A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the knee, with an emphasis on trial methodology

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Authors' objectives
To compare the efficacy of pharmacological agents for the treatment of osteoarthritis of the knee.

Searching
MEDLINE was searched from 1966 to 1994, using MeSH terms 'osteoarthritis', 'knee', 'knee joint'. Only English language publications were included. Reference lists of publications retrieved were also searched.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Nonsteroidal anti-inflammatory drugs (NSAIDs): arthrotec; aspirin; benoxaprofen; diclofenac; diflunisal; etodolac; fenbufen; flurbiprofen; ibuprofen; indomethacin; isoxicam; ketoprofen; naproxen; niflumic acid; nimesulide; osmosin; piroxicam; proquazone; sulindac; tenoxicam; tiaprofenic acid; tolmetin; zomepirac.

Analgesics: acetaminophen; glafenine; tilidine-naloxone; paracetamol; pentazocine.

Intra-articular steroids: betamethasone; methylprednisolone; prednisolone; triamcinolone; triamcinolonehexacetonide.

Biological agents: galactosaminoglycuronoglycan sulfate; glycosaminoglycan (GAG); glycosaminoglycan-peptide complex; glycosaminoglycan polysulfate; hyaluronic acid (HA); mucopolysaccharide polysulfuric acid ester (MPA); sodium hyaluronate. Other agents used in mixed trials: betamethasone; calcium lactate; glucosamine sulfate; hydrocortisone; orgotein; pantothenic acid; trolamine salicylate cream; S-adenosylmethionine; silicone oil; topical capsaicin.

Participants included in the review
There were 7,403 patients with osteoarthritis of the knee; 4,990 in 45 NSAIDs trials, 241 in 3 analgesic trials, 174 in 5 steroid trials, 438 in 9 biological agent trials, 1,587 in 18 mixed trials.

Outcomes assessed in the review
Pain; global assessments made by either investigator or patient; knee range of motion; functional status. Only trials that specifically included information about effects on the knee were included.

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

Assessment of study quality
The term random had to be specifically used in the description of allocation method. The quality of each study was assessed using a rating system derived from Gotzsche; this produced a score based on design features and analysis or reporting. The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

Data extraction
A qualitative scoring method was used to evaluate the comparative efficacy of different NSAIDs with respect to pain relief. This was based on change in pain scores from baseline associated with the use of each drug.

**Methods of synthesis**

How were the studies combined?
The studies were combined narratively and tables were presented showing comparative efficacy data.

How were differences between studies investigated?
There was no specific investigation of differences.

**Results of the review**

Eighty RCTs were included.

NSAIDs were superior to placebo in 8 out of 9 (89%) trials. Only 16% of comparative NSAIDs trials showed statistically-significant differences. Using the authors' scoring method, 14 comparisons showed differences in efficacy, with etodolac 600mg/day superior in 5 out of 9 comparisons. 41% of trials reported differences in toxicity; indomethacin and aspirin were found to be more toxic than comparator drugs in 6 and 4 trials, respectively.

Simple analgesics: glafenine was found to be superior to paracetamol, acetaminophen (4g per day) superior to placebo.

Intra-articular steroids: some (not all) studies suggest that these are superior to placebo, but only in the short term (>1 month).

Biological agents: 6 of 8 RCTs suggest that these are superior to placebo, but the optimal duration of treatment and route of administration is not clear.

Mixed regimens: 2 relatively large and well-designed trials suggested that acetaminophen was as effective as an NSAID. However, only 35% of patients completed a 2-year study, suggesting that neither drug was satisfactory in the long term. Topical capsaicin was more effective than placebo as adjunctive therapy. Intra-articular hyaluronic acid (IA HA) was superior to steroid at 8 weeks, but IA HA and dexamethasone was superior to IA HA alone.

**Authors' conclusions**

Acetaminophen, topical capsaicin, intra-articular steroids, intra-articular hyaluronic acid and NSAIDs are all effective treatments for osteoarthritis of the knee. The routine prescribing of long-term NSAIDs may not be advantageous in all patients.

**CRD commentary**

The search was limited and trials were almost certainly missed, in particular trials published in languages other than English. Although the methodological quality of trials was assessed, the method has not been validated and these results were not mentioned in the discussion of trial outcomes.

This review contains information about many different drug comparisons, but the way it is presented limits its usefulness. The authors' overall efficacy measure does not appear to allow for sample size, nor are there any figures for statistical significance of differences between treatment effects. More detail, in particular confidence intervals, would have been helpful.

**Funding**

American College of Rheumatology; Arthritis Foundation.

**Bibliographic details**

PubMedID
9144851

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Humans; Knee Joint; Osteoarthritis /drug therapy; Randomized Controlled Trials as Topic /methods; Research Design

AccessionNumber
11997000656

Date bibliographic record published
30/11/1998

Date abstract record published
30/11/1998

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.