Non-steroidal anti-inflammatory drugs

Key therapeutic topic
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Options for local implementation

- Review the appropriateness of non-steroidal anti-inflammatory drug (NSAID) prescribing widely and on a routine basis, especially in people who are at higher risk of gastrointestinal, renal and cardiovascular morbidity and mortality (for example, older people).
- If an NSAID is needed, use ibuprofen (1,200 mg a day or less) or naproxen (1,000 mg a day or less). Use the lowest effective dose and the shortest duration of treatment necessary to control symptoms.
- Co-prescribe a proton pump inhibitor with NSAIDs for people who have osteoarthritis or rheumatoid arthritis, and think about the use of gastroprotective treatment when prescribing NSAIDs for low back pain, axial spondyloarthritis, psoriatic arthritis and other peripheral spondyloarthritides.

Evidence context

There are long-standing and well-recognised gastrointestinal and renal safety concerns with all non-steroidal anti-inflammatory drugs (NSAIDs). There is also substantial evidence confirming an increased risk of cardiovascular events with many NSAIDs, including COX-2 inhibitors and some traditional NSAIDs such as diclofenac and high-dose ibuprofen. In the June 2015 edition of Drug Safety Update, the MHRA gave prescribing advice on the use of all NSAIDs. More information is also available in NICE's clinical knowledge summary on NSAIDs: prescribing issues:

- The decision to prescribe an NSAID should be based on an assessment of a person's individual risk factors, including any history of cardiovascular and gastrointestinal illness.

- Naproxen (1,000 mg a day or less) and low-dose ibuprofen (1,200 mg a day or less) are considered to have the most favourable thrombotic cardiovascular safety profiles of all NSAIDs.

- The lowest effective dose should be used for the shortest duration necessary to control symptoms. A person's need for symptomatic relief and response to treatment should be re-evaluated periodically.

In the May 2009 edition of Drug Safety Update, the MHRA reminded prescribers that NSAIDs may rarely precipitate renal failure and that people at risk of renal impairment or renal failure (particularly older people) should avoid NSAIDs if possible. The MHRA further advised that it is important to consider other concomitant disease states, conditions, or medicines that may precipitate reduced renal function when prescribing NSAIDs. For example, co-prescribing NSAIDs with renin-angiotensin system drugs may pose particular risks to renal function. This combination should be especially carefully considered and regularly monitored if continued. See NICE's medicines evidence commentary on risk of acute kidney injury with concurrent use of antihypertensives and NSAIDs for further information and the separate key therapeutic topic on acute kidney injury (AKI): use of medicines in people with or at increased risk of AKI. Also see the key therapeutic topic on multimorbidity and polypharmacy for further information on reviewing polypharmacy and deprescribing.

There have been several European Medicines Agency (EMA) reviews and MHRA Drug Safety Updates concerning the cardiovascular safety of NSAIDs:

- In the October 2016 edition of Drug Safety Update, the MHRA reminded prescribers that the cardiovascular and other important risks of etoricoxib may increase with dose and duration of exposure. Therefore, the lowest effective daily dose should be used and the need for treatment should be regularly reassessed. The prescribing information has also been updated to introduce a lower recommended daily dose of 60 mg daily for patients with rheumatoid arthritis or ankylosing spondylitis. In people with insufficient relief from symptoms, an increased dose of 90 mg once daily may improve efficacy but once the person is clinically stabilised, down titration to 60 mg once daily may be appropriate. The summary of product characteristics states that the recommended dose for osteoarthritis is 30 mg once daily and that it should not exceed 60 mg daily. In the absence of therapeutic benefit, other treatment options should be considered.

- In 2005, an EMA review on COX-2 inhibitors identified an increased risk of thrombotic events, such as heart attack and stroke, with these types of NSAIDs. In 2006, the EMA also concluded that a small increased risk of thrombotic events could not be excluded with non-selective

NSAIDs, including diclofenac, particularly when they are used at high doses for long-term treatment.

- The July 2008 edition of Drug Safety Update advised that etoricoxib should not be prescribed to people whose blood pressure is persistently above 140/90 mmHg and inadequately controlled, following advice from an EMA review. The summary of product characteristics (SPC) states that hypertension should be controlled before treatment with etoricoxib and special attention should be paid to blood pressure monitoring during treatment. Blood pressure should be monitored within 2 weeks of starting etoricoxib treatment, and periodically thereafter. If blood pressure rises significantly, alternative treatment should be considered.

- Updated contraindications and prescribing advice for diclofenac were highlighted in the June 2013 edition of Drug Safety Update following publication of an EMA review. See NICE's medicines evidence commentary on EMA review of cardiovascular risks of NSAIDs: higher risk with diclofenac compared with ibuprofen/naproxen confirmed and NICE's eyes on evidence article on non-steroidal anti-inflammatory drugs: new information and warnings about cardiovascular risk for more information on this issue. Further to these, the January 2015 edition of Drug Safety Update reported that oral diclofenac was no longer available without prescription.

- The January 2015 edition of Drug Safety Update also highlighted updated prescribing advice for aceclofenac, which is now contraindicated in people with certain cardiovascular diseases, in-line with diclofenac and COX-2 inhibitors.

- Following an EMA review, which confirmed that the cardiovascular risk of ibuprofen 2,400 mg a day or more is similar to COX-2 inhibitors and diclofenac, the June 2015 edition of Drug Safety Update issued advice on prescribing and dispensing high-dose ibuprofen. The Drug Safety Update commented that it is uncertain whether ibuprofen doses between 1,200 mg and 2,400 mg per day are associated with an increased cardiovascular risk compared with not taking ibuprofen, because there are only limited data available.

- The June 2015 edition of Drug Safety Update also discussed the possible interaction between ibuprofen and low dose aspirin, noting that occasional ibuprofen use is unlikely to have a clinically meaningful effect on the benefits of low-dose aspirin. However, the possibility that long-term, daily use of ibuprofen might reduce the cardioprotective effects of low-dose aspirin cannot be excluded.

More information is available in the MHRA guidance on COX-2 selective inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs): Cardiovascular safety.

Further to this, a systematic review and meta-analysis of observational studies, which was outlined in NICE's medicines evidence commentary on NSAIDs and risk of venous thromboembolism found that there was a statistically significant increased risk of venous thromboembolism among users of NSAIDs compared to non-users of NSAIDs. However, the meta-analysis had a number of limitations and the results should be interpreted with caution.

A nested case-control study, which was discussed in NICE's medicines evidence commentary on risk of hospital admissions for heart failure with non-steroidal anti-inflammatory drugs, evaluated the risk of admission to hospital with heart failure and current NSAID use. It found that current use of any NSAID increased the risk of admission to hospital for heart failure by nearly 20% compared with past use. The study suggests a dose–response effect, with very high doses of etoricoxib and diclofenac more than doubling the risk of admission to hospital for heart failure. This supports the MHRA advice that prescribing should be based on assessment of a person's individual risk factors, ensuring that the lowest effective dose is used for the shortest possible time.

More information on the use of NSAIDs can be found in the NICE guidelines on osteoarthritis (which is being updated following a surveillance decision in 2017), rheumatoid arthritis (which is being updated, expected publication date July 2018), low back pain and sciatica and spondyloarthritis. These guidelines include recommendations to co-prescribe a proton pump inhibitor with NSAIDs for people who have osteoarthritis and rheumatoid arthritis, and to think about the use of gastroprotective treatment when prescribing NSAIDs for low back pain, axial spondyloarthritis, psoriatic arthritis and other peripheral spondyloarthritides. All of these guidelines recommend that when prescribing NSAIDs, consideration should be given to appropriate clinical assessment and ongoing monitoring of risk factors.

NICE has also published quality standards on osteoarthritis, low back pain and sciatica in over 16s and rheumatoid arthritis in over 16s, which are concise sets of prioritised statements designed to drive measurable quality improvements within these areas.

Practice examples and shared learning

There are several NICE shared learning examples relating to management of osteoarthritis, low back pain and rheumatoid arthritis, showing how NICE guidance and standards have been put into practice by some NHS organisations:

- OASIS Group: improving quality of life in patients with lower limb osteoarthritis.
- Developing an annual review clinic for people with rheumatoid arthritis.

- Delivering practice-led integrated care for long-term conditions - a new approach to managing osteoarthritis.

Prescribing data, metrics or supporting resources

The selection of metrics to support key therapeutic topics is overseen by the NHS England Medicines Optimisation Intelligence Group, and work is ongoing in this area. At this point, the following metrics and prescribing data have been identified by this group to support this topic.

Two medicines optimisation key therapeutic topic (MO KTT) prescribing comparators are available:

- NSAIDs: ADQ/STAR-PU
- NSAIDs: Ibuprofen & naproxen % items.

The prescribing of diclofenac has reduced in recent years. In the year from April 2016 to March 2017 diclofenac accounted for approximately 900,000 prescription items (6.6% of all NSAID items) in primary care in England, but there is still variation in prescribing across localities.

The Medicines optimisation dashboard, which brings together a range of medicines-related metrics from across sectors, includes the NSAIDs: ibuprofen & naproxen % items prescribing comparator outlined above. The medicines optimisation dashboard helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

Update information

February 2018: This topic was retained for the 2018 update of medicines optimisation: key therapeutic topics. The evidence context has been updated in the light of new guidance and important new evidence.

January 2017: This topic was retained for the 2017 update of medicines optimisation: key therapeutic topics. The evidence context has been updated in the light of new guidance and important new evidence.

About this key therapeutic topic

This document summarises the evidence base on this key therapeutic topic which has been identified to support medicines optimisation. **It is not formal NICE guidance.**

For information about the process used to develop the Key therapeutic topics, see the integrated process statement.

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