A meta-analysis of controlled clinical studies with diacerein in the treatment of osteoarthritis

Rintelen B, Neumann K, Leeb B F

CRD summary
The review assessed the symptomatic efficacy of diacerein in the treatment of osteoarthritis. The authors concluded that diacerein improved symptoms and had reasonable tolerability in knee and hip osteoarthritis. Inadequate information on individual studies and the methods used to deal with the results, and differences between the studies, make it difficult to assess the reliability of the results.

Authors' objectives
To assess the symptomatic efficacy of diacerein in the treatment of osteoarthritis.

Searching
PubMed and EMBASE were searched from 1985 to 2004. In addition, Internet searches were carried out using Google, Yahoo and AltaVista. The search terms were reported. Recent issues of arthritis journals, personal files and reference lists of review articles were screened and manufacturers were contacted for unpublished reports. Only publications in English, German or French were eligible.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing treatment with diacerein to placebo or another specified active treatment were eligible for inclusion. The included studies compared diacerein with non-steroidal anti-inflammatory drugs (NSAIDs), Harpagophytum procumbens, unspecified standard treatment or placebo treatment. The duration of treatment ranged from 1 to 36 months.

Participants included in the review
Studies on patients with osteoarthritis of the knee and/or hip were eligible. The majority of the included studies were in patients with either knee or hip osteoarthritis, or both, followed by studies in patients with knee osteoarthritis only; very few studies contained only patients with hip osteoarthritis.

Outcomes assessed in the review
The studies had to report extractable data on relevant outcome measures assessing the efficacy and safety of the treatment in the active treatment phase or treatment-free follow-up phase. For the included studies, pain and function measures were extracted as the primary outcomes; the secondary outcomes were co-medication, consumption of analgesics or NSAIDs, subjective ratings of global efficacy by patients or investigators, and subjective ratings of global safety by patients or investigators. The included studies measured various types of pain: pain at rest, on active movement, on pressure, on load, on movement, spontaneous, on passive movement and on walking. Pain was most commonly measured using a 100-mm visual analogue scale. The assessment methods used to measure function varied (the scales used were reported). One study was excluded because, according to the authors, it only reported intra-patient changes. The review assessed outcomes at the end of treatment and after a treatment-free follow-up period that ranged from 1 to 3 months (where available).

How were decisions on the relevance of primary studies made?
Two reviewers, blind to the authors, publication date and journal, independently screened the studies.
Assessment of study quality
Two reviewers, blind to the authors, publication date and journal, independently assessed the studies using the Jadad scale, which assesses the method of randomisation, allocation concealment, blinding of the investigators and patients, and the handling of drop-outs and withdrawals. The availability of intention-to-treat (ITT) analysis was also reported. One study was apparently excluded because of major methodological problems.

Data extraction
Two reviewers, blind to the authors, publication date and journal, independently extracted the data; a statistician checked the extracted data. Where possible, ITT data were extracted.

Methods of synthesis
How were the studies combined?
The studies were grouped by outcome, comparator and timing of the outcome assessment. The individual results were pooled using Glass scores (standardised mean differences) corrected for small sample size bias using exact methods. The inverse normal method was used for statistical assessment (significance level p<0.05), using exact weighting techniques. Pooled results weighted by study quality were presented. Type one error control was based on the Bonferroni-Holm procedure.

How were differences between studies investigated?
The robustness of the results was investigated using two different weighting methods (weighted by sample size and by study quality) for the Glass scores. The heterogeneity assessment was based on identifying non-overlapping two-sided 95% confidence intervals (CIs).

Results of the review
Nineteen RCTs (n=2,637) were included in the review.

The mean Jadad scores varied between 0 and 5 in the documented studies.

The results below are for the Jadad weighted meta-analyses; those for the sample size-weighted meta-analyses were similar.

Diacerein was statistically superior to placebo regarding pain during the active treatment phase (Glass score 1.50, 95% CI: 0.80, 2.20; based on 8 studies) and at the end of the follow-up period (Glass score 2.67, 95% CI: 1.27, 4.07; number of studies unclear).

Diacerein was statistically superior to placebo regarding functional impairment during the active treatment phase (Glass score: 1.49, 95% CI: 0.78, 2.19; based on 8 studies).

Diacerein was not statistically superior to standard treatment (mostly NSAIDs) regarding pain during the active treatment (-0.35, 95% CI: -1.11, 0.4; based on 10 studies), but it was statistically superior at the end of the follow-up period (2.13, 95% CI: 1.32, 2.93; based on 8 studies).

Diacerein was not statistically superior to standard treatment (mostly NSAIDs) regarding function during active treatment (0.12, 95% CI: -0.68, 0.93), but it was statistically superior at the end of the follow-up period (2.58, 95% CI: 1.71, 3.45).

Diacerein was statistically inferior to placebo regarding tolerability ratings (-1.51, 95% CI: -2.21, -0.81; number of studies unclear), but there were no significant differences between diacerein and NSAIDs (0.09, 95% CI: -0.66, 0.85; number of studies unclear).

Authors' conclusions
There is evidence that diacerein has symptomatic efficacy and reasonable tolerability in the treatment of knee and hip
osteoarthritis.

**CRD commentary**
The review addressed a clear research question but some of the exact inclusion criteria remained unclear: for example, studies had to fulfil an undefined methodological quality threshold and it was not entirely clear what kind of data a study had to report to be eligible for inclusion. The search was limited in terms of the databases searched and only studies published in selected languages were eligible; a procedure that could have introduced language bias into the review. Efforts were made to locate unpublished data, which helped prevent publication bias. Study quality was assessed and the Jadad scores were integrated in the analysis. There was no information on the drug doses used in the included studies, so the comparability of the studies and equivalence of comparator drugs could not be assessed.

For some analyses it was unclear on which studies (and how many) the results were based. The assessment methods for the outcomes in the individual studies varied widely; it remains unclear whether the pooled results are clinically meaningful or clinically significant. It was not clear how the authors dealt with multiple measures of pain or function reported in the same study. The methods used to measure the patients’ tolerability ratings were not examined, which meant it was not possible to adequately evaluate the validity of the results for this outcome. Several of the meta-analysis graphs showed non-overlapping CIs and different directions of effects, indicating the presence of heterogeneity; this suggests that pooled effect sizes might not have been an appropriate summary measure. Potential reasons for differing results among the studies were not explored or discussed. The lack of adequate information on the individual studies and methods used to extract and deal with the results data, as well as differences between the studies, make it difficult to assess the reliability of results.

The review was funded by TRB Chemedica and two of the authors have received consultancy fees from various pharmaceutical companies.

A correction of the flow diagram has been published.

**Implications of the review for practice and research**
Practice: The authors stated that, given the documented cardiovascular adverse events for NSAIDs, the administration of diacerein may have some advantages.

Research: The authors stated that a trial with sufficient statistical power to ultimately prove the usefulness of diacerein as a symptom-modifying drug in osteoarthritis can be expected to give similar results.

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**Other publications of related interest**

This additional published commentary may also be of interest. Hunter DJ, Wise B. Review: diacerein is more effective than placebo and is as effective as NSAIDs for knee and hip osteoarthritis. Evid Based Med 2007;12:74.

**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.