Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

Published: August 2016

Osteoarthritis: network meta-analysis finds no statistically significant benefit with lower doses of some NSAIDs and paracetamol on pain or physical functioning compared with placebo

A network meta-analysis (NMA) of drug treatments for osteoarthritis (OA) has found limited average benefits on pain reduction from celecoxib at any licensed dose or ibuprofen 2400 mg/day, naproxen 1000 mg/day or paracetamol 4000 mg/day. It also found no statistically significant benefit from ibuprofen, naproxen or paracetamol at lower doses. Of non-steroidal anti-inflammatory drugs (NSAIDs) that have not been withdrawn from the UK on safety grounds, diclofenac 150 mg/day and etoricoxib 60 mg/day were the most effective compared with placebo. There were some limitations in the design of the NMA. There are well-recognised safety concerns with all NSAIDs, with particular concerns about diclofenac and etoricoxib. Naproxen (1000 mg a day or less) and low-dose ibuprofen (1200 mg a day or less) are considered to have the most favourable thrombotic cardiovascular safety profiles of all NSAIDs. The NICE OA guideline (CG177) recommends that the lowest effective dose of NSAID should be used for the shortest duration necessary to control symptoms, and recommends use of a low-cost proton pump inhibitor (PPI) for gastroprotection when an NSAID is prescribed.

Overview and current advice

Osteoarthritis (OA) is a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life. The most commonly affected peripheral joints are the knees, hips and small hand joints. Pain, reduced function and effects on a person's ability to carry out their day-to-day activities can be important consequences of OA. However, there are also limitations to the published evidence on treating OA. Most studies have focused on knee OA, and are often of short duration using single therapies. Although most trials have looked at single joint involvement, in reality many people have pain in more than one joint, which may alter the effectiveness of interventions.

NICE guidance on OA published in 2008 (CG59) recommended that paracetamol and/or topical non-steroidal anti-inflammatory drugs (NSAIDs) should be considered ahead of oral NSAIDs including cyclo-oxygenase 2 (COX-2) inhibitors, or opioids. The guideline was updated in 2014 (Osteoarthritis: care and management; CG177). An evidence review for this update identified reduced effectiveness of paracetamol in the management of OA. In addition, an MHRA review of the safety of over-the-counter analgesics is underway. NICE intends to commission a full review of evidence on the pharmacological...
management of OA, which will start once the MHRA review is completed, to inform a further guideline update. Until that update is published, the original recommendations (from 2008) on the pharmacological management of OA remain current advice. However, the Guideline Development Group (GDG) believed that the evidence of potential reduced effectiveness of paracetamol should be taken into account in routine prescribing practice until the updated OA guideline is published.

The NICE pathway on osteoarthritis brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams. The NICE quality standards on osteoarthritis describe concise sets of prioritised statements designed to drive measurable quality improvements within this area. A NICE key therapeutic topic on NSAIDs discusses the evidence base for these drugs.

**New evidence**

Swiss researchers have conducted a network meta-analysis to compare the effectiveness of paracetamol and several NSAIDs with placebo in treating pain in hip or knee OA. They used a comprehensive search strategy to identify large-scale randomised controlled trials (RCTs). Studies had to include at least 100 participants per group and studies that included people with OA in other joints had either to report results separately for different subgroups or have at least 80% of included people with hip or knee OA. The primary outcome was pain, with a predefined hierarchy of pain scores used. The secondary outcome was physical function, again with a predefined hierarchy of assessment scores. A minimum clinically important difference (MCID) of 0.37 standard deviations of the pooled effect size was established for both outcomes. This was based on the median MCID in studies of people with OA and the authors state that this corresponds to a difference of 9 mm on a 100 mm visual analogue scale.

The analysis included 74 RCTs that examined celecoxib, diclofenac, etoricoxib, ibuprofen, lumiracoxib (withdrawn in the UK), naproxen, rofecoxib (withdrawn in the UK), or paracetamol, at differing doses. The mean age was 58 to 71 years, the percentage of females ranged from 49% to 90% and the median follow-up was 12 weeks (range 1–52 weeks). In total, 58,556 people were included in the primary analysis. The interventions with the most participants were celecoxib 200 mg/day (n=11,411) and naproxen 1000 mg/day (n=8195); interventions with the fewest participants were etoricoxib 90 mg/day (n=112) and diclofenac 70 mg/day (n=104).

For the primary outcome of pain reduction, the pooled effect sizes for 5 interventions (paracetamol less than 2000 mg/day and 3000 mg/day, diclofenac 70 mg/day, ibuprofen 1200 mg/day and naproxen 750 mg/day), were not statistically significantly different from placebo (p>0.05).

For 5 interventions, the lower 95% credible intervals (CrI, analogous to confidence interval) for the pooled effect sizes equalled or exceeded the MCID of −0.37:

- diclofenac 150 mg/day (effect size −0.57, 95% CrI −0.69 to −0.46),
- etoricoxib 30 mg/day and 60 mg/day (effect sizes −0.49 [95% CrI 0.61 to −0.37] and −0.58 [95% CrI −0.73 to −0.43], respectively). Note that the maximum licensed dose of etoricoxib for OA is 60 mg/day
- rofecoxib (withdrawn in the UK) 25 mg/day and 50 mg/day (effect sizes −0.51 [95% CrI −0.58 to −0.43] and −0.62 [−0.84 to −0.39], respectively).

For 7 interventions, there was a statistically significant difference from placebo but the lower 95% credible intervals for the pooled effect sizes was less than the MCID of −0.37:

- celecoxib 100 mg/day, 200 mg/day and 400 mg/day (effect sizes −0.16 [95% CrI −0.29 to −0.03], −0.36 [95% CrI −0.41 to −0.32] and −0.33 [95% CrI −0.45 to −0.21], respectively)
- etoricoxib 90 mg/day (effect size −0.61, 95% CrI −0.90 to −0.33). Note that the maximum licensed dose of etoricoxib for OA is 60 mg/day
• ibuprofen 2400 mg/day (effect size −0.43, 95% CrI −0.55 to −0.31)
• naproxen 1000 mg/day (effect size −0.40, 95% CrI −0.47 to −0.33)
• paracetamol 3900–4000 mg/day (effect size −0.17, 95% CrI −0.27 to −0.06).

For the secondary outcome of physical functioning, the pooled effect sizes for paracetamol less than 2000 mg/day or 3000 mg/day, rofecoxib 50 mg/day, diclofenac 70 mg/day and ibuprofen 1200 mg/day, were not statistically significantly different from placebo. For only 2 interventions (diclofenac 150 mg/day and rofecoxib 25 mg/day) did the smaller 95% credible intervals for the pooled effect sizes equal or exceed the MCID.

The authors note certain limitations to their work. These inevitably include the quality of the individual RCTs but also include some assumptions within the methodology of the network meta-analysis. In addition to these acknowledged limitations, it should be noted that the analysis was based on mean effect sizes. For an individual person choosing an analgesic, the mean effect size is less important than the chance of obtaining a certain degree of pain relief or mobility: it is more helpful to know the proportion of people who obtained, say, a 50% or greater reduction in pain score with a treatment compared with placebo instead of the average pain reduction, which will include some people who gained no or only a small benefit and some who gained much more benefit. In addition, the perceived benefit from a certain reduction in pain score depends on the starting point: consider a scale of 0 to 10, where 0 is no pain at all and 10 is the worst pain imaginable. A reduction in 2 points from 2 to 0 (that is, mild pain is abolished) is qualitatively different from a reduction from 10 to 8 (still considerable pain, although perhaps it is no longer intolerable), and arguably both these changes are subjectively more significant than a reduction from 6 to 4 points on the same scale.

The authors also note that their analysis does not take account of safety aspects. There are longstanding and well-recognised gastrointestinal and renal safety concerns with all 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 (2400 mg/day or greater).

Commentary

Commentary provided by Philip G Conaghan, Professor of Musculoskeletal Medicine, University of Leeds.

It is a little disappointing to see the opening line of the meta-analysis abstract stating “..NSAIDs are the backbone of OA pain management”. While they remain the most effective oral analgesic, NICE OA guidance (2008 and 2014) highlighted that non-pharmacological interventions are key: information provision, muscle strengthening and fitness (which has great efficacy with no side effects) and weight loss if overweight, should be the core of OA management.

That aside, the findings of lack of OA analgesic benefits for paracetamol from this analytically-complex network meta-analysis should not be surprising to clinicians in view of other studies. In 2010, Zhang et al reported a negligible effect size of 0.14 in the meta-analysis that underpinned the Osteoarthritis Research Society International (OARSI) guidelines. In another meta-analysis, Machado and colleagues reported “high quality” evidence that paracetamol did not provide clinically important benefits for pain in hip and knee OA. Findings from the new analysis that various NSAIDs (at expected doses, for example diclofenac 150 mg daily or etoricoxib 60 mg daily) are indeed effective also reflect previous clinical studies and clinical experience. The current meta-analysis authors have appropriately discussed the considerable toxicity associated with NSAIDs.

Many patients (and doctors) are disenchanted with paracetamol but many cannot take NSAIDs or opioids, so pharmacological options are few, with topical NSAIDs perhaps the only option for many
(and these have no proven benefits in hip OA). For people with no contraindications to NSAIDs, clinicians will often need to reconsider whether the correct NSAID (based on dose and side-effect profile) has been adequately trialled in a given individual, and also consider whether optimal gastroprotection was provided. However the move from a pharmacological-based paradigm to the NICE core management is more crucial than ever. Nevertheless, this has major implications for how we deliver effective OA therapy to a large proportion of the population.

Commentary by NICE

Safety issues with NSAIDs are discussed in the NICE key therapeutic topic: non-steroidal anti-inflammatory drugs. In addition, 2 of the NSAIDs included in the network meta-analysis, rofecoxib and lumiracoxib, have both been withdrawn from the UK for safety reasons: rofecoxib in 2004 because of cardiovascular toxicity and lumiracoxib in 2007 because of hepatotoxicity. The July 2008 edition of Drug Safety Update also advised that etoricoxib should not be prescribed to people whose blood pressure is persistently above 140/90 mmHg and inadequately controlled: the summary of product characteristics states that hypertension should be controlled before treatment with etoricoxib and special attention should be paid to blood pressure monitoring during treatment. NICE guidance on OA recommends against etoricoxib 60 mg as first choice NSAID.

The NICE Clinical Knowledge Summary on NSAIDs: prescribing issues advises:

- 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 (1000 mg/day or less) and low-dose ibuprofen (1200 mg/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 addition, NICE OA guidance recommends use of a low-cost proton pump inhibitor (PPI) for gastroprotection when an NSAID is prescribed.

Study sponsorship

The network meta-analysis was funded by the Swiss National Science Foundation and by a grant from the Arco Foundation, Switzerland.

References

About this Medicines Evidence Commentary

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