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Non-steroidal anti-inflammatory drugs (NSAIDs)

Over £70 million is spent annually on all non-steroidal anti-inflammatory drugs (NSAIDs), including cyclo-oxygenase II (COX-2) inhibitors, in England (ePACT Nov 14 - Jan 15). QIPP projects in this area focus on reducing prescribing of NSAIDs for cost and safety reasons, by adhering to current guidance.

Recommendations

- Regularly review the appropriateness of NSAID prescribing, especially in people who are at higher risk of both gastrointestinal (GI) and cardiovascular (CV) and renal morbidity and mortality, e.g. older people.[1] Consider switching to a lower risk NSAID where appropriate.
- Advise patients to exercise as a core treatment for osteoarthritis, to improve muscle strength and general aerobic fitness.[2]
- Consider paracetamol and/or topical NSAIDs (according to local formulary) before oral NSAIDs, COX-2 inhibitors or opioids.[2]
- Choose the NSAID with the lowest CV, renal and/or GI risk, depending upon the individual patient's risk factors.[2]
- Do not prescribe NSAIDs where contraindicated (CI). Only prescribe NSAIDs in patients at risk of renal impairment/failure (particularly the elderly) where unavoidable.[3]
- If an NSAID is needed then prescribe the lowest dose for the shortest duration,[1-3] e.g. ibuprofen (≤1200mg daily in divided doses) or naproxen (≤1000mg daily in divided doses).[1,3] These are associated with a lower CV risk than other NSAIDs.[1,3]
- 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.[3]
- Diclofenac has been associated with increased risk of recurrent myocardial infarction (MI) or death, from the beginning of treatment.[4]
- Co-prescribe a proton pump inhibitor (PPI) with lowest acquisition cost for gastroprotection in patients with a high risk of GI bleeds in:
  - Patients ≥65 years[2]
  - Long term NSAID use, e.g. for osteoarthritis,[2] rheumatoid arthritis[5] and persistent low back pain in those >45 years[6]
  - Prescribe low acquisition cost NSAIDs in preference to higher cost NSAIDs.

Background

There are long-standing and well-recognised GI and renal safety concerns with all NSAIDs.[1] There has also been an increase in CV safety concerns with NSAIDs, since the withdrawal of Vioxx® (rofecoxib) ten years ago.[7] Therefore the substantial use of NSAIDs needs addressing. Prescribing of ibuprofen and naproxen (NSAIDs with a lower CV risk) as a percentage of all NSAIDs is increasing, which is a positive trend. The prescribing of diclofenac has reduced in recent years. However, diclofenac still accounts for

approximately 2 million prescription items (13% of all NSAID items) per year in primary care in England. There is also variation in prescribing across localities.[1] This trend needs to be addressed due to CV safety concerns with diclofenac, as stated in the Medicines and Healthcare products Regulatory Agency (MHRA) Drug Safety Update (DSU) of June 2013.[8]

National guidance

The National Institute for Care and Excellence (NICE) Clinical Guidelines (CG) which cover treatment with NSAIDs are:

- CG177 Osteoarthritis care and management in adults.
- CG79 Rheumatoid arthritis.
- CG88 Low back pain - early management of persistent non-specific low back pain (being updated, publication is expected November 2016).

NICE CG177, osteoarthritis care and management in adults, advises the following:[2]

- 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) have 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.
- 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.

NICE CG79, rheumatoid arthritis management in adults, also recommends the above points.[5] NICE CG88 on early management of persistent non-specific low back pain, recommends an adaption of the fifth point. It recommends co-prescribing with a PPI only in patients over 45 years of age.[6] See each NICE CG for further details.

In 2012, the European Medicines Agency (EMA) published an assessment of the CV risks associated with NSAIDs. This was based on a meta-analysis of clinical trials, observational studies and individual epidemiological studies. The assessment also included results of the project 'safety of non-steroidal anti-inflammatory drugs' (SOS) led by the Erasmus University in Rotterdam. The final report, adapted by the Committee for Medicines Products for Human Use (CHMP) overall confirmed the findings of previous reviews which were conducted in 2005 and 2006. So current treatment advice reflects safety and efficacy of naproxen and ibuprofen as NSAIDS with lower cardiovascular risk, at appropriate treatment doses. Diclofenac may be associated with an increased risk of CV side-effects compared with naproxen and ibuprofen, and has risks similar to COX-2 inhibitors.[9]

Evidence base

The VIGOR study compared rofecoxib with naproxen in terms of GI toxicity in patients with rheumatoid arthritis. The results found similar efficacy for rofecoxib and naproxen in rheumatoid arthritis, with fewer GI events in the rofecoxib group. However the incidence of MI was lower in the naproxen group, although overall death rate from CV causes were similar in the two groups.[10]

The APPROVe study assessed 3-year treatment with rofecoxib (25mg) on recurrence of neoplastic

polyps of the large bowel. It also reported CV outcomes of long-term follow-up. Study treatment was terminated early due to CV toxicity. A 1-year follow-up after stopping study treatment, assessed potential for serious CV events. This focussed on combined incidence of non-fatal MI, non-fatal stroke and death from CV, haemorrhagic and unknown causes (Antiplatelet Trialists's Collaboration (APTC) combined endpoint). There were more patients with an APTC endpoint in the rofecoxib group (n=59) than placebo group (n=34) (p=0.006). In the first year after stopping treatment, there was a non-significant increase in the risks of APTC endpoints.[11]

A Danish cohort study in 2011 investigated duration of NSAID treatment and CV risk, in patients with prior MI. It concluded that even short term treatment was associated with increased risk of death and recurrent MI, in patients with prior MI. Diclofenac was associated with the highest risk for MI/death at day 1 to 7 of treatment. The authors discuss that it is particularly worrying that diclofenac was associated with a higher CV risk than the withdrawn COX-2 inhibitor rofecoxib due to its unfavourable CV risk profile. Short-term or long-term NSAID treatment is not advised in the studied patient population. Any NSAID use should be limited for CV safety purposes. Further studies, preferably randomised clinical trials are required to establish the CV safety of NSAIDs.[4] An NPC Review of this study stated: although coxibs are associated with a lower risk of GI side effects than NSAIDs, there is no good evidence to support use of coxibs alone ahead of NSAIDs co-prescribed with a PPI. Coxibs have a higher CV risk than ibuprofen ≤1200mg/day or naproxen 1000mg/day. There were a number of study limitations: results not stratified by dose so it is unknown if an increased risk with ibuprofen would have been apparent at doses less than 1200mg. Many confounding factors may influence results in this observational study: there was no information on adjusting for important CV risk factors e.g. blood pressure, smoking habit, lipid levels, body mass index. It was not possible to adjust for the specific NSAID indication. Duration of treatment was estimated from prescription data, only providing indirect assessment of dose and period of NSAID use.[12]

McGettigan et al (2011) performed a systematic review of community-based controlled observational studies on the CV risk with NSAIDs. They conclude that naproxen and low-dose ibuprofen are least likely to increase CV risks. Diclofenac (even at lower doses) elevates risk. Data for etoricoxib was sparse, but it had a significantly higher relative risk in pair-wise comparisons than naproxen or ibuprofen. Indometacin appears to have a risk profile similar to that of diclofenac in both unpaired and pair-wise analyses and is associated with a high risk of gastrointestinal damage, as well as adverse effects in the central nervous system. Indometacin is an older, rather toxic drug, and the evidence for CV risk casts doubt on its continued clinical use.[13] Another NPC Review critically evaluated the McGettigan et al meta-analysis, highlighting that it adds to the evidence base, confirming an increased risk of CV events with coxibs and NSAIDS. The study suggests that diclofenac elevates CV risk at 100mg/day or less (close to the maximum dose for over-the-counter products, when they were available). It also confirms that naproxen (low or high dose) or low-dose ibuprofen are least likely to increase CV risk. It suggests a high relative risk with less well studied drugs such as etoricoxib and etodolac. Study limitations are that the trials included in the systematic review were unrandomised and included patients from different populations. However the results are in keeping with the accumulating body of evidence.[14]

A NICE Medicines Evidence Commentary in December 2012, discussed the EMA review on CV safety of NSAIDs. Previous findings that diclofenac is associated with CV risks higher than ibuprofen or naproxen and similar to COX-2 inhibitors, were confirmed. Naproxen and low-dose ibuprofen still have the most favourable CV safety profiles of all non-selective NSAIDs. The lowest dose and shortest duration of NSAIDs should be used. In addition prescribing should be based upon safety profiles of individual NSAIDs or COX-2 inhibitors and individual patient risk profiles (e.g. GI, CV or renal). Prescribers should only switch between NSAIDs with careful consideration of the above factors and patient preferences.[15]

A meta-analysis by the Coxib and traditional NSAID Trialists (CNT) Collaboration in 2013 aimed to describe the characteristics of vascular and GI effects of NSAIDs and COX-2 inhibitors, particularly in patients at increased risk of vascular disease. Overall the indication for NSAID treatment was rheumatoid or osteoarthritis in about four-fifths of participants. The CNT Collaboration's interpretation

of results was that vascular risks of high-dose diclofenac and possibly ibuprofen are comparable to coxibs, but high-dose naproxen is associated with less vascular risk than other NSAIDs. Although NSAIDs increase vascular risk and GI risk, the risk size can be predicted, which could help guide clinical decision making.[16]

NICE Eyes on Evidence reviewed the CNT new evidence. The results and subsequent MHRA alert, reinforce existing information and guidance about CV and GI risks of NSAIDs. The meta-analysis aimed to quantify the CV and GI risks of NSAIDs using data from randomised controlled trials (RCTs). The primary outcomes were major vascular events (non-fatal MI, non-fatal stroke or vascular death) and upper GI complications (perforation, obstruction or bleed). Compared with placebo, major vascular events were significantly increased by more than a third for COX-2 inhibitors and diclofenac 150mg daily. The absolute increase in risk was small but serious. They caused around 3 additional major vascular events per 1000 participants per year, of which 1 was fatal. Ibuprofen 2400mg daily did not significantly increase the risk of major vascular events compared with placebo. However it doubled the risk of major coronary events. Naproxen 1000mg daily did not significantly increase major vascular or coronary events compared with placebo. The proportional CV and GI risks of all NSAIDs appeared independent of baseline characteristics, including vascular risk. The risk of hospitalisation due to heart failure (HF) was approximately doubled by all NSAIDs studied, compared with placebo. In addition COX-2 inhibitors and diclofenac doubled the risk of upper GI complications (mainly bleeds) and ibuprofen and naproxen quadrupled the risk, compared with placebo.[17]

Measures to minimise risk

The June 2013 Drug Safety Update states diclofenac is CI in patients with: established ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or congestive heart failure.[8] The MHRA have withdrawn diclofenac as a Pharmacy (P) medicine. Since January 2015 oral diclofenac has been made a Prescription Only Medicine (POM).

COX-2 inhibitors, diclofenac 150mg daily and ibuprofen 2.4g daily are associated with increased risk of thrombotic events. Diclofenac risk is similar to licensed doses of etoricoxib.[3] Etoricoxib may be associated with more frequent and severe effects on blood pressure (BP) than some other COX2 inhibitors and NSAIDs, particularly at high doses. Hypertension should be controlled before starting etoricoxib and BP monitored within 2 weeks, then periodically. If BP rises significantly consider alternative treatment.[1]

1. NSAID choice

First line

- Low dose ibuprofen, 1200mg daily[1] or less (in divided doses) is not associated with an increased risk of MI, but has weaker anti-inflammatory action than naproxen.
- **Or** Naproxen 1000mg daily[1] (in divided doses) is associated with a lower thrombotic risk than other NSAIDs.
- Alternative choice based on risk factors of individual patient.

2. Pharmacology of NSAID adverse events (AEs):[19]

CV: COX-2 inhibition leads to prostacyclin inhibition without thromboxane A2 inhibition, creating a potentially thrombotic state. This leads to a significant risk increase for thrombotic, cardio and cerebrovascular events.[20] This is because prostacyclin inhibits platelet aggregation whilst thromboxane A2 is a platelet activator and aggregator.[19]

Renal: NSAIDs inhibit prostaglandins PGE2 and PG12, which may result in sodium retention, reduced renal blood flow and renal failure.[20]

GI: NSAIDs inhibit cyclo-oxygenase-I (COX-1) which is thought to be responsible for GI toxicity.[20] Selective inhibition of COX-2 is associated with less GI intolerance.[3]

3. Risk factors for serious adverse events (AEs) with NSAIDs[19]

CV or **renal AE** risk is increased in people with:

- Cerebrovascular, ischaemic heart or peripheral arterial disease, heart failure, hypertension or risk factors for CV disease.
- All >65 years of age.
- Renal impairment (e.g. creatinine clearance <20mL/min).[19] Avoid NSAIDs if possible, or use with caution, as use may provoke renal failure. Use lowest dose for the shortest duration and monitor renal function. Rarely, papillary necrosis or interstitial fibrosis associated with NSAIDs can lead to renal failure.[3]

GI AE risk is increased with one or more of the following factors:[19]

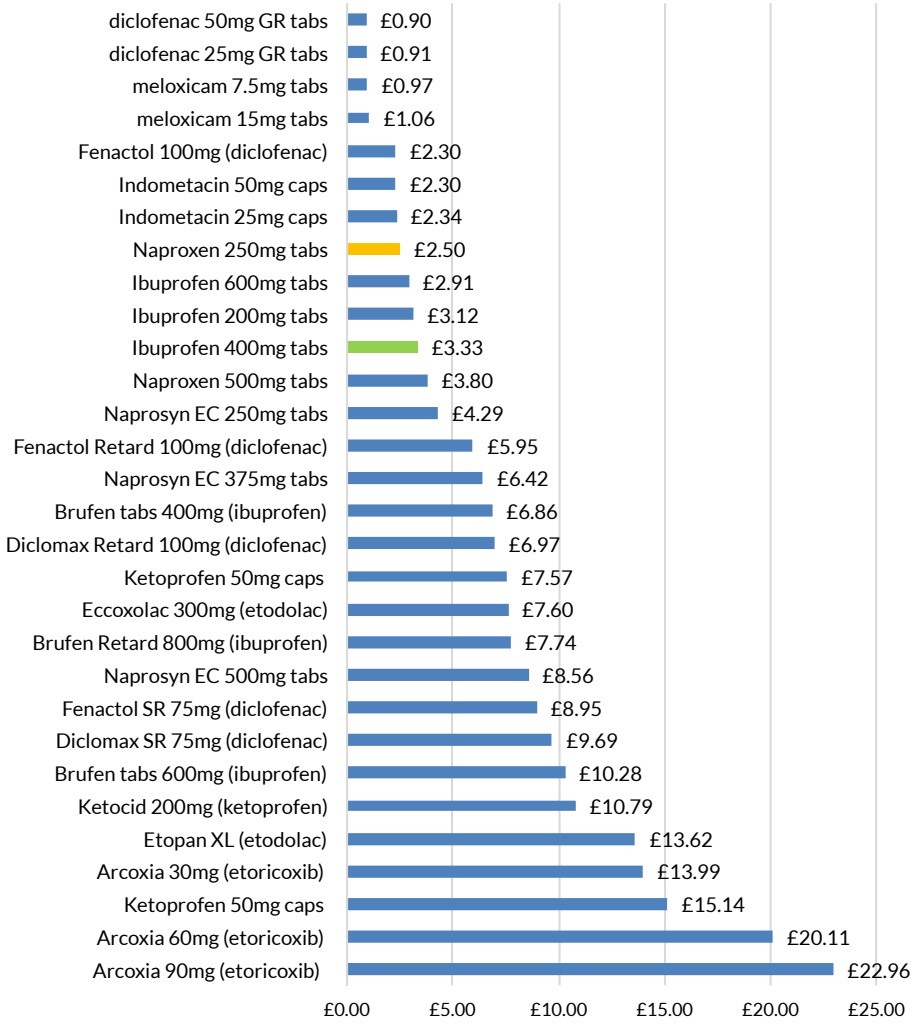
- Patient ≥ 65 years old, taking maximum recommended NSAID dose, or prolonged NSAID use in osteoarthritis or rheumatoid arthritis (any age) or chronic low back pain (≥ 45 years of age).
- History of gastro-duodenal ulcer or perforation, or GI bleeding.
- Taking other medications that increase risk of upper GI adverse events e.g. anticoagulants, aspirin, corticosteroids and antidepressants such as SSRIs, venlafaxine or duloxetine.
- Serious co-morbidity such as CV disease, diabetes, hypertension, renal impairment (including dehydration)[19] or hepatic impairment use with caution and avoid in severe liver disease.[3]
- Additional risk factors for NSAID-induced GI adverse events include, type of NSAID used, H. pylori infection, excessive alcohol use, or heavy smoking.

See the British National Formulary for further side effects including hypersensitivity (e.g. bronchospasm) and rare side effects.[3]

Cost

Chart 1 shows costs for 28 days treatment for generic and brands of NSAIDs. Generic naproxen are the preferred option clinically and on grounds of cost at £2.50 for 56 tablets (28 days of treatment). Similarly generic ibuprofen are an alternative preferred option clinically and on grounds of cost at £3.33 for 84 tablets. Branded products and COX 2 inhibitors, Brufen® products (ibuprofen) and Naprosyn® (naproxen) products are the non-preferred options, due to their comparatively high cost.

Chart 1. Cost comparison of generic NSAIDs with brands for 28 days[21]



Summary

- Review NSAID prescribing widely and routinely, especially in people who are at higher risk of GI and CV morbidity and mortality (e.g. older people).[1]
- If an NSAID is needed, use ibuprofen (≤1200mg daily) or naproxen (≤1000mg daily) for the shortest duration and the lowest dose.[1] Co-prescribe a PPI with lowest acquisition cost for gastroprotection in patients with a high risk of GI bleeds.[2] 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 3 additional major vascular events per 1000 participants per year, compared with placebo, 1 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.[16,17]
  - COX-2 inhibitors and diclofenac almost double the risk of upper GI complications (mainly bleeds) and ibuprofen and naproxen quadruple the risk compared to placebo.[16,17]
- If prescribing of NSAIDs reduced by 30%, this would save more than £21 million over 12 months, which equates to £37,247 per 100,000 patients.

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Information compiled by Sandra Hicks PrescQIPP NHS Programme, April 2015 and reviewed by Katie Smith, East Anglia Medicines Information Service, May 2015.

Non-subscriber publication September 2015.

At the time of publication the PrescQIPP NHS Programme was hosted by Papworth NHS Trust and the Eastern Academic Health Science Network.

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This document represents the view of PrescQIPP CIC at the time of publication, which was arrived at after careful consideration of the referenced evidence, and in accordance with PrescQIPP's quality assurance framework.

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