Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials

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CRD summary
The review assessed the analgesic efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with osteoarthritis of the knee. The authors concluded that NSAIDs reduce short-term pain slightly better than placebo, but evidence on long-term use is lacking. The conclusion appears to be appropriate given the evidence presented, although there were limitations in the reporting of the review process.

Authors' objectives
To determine the analgesic efficacy of non-steroidal anti-inflammatory drugs (NSAIDs), including cyclo-oxygenase-2 inhibitors in patients with osteoarthritis of the knee.

Searching
MEDLINE, EMBASE and the Cochrane CENTRAL Register were searched from 1966 to April 2004 for studies published in English, German or Scandinavian; the search terms were reported. Additional studies were searched for in the reference lists of systematic reviews, conference abstracts and by contact with clinical experts.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that were blinded, placebo-controlled and of a parallel design were eligible for inclusion.

Specific interventions included in the review
Studies that evaluated an NSAID of adequate dosage were eligible for inclusion. The daily dose had to equal or exceed the following for the specified NSAIDs (except indomethacin): celecoxib 200 mg, diclofenac 100 mg, etodolac 400 mg, etoricoxib 30 mg, ibuprofen 2,400 mg, meloxicam 7.5 mg, nabumetone 1,500 mg, naproxen 1,000 mg, oxaprozin 1,200 mg, rofecoxib 12.5 mg, tiaprofenic acid 600 mg, or valdecoxib 10 mg.

Participants included in the review
Studies of patients with osteoarthritis of the knee clinically confirmed according to the American College of Rheumatology criteria and by X-ray, in whom symptoms had persisted for more than 3 months, were eligible for inclusion. The median age of the patients was 62.5 years and the median duration of symptoms was 8.2 years.

Outcomes assessed in the review
Studies that evaluated pain intensity using the subscale of pain on the Western Ontario and McMaster Universities osteoarthritis (WOMAC) index, or a 100-mm visual analogue scale (VAS) for one or more pain dimensions, or evaluated functional disability using the WOMAC subscale for function, were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors assigned a quality score to each study (1 being the lowest and 5 the highest) using predefined criteria to assess the method of randomisation, concealment of allocation, blinding, handling of drop-outs and withdrawals, and analysis according to intention-to-treat. The selection criteria used in the included studies were assessed for possible selection bias, or variation from a typical population with osteoarthritis of the knee. Two reviewers assessed the validity
of the included studies.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on the mean response and standard deviation (SD) on the WOMAC pain subscale or 100-mm VAS were extracted from each individual study. Where the SDs were not reported, they were computed using measures of sample size and other variance data.

**Methods of synthesis**
How were the studies combined?
The results from the individual studies were combined using a random-effects (when significant heterogeneity was detected) or a fixed-effect (when no significant heterogeneity was detected) meta-analysis. A weighted mean difference (WMD) and effect size (ES), along with corresponding 95% confidence intervals (CIs), were calculated separately for pain and functional ability.

How were differences between studies investigated?
Statistical tests for homogeneity were performed as part of the meta-analysis using a significance level of P less than 0.1. Post hoc subgroup analyses were performed separately on studies of short duration (less than 6 weeks) and studies free from selection bias (defined as those that did not have a predefined minimum flare of symptoms when treatment with NSAIDs were discontinued in a pre-treatment washout period).

**Results of the review**
Twenty-three studies (n=10,845) were included in the review.

The methodological quality of the included studies was considered adequate to good according to the Jadad instrument (mean score 3.8, range: 3 to 5). Selection bias was present in 13 studies.

**Pain** (23 RCTs, n=10,845).

NSAIDs were associated with a significantly greater short-term (2 to 13 weeks) pain relief compared with placebo; the ES was 0.32 (95% CI: 0.24, 0.39, P<0.001) and the WMD was 10.1 mm (95% CI: 7.4, 12.8). There was evidence of statistical heterogeneity (P<0.01). One study (n=307) evaluated the long-term effect on pain and found no significant difference between tiaprofenic acid and placebo at 1, 2, 3 or 4 years after treatment.

The subgroup analysis of studies with no evidence of selection bias (10 RCTs, n=4,564) found that NSAIDs were associated with significantly greater pain relief compared with placebo (ES 0.23, 95% CI: 0.16, 0.31, P<0.001). There was no evidence of statistical heterogeneity (P=0.263). The subgroup analysis of studies that evaluated treatment duration of less than 6 weeks, or those using a WOMAC subscale for pain, did not influence the results.

**Functional ability** (11 RCTs, n=7,433).

NSAIDs were associated with a significantly greater reduction in functional disability compared with placebo (ES 0.29, 95% CI: 0.18, 0.40). There was evidence of statistical heterogeneity (P<0.01).

The subgroup analysis of studies with no evidence of selection bias (3 RCTs, n=2,928) found that NSAIDs were associated with a significantly greater reduction in functional disability compared with placebo (ES 0.20, 95% CI: 0.09, 0.3). There was no evidence of statistical heterogeneity (P=0.275).

**Authors’ conclusions**
Compared with placebo, NSAIDs are slightly more effective at reducing short-term pain in patients with osteoarthritis of the knee. There is insufficient evidence to support long-term usage in this population.
CRD commentary
The review addressed a clear research question and the inclusion criteria appeared appropriate. Several sources were used to identify relevant studies and attempts were made to limit language bias. Limited details of the review process (e.g. how the studies were assessed for inclusion or how the data were extracted) were reported; therefore, it is not possible to assess whether steps were taken to reduce errors and reviewer bias. The validity of the included studies was assessed systematically by two reviewers and was used to inform post hoc subgroup analyses. Adequate details of the included studies were reported, and appropriate methods were used to combine the studies. Differences between the studies were formally assessed and considered in subgroup analyses. The authors’ conclusion appears appropriate given the evidence presented, although there were limitations in the reporting of the review process.

Implications of the review for practice and research
Practice: The authors stated that the short-term pain relief offered by oral NSAIDs over placebo in patients with osteoarthritis may be too small to be clinically meaningful, which may contribute to non-compliance. The authors also recommended limited use of oral NSAIDs because of serious adverse events. However, these were not evaluated in the included studies and need to be confirmed.

Research: The authors did not explicitly state any implications for research, although the lack of evidence of long-term effects associated with oral NSAIDs was highlighted.

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