Lowest risk non-selective NSAIDs, e.g. low dose ibuprofen
- COX-2 inhibitors (lower risk than non-selective NSAIDs), e.g. celecoxib, etoricoxib

An intention-to-treat analysis of 287 patients (144 taking celecoxib 200mg twice daily and 143 taking diclofenac 75mg twice daily plus 20mg omeprazole daily for six months) found that PPIs were effective at reducing the GI risks associated with NSAIDs and reduce the risks to a similar level as using a COX-2 inhibitor alone.[1,14] The end point was recurrent ulcer bleeding which occurred in 7 patients receiving celecoxib and 9 patients on diclofenac plus omeprazole. The probability of recurrent bleeding during the six-month period was 4.9% (95% CI 3.1 - 6.7) for patients taking celecoxib and 6.4% (95% CI, 4.3 - 8.4) for patients taking diclofenac plus omeprazole (difference, –1.5 percentage points; 95% CI for the difference, –6.8 to 3.8).[14]

A network meta-analysis based on 82 trials including 125,053 participants, found that the combination of selective COX-2 inhibitors plus PPIs provides the best gastrointestinal protection, followed by selective COX-2 inhibitors alone, and thirdly by non-selective NSAIDs plus PPI. The comparison of clinical GI events (ulcer complications and symptomatic ulcers) are set out in table 2 below.[1,15]

Table 2 - Risk of ulcer complications and symptomatic ulcers with selective COX-2 inhibitors + PPI, COX-2 inhibitors, nonselective NSAIDs + PPIs and nonselective NSAIDs + misoprostol

	Ulcer complications		Symptomatic ulcers	
	RR	95% CrI*	RR	95% CrI*
Selective COX-2 inhibitors + PPI	0.07	0.02 - 0.18	-	-
COX-2 inhibitors	0.25	0.15 - 0.38	0.12	0.04 - 0.30
Nonselective NSAIDs + PPIs	0.28	0.18 - 0.41	0.11	0.04 - 0.23
Nonselective NSAIDs + misoprostol	0.47	0.24 - 0.81	0.41	0.13 - 1.00

***Credible interval**

NSAID Cardiovascular adverse events

Inhibition of COX-2 leads to suppression of prostacyclin (which normally protects endothelial cells, produces vasodilation and interacts with platelets to antagonize aggregation) whereas inhibition of COX-1 inhibits conversion of arachidonic acid to thromboxane A2 (a potent platelet aggregator and vasoconstrictor).[1] Selective COX-2 inhibition presents a CV risk, as it shifts the prothrombotic/antithrombotic balance and favours thrombosis.[1]

The Vioxx Gastrointestinal Outcomes Research (VIGOR) study first signalled concerns over the cardiovascular safety of COX-2 inhibitors. In the VIGOR study, patients with rheumatoid arthritis were randomised to receive rofecoxib 50mg daily or naproxen 500mg twice daily and the primary endpoint was confirmed upper GI events. Patients in the rofecoxib group had fewer upper GI events than naproxen with similar efficacy against rheumatoid arthritis. However, the incidence of MI was lower in patients in the naproxen group than those in the rofecoxib group. The overall mortality rate and rate of death from cardiovascular causes were similar in both groups.[16]

The increased cardiovascular risks were also seen in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial which was terminated early.[17] A one-year follow-up after treatment was stopped, looked at the combined incidence of non-fatal MI, non-fatal stroke and death from cardiovascular, haemorrhagic and unknown causes (Antiplatelet Trialists' Collaboration (APTC) combined endpoint). The study found that rofecoxib was associated with increased rates of APTC events with a total of 59 APTC events in the rofecoxib group and 34 APTC events in the placebo group (hazard ratio 1.79, 95% CI 1.17 - 2.73; p=0.006).[17] The manufacturer voluntarily withdrew rofecoxib from the market in 2004.[18]

A pooled analysis of the Adenoma Prevention with Celecoxib (APC) trial and the Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial found that celecoxib at doses of 200mg or 400mg twice daily or 400mg once daily showed nearly a 2-fold increased cardiovascular risk compared to placebo.[19] Eighty three patients experienced cardiovascular death, non-fatal MI, non-fatal stroke, or heart failure. The hazard ratio for this prespecified composite end point was 2.6 (95% CI, 1.1 - 6.1) in patients taking celecoxib 200mg twice daily, 3.4 (95% CI, 1.5 - 7.9) in patients taking 400mg twice daily in the APC trial, and 1.3 (95% CI, 0.6 - 2.6) in patients taking 400mg once daily in the PreSAP trial (P for heterogeneity = 0.13 comparing the combined doses in the APC trial with the dose in the PreSAP trial). The overall hazard ratio for celecoxib for this composite end point was 1.9 (95% CI, 1.1 - 3.1). Both dose groups in the APC study showed significant systolic blood pressure elevations at 1 and 3 years (200 mg twice daily: 1 year, 2.0mm Hg; 3 years, 2.6mm Hg; 400mg twice daily: 1 year, 2.9mm Hg; 3 years, 5.2mm Hg). However, the 400mg once daily group in the PreSAP study did not ($p<0.0001$ between studies).[19]

The meta-analysis from the CNT Collaboration found that the vascular risks of diclofenac (RR = 1.41, 95% CI 1.12 - 1.78; p=0.0036) were comparable with COX-2 inhibitors (RR = 1.37, 95% CI 1.14 - 1.66; p=0.0009).[13] Ibuprofen also significantly increased major coronary events (RR = 2.22, 95% CI 1.10 - 4.48; p=0.0253), but not major vascular events (RR = 1.44, 95% CI 0.89 - 2.33). Compared with placebo, of 1000 patients allocated to a COX-2 inhibitor or diclofenac for a year, three more had major vascular events, one of which was fatal. Naproxen (RR = 0.93, 95% CI 0.69 - 1.27) did not increase the risk of major vascular events. All non-aspirin NSAIDs approximately double the risk of heart failure.[13]

The US Food and Drug Administration (FDA) reviewed the CNT collaboration meta-analysis, observational studies and other scientific literature in 2015.[20] The findings were discussed at a joint advisory committee meeting. Based on the comprehensive review and recommendations from the advisory committee they drew the following conclusions:

- A large number of studies support the finding that NSAIDs cause an increased risk of serious cardiovascular thrombotic events, with varying estimates of how much the risk is increased. Estimates of increased relative risk range from 10% to 50% or more, depending on the drugs and the doses studied.
- Several observational studies found a significant cardiovascular risk within days to weeks of NSAID initiation. Some data also showed a higher risk with longer NSAID treatment.
- There are observational data indicating that the thrombotic cardiovascular risk from NSAID use is dose-related. There is also some evidence of this dose-response effect from clinical trials of celecoxib.
- Some observational studies and the CNT meta-analysis suggested that naproxen may have a lower risk for cardiovascular thrombotic events compared to the other NSAIDs; however, the observational studies and the indirect comparisons used in the meta-analysis to assess the risk of the nonselective NSAIDs have limitations that affect their interpretability. The variability in patients' risk factors, comorbidities, concomitant medications and drug interactions, doses being used, duration of treatment, etc., also need to be taken into consideration to make valid comparisons. Importantly, these studies were not designed to demonstrate superior safety of one NSAID compared to another.
- There is evidence of an increased cardiovascular risk from NSAID use by apparently healthy patients. Data from the CNT meta-analysis, individual randomised controlled trials, and observational studies showed that the relative increase in cardiovascular thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known cardiovascular disease or risk factors for cardiovascular disease. However, patients with known cardiovascular disease or risk factors had a higher absolute incidence of excess cardiovascular thrombotic events due to their increased baseline rate.
- The CNT meta-analysis demonstrated an approximately two-fold increase in hospitalisations for heart failure with use of both COX-2 selective and nonselective NSAIDs. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalisation for heart failure, and death.

In January 2015, the MHRA summarised the cardiovascular safety of COX-2 inhibitors and non-selective NSAIDs:[21]

- COX-2 inhibitors slightly increase the risk of cardiovascular events including MI and stroke with approximately three additional thrombotic events per 1000 patients per year in the general population.
- Some non-selective NSAIDs may be associated with a small increased risk of thrombotic events such as MI and stroke. The lowest effective dose of non-selective NSAID should be prescribed for the shortest possible time.
- Diclofenac has a thrombotic risk profile similar to selective COX-2 inhibitors and precautions to minimise the risks of arterial thromboembolic events with selective COX-2 inhibitors should be applied to diclofenac.
- There is some evidence that naproxen may have a lower risk of MI and stroke than selective COX-2 inhibitors.
- Current evidence does not suggest an increased thrombotic risk for short-term, low-dose ibuprofen. However, high-dose ibuprofen may be associated with a small increased thrombotic risk.
- Less evidence is available for other NSAIDs, but it is possible that they may be associated with a small risk of thrombotic events, especially with long duration of treatment and high doses.
- All NSAID users may be at an increased risk of cardiovascular events, not only those with baseline cardiovascular risk factors.

In June 2015, the MHRA advised that high-dose ibuprofen (≥2400mg/day) presents a similar cardiovascular risk to COX-2 inhibitors and diclofenac.[22] No increased risk of arterial thrombotic events is seen with ibuprofen at doses up to 1200mg per day compared with not taking ibuprofen. For ibuprofen doses between 1200mg and 2400mg there is insufficient data to say whether there is an increased cardiovascular risk compared with not taking ibuprofen. This MHRA advice was based on data from the CNT collaboration meta-analysis.[13,22] The advice also applies to dexibuprofen (a high dose of dexibuprofen is 1200mg or more per day, which is equivalent to 2400mg of ibuprofen).

The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial (n = 24,081) assessed cardiovascular, GI, renal and other outcomes with celecoxib compared to naproxen and ibuprofen. The study concluded that celecoxib at moderate doses was non-inferior to naproxen and ibuprofen in terms of cardiovascular safety.[23] The FDA concluded that the results of the PRECISION trial demonstrated that celecoxib, at the lowest approved dose of 100mg twice daily, is non-inferior to ibuprofen 600–800mg three times daily, or naproxen 375–500mg twice daily on a composite cardiovascular endpoint consisting of cardiovascular death, non-fatal MI, and non-fatal stroke. However, too few people received higher doses of celecoxib to evaluate the risk of cardiovascular events or the effect on blood pressure for doses greater than 100mg twice daily, so this result cannot be extrapolated to higher doses (200mg or 400mg).[24]

A bayesian meta-analysis of individual patient data from four studies (involving 61,640 acute MIs, across a population of 446,763 individuals), compared the risk of acute MI in NSAID users (COX-2 inhibitors and traditional NSAIDs) with non-users.[25] They concluded that:

- All NSAIDs, including naproxen, were associated with an increased risk of acute MI.
- The risk of MI with celecoxib was comparable to that of traditional NSAIDS and was lower than for rofecoxib.
- The risk was greatest during the first month of NSAID use and with higher doses.
- The risk for longer than one month was no greater than for short term use.

NSAID Renal adverse effects

NSAIDs inhibit prostaglandins PGE2 and PG12 synthesis, which may result in sodium retention, reduced renal blood flow and renal failure.[1]

A nested case-control study using the UK General Practice Research Database found that current NSAID users had a three-fold greater risk for developing a first ever diagnosis of acute renal failure (ARF) compared with non-NSAID users in the general population (RR for ARF = 3.2 (95% CI 1.8 - 5.8).[26] The risk declined after treatment was discontinued. Increased risk was present with both short and long-term therapy. The risk was slightly greater among users of high doses. A history of heart failure (HF), hypertension, diabetes, and hospitalisations and consultant visits in the previous year were all associated with a greater risk for ARF. Use of selected cardiovascular drugs was associated with a 5-fold increase in risk for ARF. Risk increased with concomitant use of NSAIDs and diuretics (RR 11.6; 95% CI 4.2 - 32.2) and NSAIDs and calcium channel blockers (RR 7.8; 95% CI 3.0 - 20.5).[26]

In May 2009, the MHRA advised caution when using NSAIDs in patient with renal impairment or who are at risk of developing ARF.[27] NSAIDs, including COX-2 inhibitors may rarely precipitate renal failure, and vulnerable (particularly elderly) patients may be at increased risk. Patients with conditions such as hypovolaemia, congestive heart failure, liver cirrhosis, or multiple myeloma are at particular risk. Contributing risk factors include the current administration of medicines such as angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptors antagonists, and diuretics. NSAID use accounts for an estimated 15% of all cases of drug-induced acute renal failure.[27]

Measures to minimise NSAID risk

A number of measures can be put in place to attempt to reduce NSAID risk. These include using treatment alternatives to NSAIDs, NSAID choice, addressing patient factors which put patients at higher risk of adverse events, regularly monitoring and reviewing treatment, empowering patients to KNOW, CHECK, ASK about their medicine in line with the WHO Medication without harm challenge, and deprescribing NSAIDs through shared decision making.

Consider using alternatives to NSAIDs

Alternatives to NSAIDs include a topical NSAID, physiotherapy, a different analgesic such as paracetamol or an opioid, or referral for consideration for surgery.[1] Become familiar with the local availability of services providing non-pharmacological interventions that are effective for reducing symptoms and disability in people with chronic pain.[2]

NSAID choice

First consider non-NSAID alternatives. When NSAID alternatives have been tried unsuccessfully, declined or services are not available locally, consider whether the following are suitable for the individual (taking into account any patient factors):

- Low dose ibuprofen (≤1200mg daily in divided doses). At this dose ibuprofen is not associated with an increased risk for MI.[4] Ibuprofen has fewer side-effects than other non-selective NSAIDs but has weaker anti-inflammatory action.[4]
- Naproxen 1000mg daily in divided doses is associated with a lower thrombotic risk than other NSAIDs.[1] It is considered one of the first choices because it combines good efficacy with a low incidence of side effects (but more than ibuprofen).[4]
- If ibuprofen and naproxen are not appropriate choices, and should a further NSAID choice be necessary, take into account the risk factors for the individual patient (see attachment 1), any contraindications or warnings listed in the summary of product characteristics and cost when selecting an alternative NSAID.[1]

- Attachment 1 (a medicine safety checklist) and attachment 2 (a review and monitoring checklist) provide information to support NSAID selection in new and existing patients.

Addressing patient factors

An NSAID medicine safety checklist of patient factors to consider when assessing the potential risks associated with prescribing an NSAID or COX-2 inhibitor is provided in attachment 1. The checklist can be used when considering NSAID initiation, NSAID choice and also during a medication review. The checklist is based upon the advice given in the NICE CKS for NSAID - prescribing issues and the BNF.[1,4]

Monitoring and review treatment

A checklist of when and what to monitor for NSAID safety is provided in attachment 2. The checklist is based upon the advice given in the NICE CKS for NSAID - prescribing issues.[1]

Empower patients to KNOW, CHECK, ASK about their medicine

The call for action of the global World Health Organisation (WHO) campaign Medication Without Harm encourages and empowers both patients and their caregivers and healthcare professionals to take an active role in ensuring safer medication practices and medication use processes including prescription, preparation, dispensing, administration and monitoring.[28]

Patient resources assist in making sure that patients are involved in knowing their medication, checking they know how to take it and asking a healthcare professional if they are unsure or need any additional information.[28]

Further information and implementation resources supporting the WHO Medication Without Harm Challenge - Focus on NSAIDs are available at https://www.prescqipp.info/our-resources/bulletins/bulletin-252-medicines-without-harm/

Deprescribing NSAIDs through shared decision making

The continued need for an NSAID and its safe use in the individual should be reviewed regularly. An NSAID algorithm to support the review of benefits to risks of NSAIDs is available at https://www.prescqipp.info/umbraco/surface/authorisedmediasurface/index?url=%2fmedia%2f4968%2fattachment-2-nsaid-algorithm-20.pdf. The algorithm also supports NSAID deprescribing through shared decision making if this is suitable for the individual.

Self care for common conditions

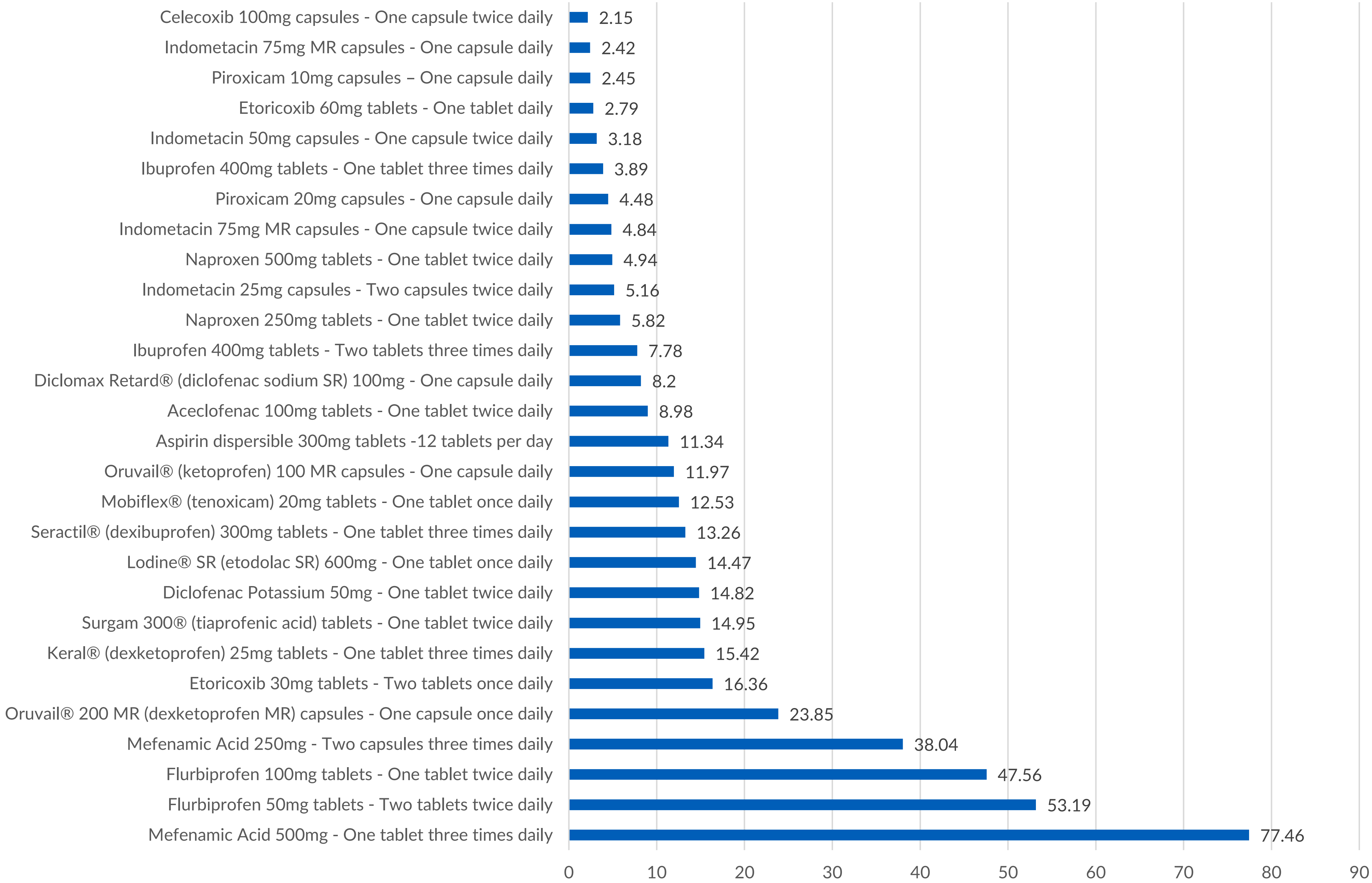
The PrescQIPP self care webkit contains resources to support the planning and implementation of self care projects in line with the NHS England over the counter items which should not routinely be prescribed in primary care. The OTC guide lists self care medicines, including NSAIDs which can be purchased OTC to treat self-limiting and minor illnesses and includes their OTC sales restrictions.

Costs and savings

The total number of NSAIDs items prescribed across England and Wales has increased by 4.1% over the last 12 months, with 10 million NSAID items prescribed annually at a cost of just over £74 million (NHSBSA Dec19-Feb20). **Reducing NSAID prescribing by 30% through appropriate review and deprescribing could result in savings of around £22 million per annum across England and Wales, which equates to £35,8538 per 100,000 people.**

There are significant differences in cost between NSAID preparations ranging from £2.15 to £77.46 per 28 days.[29] Chart 1 illustrates some examples of these cost differences.

Chart 1. Example NSAID cost comparisons per 28 days



Approximately 21% of NSAID prescriptions across England and Wales are not for the preferred first choice NSAIDs, ibuprofen and naproxen (NHSBSA Dec 19-Feb20). **A 50% switch of all other NSAIDs to ibuprofen or naproxen could save £2.8 million per annum or £4,577 per 100,00 people across England and Wales.**

Mefenamic acid is the second leading cost NSAID across England and Wales and is the most expensive NSAID on the market currently. Over £8.3 million per annum is spent on mefenamic acid (NHSBSA Dec19-Feb20). The choice of NSAID in menorrhagia includes ibuprofen, naproxen, or mefenamic acid.

Switching 50% of mefenamic acid prescriptions to ibuprofen or naproxen could save £3.7 million annually across England and Wales. This equates to savings of £6,044 per 100,000 patients across England and Wales.

Diclofenac has a higher cardiovascular risk than low-dose ibuprofen or naproxen.[4] The number of diclofenac items prescribed has declined by over 24% in the last 12 months across England and Wales and it is the most expensive NSAID on the market currently (NHSBSA Dec19-Feb20). However, there remains 496,472 diclofenac items prescribed at a cost of over £3.3 million per annum. (NHSBSA Dec19-Feb20). **Switching 50% of diclofenac prescriptions to ibuprofen or naproxen would be a medicine safety project aimed at reducing cardiovascular risk and could provide savings of £362,045 per annum. This equates to savings of £583 per 100,000 patients across England and Wales.**

Licensed doses of proton pump inhibitors used for NSAID gastroprotection and their 28 day costs are given below.[1,29] Choose a PPI with the lowest acquisition cost suitable for the individual patient.[3]

- Lansoprazole capsules 15-30mg once daily: £0.94 - £1.21
- Omeprazole capsules 20mg once daily: £1.02
- Esomeprazole capsules 20mg once daily: £1.83
- Pantoprazole tablets 20mg once daily: £2.80

Currently, lansoprazole and omeprazole capsules are the lowest cost PPI licensed for NSAID gastroprotection.

Summary

- Alternatives to NSAIDs include a topical NSAID, physiotherapy or a different analgesic such as paracetamol or an opioid or referral for consideration for surgery.[1]
- If an NSAID is prescribed, this should be used at the lowest effective dose for the shortest possible duration.[1] Ibuprofen (1200mg or less per day) or naproxen (1000mg or less per day) are preferred choices for safety reasons.[1]
- Co-prescribe a PPI with lowest acquisition cost, lansoprazole or omeprazole capsules, when NSAID gastroprotection is warranted.[3]
- All NSAIDs (including COX-2 inhibitors have been associated with serious GI toxicity, a small increased risk of thrombotic events (e.g. MI and stroke) and rarely precipitating renal failure.[4,6,7]
- The size of vascular and GI risks of NSAIDs can be predicted from the CNT Collaboration trial:
  - Major vascular events were significantly increased by more than a third for COX-2 inhibitors and diclofenac 150mg daily compared with placebo. COX-2 inhibitors or diclofenac 150mg daily caused around three additional major vascular events per 1000 participants per year, compared with placebo, one of which was fatal. Ibuprofen 2400mg doubled the risk of major coronary events. Naproxen 1000mg did not significantly increase major vascular or coronary events versus placebo. All NSAIDs studied approximately doubled the risk of hospitalisation due to heart failure compared with placebo.[13]

Summary

- The appropriateness of NSAID prescribing should be reviewed on a routine basis, especially in people who are at higher risk of GI, renal and cardiovascular morbidity and mortality, e.g. older people.[1]

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Additional PrescQIPP resources

	Bulletin	https://www.prescqipp.info/our-resources/bulletins/bulletin-265-nsaids/
	Implementation tools	
	Data pack	https://data.prescqipp.info/views/B265_NSAIDs/FrontPage?:iid=1&:isGuestRedirectFromVizportal=y&:embed=y#1

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Contact help@prescqipp.info **with any queries or comments related to the content of this document.**

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