Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials
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CRD summary
This review assessed the efficacy of topical non-steroidal anti-inflammatory drugs (NSAIDs) in patients with osteoarthritis. The authors concluded that there is no evidence that topical NSAIDs are more effective than placebo beyond two weeks. The authors’ conclusions are likely to be reliable.

Authors' objectives
To assess the efficacy of topical non-steroidal anti-inflammatory drugs (NSAIDs) in patients with osteoarthritis.

Searching
MEDLINE, EMBASE, CINAHL, the Science Citation Index and the Cochrane Library were searched from 1966 to October 2003 with no language restrictions. The reference lists in identified studies and reviews were checked, and abstracts from conferences of international rheumatology societies (for 2002 and 2003) were searched. The search terms were provided in the full report, which is available on the BMJ website (accessed 31/05/2005). See Web Address at end of abstract.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. The review included double-blind parallel-group or crossover RCTs.

Specific interventions included in the review
Studies that compared topical NSAIDs with placebo or oral NSAIDs were eligible for inclusion. The included studies used different topical NSAIDs (salicylate, diclofenac, etodolac and ibuprofen) and lasted from 2 hours to 4 weeks.

Participants included in the review
Studies of patients with clinical or radiological evidence of osteoarthritis were eligible for inclusion. Studies of non-osteoarthritis, joint pain, rheumatoid arthritis, or pain due to dental extraction, surgery or injury, were excluded. Studies of patients with osteoarthritis or rheumatoid arthritis were only included if data were available separately for patients with osteoarthritis. The included participants had osteoarthritis of the knee, hip or hand.

Outcomes assessed in the review
The primary outcome in the review was reduction in pain (global or pain at rest) from baseline. The review also assessed function and stiffness, clinical response rate and adverse events. Clinical response rate was defined as moderate to excellent, as greater than 50% pain relief, or as improvement in symptoms.

How were decisions on the relevance of primary studies made?
Two rheumatologists checked and agreed on the diagnostic criteria for participants used in each study (no further details were given).

Assessment of study quality
The studies were assessed for randomisation, blinding and withdrawal. The authors did not state who performed the validity assessment.
Data extraction
Three reviewers independently extracted the data using a customised form and resolved any disagreements through discussion. The standard mean difference or effect size (ES), together with the 95% confidence interval (CI), was calculated for each study. Rate ratios and 95% CI were calculated for dichotomous data. The number-needed-to-treat (NNT) and 95% CI were also estimated.

Methods of synthesis
How were the studies combined?
The pooled ES or rate ratios and 95% CIs were calculated using a fixed-effect model, or a random-effects model if statistical heterogeneity was detected. The pooled NNT and 95% CI for clinical response were calculated where there was a statistically significant difference between treatments. The possibility of publication bias was explored using a funnel plot and Egger's test.

How were differences between studies investigated?
Statistical heterogeneity was investigated using the Q statistic. A sensitivity analysis was used to explore the influence on the results of study design (double-blind parallel or crossover), withdrawal rate (less than 10% or 10% or more), site of osteoarthritis (hand or knee), baseline pain score (less than 50% or 50% or more) and specific topical NSAID.

Results of the review
Thirteen RCTs (n=1,983) were included.

None of the RCTs reported the method of randomisation. The withdrawal rates ranged from 1 to 23%. The funnel plot was asymmetrical, suggesting the possibility of publication bias.

Topical NSAIDs versus placebo.
Compared with placebo, topical NSAIDs significantly improved pain relief at 1 week (ES 0.41, 95% CI: 0.16, 0.66; 7 RCTs, n=1,000) and 2 weeks (ES 0.40, 95% CI: 0.15, 0.65; 6 RCTs, n=893). Statistically significant heterogeneity was found for both meta-analyses. There was no statistically significant difference at 3 or 4 weeks.

Topical NSAIDs significantly improved function compared with placebo at 1 week (ES 0.37, 95% CI: 0.20, 0.53; 4 RCTs, n=566) and 2 weeks (ES 0.35, 95% CI: 0.19, 0.53; 4 RCTs, n=540). Statistically significant heterogeneity was found for both meta-analyses. There was no statistically significant difference at 3 or 4 weeks.

Topical NSAIDs significantly increased the clinical response rate at 1 week but not at 4 weeks. Adverse event rates were similar for topical NSAIDs and placebo (see URL).

Topical NSAID versus oral NSAIDs.
Topical NSAIDs were less effective than oral NSAIDs for pain, stiffness and function at 1, 2, 3 and 4 weeks. The difference was statistically significant only at week 1 for pain (ES -0.38, 95% CI: -0.66, -0.10; 1 RCT, n=208) and function (ES -0.32, 95% CI: -0.60, -0.04; 1 RCT, n=208). There was no difference in clinical response rate between topical and oral NSAIDs (see URL).

Compared with oral NSAIDs, topical NSAIDs reduced the proportion of patients with any adverse event, withdrawal due to adverse events and gastrointestinal events, but statistically significantly increased the proportion of patients with local adverse events (rate ratio 5.29, 95% CI: 1.14, 24.51).

In the sensitivity analyses, only the type of topical NSAID used significantly influenced the ES.

Authors’ conclusions
There was no evidence that topical NSAIDs were more effective than placebo beyond 2 weeks.
CRD commentary
The review addressed a clear question in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to minimise publication and language bias. The methods used to select studies were not reported in full, whereas the methods used to assess validity were not described; it is therefore not known whether any efforts were made to reduce errors and bias. Methods were used to minimise bias in the extraction of data. Study quality was assessed using specified established criteria, but this did not include an assessment of the validity of methods used for randomisation or to measure outcomes.

The data were combined in a meta-analysis and statistical heterogeneity was assessed. The forest plot of ES for pain demonstrated that, although statistically significant heterogeneity was found, the direction of effect among those studies reporting an effect appeared consistent. A sensitivity analysis was used to explore the influence of various relevant factors on the results. The authors’ conclusions on the lack of evidence for the long-term use of topical NSAIDs are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that there is a need to revise the current recommendations on the use of topical NSAIDs in osteoarthritis.

Research: The authors stated that more well-designed long-term studies that last months, rather than weeks, are required.

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Other publications of related interest
This additional published commentary may also be of interest. Kessenich CR.Review: topical NSAIDs reduce pain in osteoarthritis only during the first 2 weeks of use. Evid Based Nurs 2005;8:20.

Indexing Status
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.