Published meta-analyses of pharmacological therapies for osteoarthritis

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The objectives of this commentary are twofold: (1) to identify which pharmacological agents used in the management of osteoarthritis (OA) have published evidence in the form of systematic reviews (SR) and meta-analyses (MA) which supports their efficacy and/or toxicity, and (2) to summarize the main findings from these studies.

An MA can be defined as an SR that employs statistical methods to combine and summarize the results of several studies. In evidence-based medicine, MA of randomized controlled trials (RCTs) may well constitute the strongest evidence for the value of an intervention. For example, a commonly used grading scheme for evaluating the quality of the evidence is one adapted from the US Agency for Health Care Policy and Research. Grades 1A and 1B evidence are the most robust and least biased sources of evidence1. Grade 1A evidence is evidence obtained from at least one RCT. There have been a total of 10 published MA evaluating the following therapies for OA: conventional NSAIDs, simple analgesics (e.g. acetaminophen), COX-2 selective NSAIDs, topical NSAIDs, topical capsaicin, chondroitin sulfate and glucosamine2–12.

The meta-analyses of pharmacological therapies for OA of the hip analysed 43 RCTs covering the time period of 1966 to August 19942,3. Main findings from these reviews included the following: (1) the quality of the RCTs was generally poor, (2) there was a lack of standardization of case definition of OA and also a lack of standardization of the outcome assessments, (3) NSAIDs were always better than placebo, (4) it was rare to find differences in efficacy between NSAIDs, and (5) there was a tendency for indometacin to be found more effective than comparator NSAIDs, but also more toxic. Low dosages of naproxen (<750 mg/day) and ibuprofen (<1600 mg/day) were less efficacious than other NSAIDs.

The meta-analyses of pharmacological therapies for OA of the knee involved two publications3,9. The first analysed 80 RCTs covering the time period of 1966 to August 19944. The second analysed 16 RCTs covering the time period of 1966 to 19965. The main findings from these reviews included the following: (1) evidence exists for the efficacy of acetylaminophen, topical capsaicin, intra-articular (IA) steroids, IA hyaluronate, and NSAIDs in the treatment of OA of the knee, (2) the quality of the RCTs was generally poor, and (3) no substantial evidence is available related to efficacy, to distinguish between equivalent recommended doses of NSAIDs.

Eccles et al.6 analysed three RCTs in an attempt to rank the relative efficacy of acetylsalicylic acid and NSAIDs in the treatment of OA. Their main finding was that NSAIDs were slightly superior to acetylsalicylic acid in the outcomes of pain at rest (effect size 0.35, 95% confidence interval, 0.17–0.53) and pain on motion (effect size 0.28, 95% confidence interval, 0.08–0.48). However, there was no significant difference in the time to walk 50 feet, or in the quality of life improvements produced by the two therapies.

Moore et al.7 published an MA evaluating the efficacy and safety of topical NSAIDs vs placebo. Twenty-five RCTs evaluating subjects with ‘chronic pain conditions’ (including OA) were analysed covering the time period of 1966 to September 1996. The main findings were: (1) 8/13 RCTs found that topical NSAIDs were superior to placebo with a pooled relative risk (RR) for benefit of 2.0 (95% confidence interval, 1.5–2.7). The number needed to treat (NNT) was only 3.1 (95% confidence interval, 2.7–3.8), (2) two RCTs compared topical NSAIDs to oral NSAIDs and found equal efficacy, and (3) the safety of topical NSAIDs was equivalent to placebo.

Zhang et al.8 published an MA evaluating the efficacy and safety of topical capsaicin in a number of chronic painful conditions, including OA. Three RCTs were analysed covering the time period of 1980 to February 1994. The main findings were: (1) capsaicin cream was better than placebo in providing pain relief in OA (odds ratio of 4.36, 95% confidence interval of 2.8–6.9), (2) true blinding was probably difficult to conduct with capsaicin.

The UK’s National Institute of Clinical Excellence (NICE) published on their website an MA which evaluated the efficacy and safety of the four available COX-2 selective NSAIDs: celecoxib, rofecoxib, meloxicam, and etodolac9. Fifty-three RCTs involving 61 731 patients with OA and RA were analysed. The main findings of the NICE review were: (1) COX-2 selective inhibitors have equivalent efficacy to conventional NSAIDs, (2) COX-2 selective inhibitors are effective in reducing the incidence of gastrointestinal (GI) toxicity compared to conventional NSAIDs, (3) there is no direct evidence to suggest that any one of the four COX-2 selective drugs is superior to another, (4) cost-effectiveness of the COX-2 selective inhibitors is more likely to be favorable in patients at high risk for gastrointestinal toxicity, (5) COX-2 selective inhibitors are not recommended for routine use in OA, and (6) COX-2 selective inhibitors are recommended for use in patients at high risk for GI toxicity.
Leeb et al. published an MA evaluating the efficacy and safety of chondroitin sulfate (CS) in OA. Seven RCTs published between 1991 and 1998 were analysed. The main findings of this review were: (1) CS was more effective than placebo in relieving the pain of OA with an effect size of 0.9, (2) in terms of pain reduction, 65% of patients taking CS will benefit more than from taking a placebo, (3) the effect size for improvement in the Lequesne Index was 0.74, and (4) adverse effects were greater for the placebo treated patients vs the CS treated patients.

McAlindon et al. published an MA evaluating the efficacy of both glucosamine and CS in OA. Fifteen RCTs were analysed covering the time period of 1966 to June 1999. The main findings of this review were: (1) there were moderate effect sizes for glucosamine (0.44, with a 95% confidence interval of 0.24–0.64) and large effect sizes for CS (0.78, with a 95% confidence interval of 0.60–0.95), (2) quality scores were generally low, with scores ranging from 12% to 55% of the maximum score, with a mean of 35%, (4) the effects of both compounds are likely to be exaggerated given the methodological weaknesses inherent in the RCTs (for example, lack of intention-to-treat analyses, lack of allocation concealment and publication bias) and (3) despite the methodological weaknesses, some degree of efficacy does appear probable for both glucosamine and CS.

Towheed et al. published an MA evaluating the efficacy and toxicity of glucosamine compounds in OA. Sixteen RCTs were analysed covering the time period of 1966 to December 1999. The main findings of this review were: (1) Glucosamine was superior to placebo in terms of pain reduction (effect size 1.40, with a 95% confidence interval of 0.65–2.14), (2) glucosamine was superior to placebo in terms of improvements in the Lequesne Index (odds ratio of 2.04 with a 95% confidence interval of 1.38–3.02), (3) glucosamine was superior to NSAIDs in terms of pain reduction (effect size 0.86 with a 95% confidence interval of 0.58–1.14), and (4) glucosamine demonstrated an excellent safety profile (only 14 of the nearly 1000 subjects randomized to glucosamine were withdrawn because of toxicity, and only 61 subjects reported any adverse reactions).

In summary, SR and MA are useful techniques which can be used to efficiently summarize and document the relative value of pharmacological therapies in OA. This methodology will continue to be very useful for the future development of evidence-based guidelines for the management of OA. The Cochrane Musculoskeletal Group is taking an active leadership role in this regard with the publication of systematic reviews of OA therapies in the Cochrane Library.

References