Clinical trials of homoeopathy in osteoarthritis: a systematic review

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Abstract
Introduction
Homoeopathy seems scientifically implausible and is the most controversial form of complementary and alternative medicine therapies. This review aims to summarise the treatment effects of homoeopathy in osteoarthritis.

Materials and methods
Relevant studies from 1980 to 2013 were identified by a comprehensive literature search in electronic databases, reference list of relevant papers and contacts with experts. Clinical trials comparing homoeopathic treatment strategy with controls (placebo or conventional therapies) were eligible. Information on patients, interventions and comparators, outcomes, study designs and results was extracted in a standardised manner, and quality was assessed using the Jadad scoring and Cochrane bias minimisation criteria. Trials providing sufficient data were summarised and tabulated systematically.

Results
A total of eight controlled clinical trials involving 1444 patients were included in the analysis. None of the studies used individualised homoeopathy, rather tried 'complex homoeopathy' and 'combination formulae'. Methodological quality of the trials was variable.

Conclusion
Overall results of our review show that homoeopathic complexes have a clear advantage in the treatment of osteoarthritis. However, the evidence is not convincing to arrive at a definite conclusion because of methodological inconsistencies and insufficient trial reporting. Further replications are warranted, provided the trials are rigorous, systematic and, above all, individualised.

Introduction
Osteoarthritis (OA) is a heterogeneous group of degenerative joint disease of multi-factorial origin, characterised by defective integrity and progressive loss of articular cartilage, subchondral bone remodelling, joint space narrowing and bone spur formation, as well as synovial inflammation\(^1\). Pain and functional impairment are the key domains of the burden of suffering experienced by people with OA that is of primary concern, and that burden can be significant, and taken together they often exert a significant reduction in quality of life\(^2,3\). Since the last decade, recommendations for managing OA have focused persistently on relieving pain and stiffness and improving physical function as important goals of therapy\(^4,5\). However, conventional drug therapy for OA successfully relieves pain only, alongside producing adverse gastrointestinal and cardiovascular effects, especially with long-term use\(^6\).

Rheumatologic problems are among the most common disease conditions encountered by CAM practitioners\(^7,8\). Many patients use CAM therapies including homoeopathy to prevent, control and manage the pain of rheumatologic conditions\(^9,10\). However, scientific research has so far not provided evidences solid enough to support the effectiveness of CAM as treatment options for rheumatologic conditions including OA and has remained ambiguous\(^11\). Reviews have remained contradictory in conclusions\(^12-18\). Few low-potency homoeopathic complexes in the randomised controlled trials seemed to possess significant effects in OA\(^19\), but the potential of individualised homoeopathy remained untested. Hence, based on small-to-moderate effect sizes for the wide range of symptomatic treatments, conventional medicine in individualised approach still remains the mainstay of treatment\(^20,21\).

The aim of this systemic review was to identify, evaluate and summarise the findings of all relevant individual studies, thereby making the available evidence more accessible to decision makers.

Materials and Methods
Protocol and registration
A specific protocol (03/2013-14/CRU(H)/Slg/MTA/SS; version 1.1, 1 June 2013) was developed for conducting this systematic review. The protocol was registered vide CRD42013004970, 1 July 2013 with the PROSPERO International prospective register of systematic reviews, Centre for Reviews and Dissemination, the University of York, National Institute of Health Research, York, UK. PRISMA guidelines\(^22\) were followed in structuring this review.

Eligibility criteria
Trials were eligible for this review if they compared homoeopathy applied for treatment of OA with placebo or
conventional therapies and a complete, accessible, research journal paper was available in English (paper in German was also considered eligible if a translated reprint in English was available) and published between 1980 and 2013. Eligibility was assessed by the reviewers.

Search strategy
Different electronic bibliographic databases like MEDLINE (via PubMed), Cochrane, Google Scholar, EMBASE (Elsevier), AMED (British Library), CCRH (India), CINAHL (EBSCO Publishing, Ovid Technologies, ProQuest), CISCOM (RCCM, London), CAM (University of Maryland, School of Medicine), HomInform (Glasgow Homeopathic Hospital), LILACS (Virtual Health Library, Brasil), MANTIS (ChiroAccess) and SIGLE (Europe) were searched for relevant literature. Search terms used were ‘osteoarthritis’, ‘osteoarthrosis’, ‘gonarthrosis’, ‘homeopathy’, ‘homeoopathy’, ‘alternative medicine’ and ‘complementary medicine’. Data were also obtained by contact with individual researchers. We also searched comprehensively electronic databases to identify any reviews conducted in the relevant field, namely MEDLINE (via PubMed), Database of Abstracts of Reviews of Effects (DARE), Cochrane Database of Systematic Reviews (CDSR), Campbell Library of Systematic Reviews (CLSR), National Institute for Health and Clinical Excellence (NICE), NIHR Health Technology Assessment (NIHR HTA), Evidence for Policy and Practice Information (EPPi), Database of systematic and non-systematic reviews of Public Health interventions (DoPHER), National Guidelines Clearinghouse (NGC) and Scottish Intercollegiate Guidelines Network (SIGN). We visually scanned reference lists from relevant studies; hand searched key journals and trial registers; contacted study authors, experts, manufacturers and other organisations and conducted citation searching.

Study selection
Only prospective controlled clinical trials with clearly defined predetermined outcomes and published research journal literature in English were included.

Data collection process
A standardised data extraction form was designed by the reviewers and pilot tested on three studies to provide consistency in the review, whilst reducing bias and improving validity and reliability. For each trial, main characteristics and results were extracted independently by two reviewers.

Data items
Data were extracted on the following grounds: patients (number included/analysed, condition treated, demographics, setting), intervention and comparator (homeopathic intervention, comparator/control), outcomes (overall assessment, patients assessed globally as improved), study design (allocation to group, blinding, concealment of allocation, selection bias after allocation, duration of observation), two scoring indices–Jadad scoring index (maximum score 5; five items; Yes: 1; No: 0) and Cochrane bias minimisation index (10 items scale–Yes: 1; No: 0), and overall result with P-values.

Summary measures
Descriptive summary was deduced from each study using the standardised data extraction form focusing on population recruited, interventions and comparator used, outcome measures, methods adopted, methodological scorings and overall result.

Results
Study selection and characteristics
From 1980 till 2013, a total of eight peer-reviewed published papers on clinical trials on homoeopathic treatment of OA were identified to be eligible (Figure 1). None of these trials tested individualised homoeopathy, rather used ‘complexes’ and ‘combination formulæ’ versus either placebo control or adopted pragmatic study designs. Besides, we could identify also one prospective multi-centric open observational clinical study using individualised...
homoeopathy from 1984 to 2005 by the Central Council for Research in Homoeopathy, India, which yielded positive results favouring homoeopathy; however, methodological qualities were inadequate. An overview of the patients, methods, interventions and results of the 10 included trials is given in Table 1.

Results of individual studies
The highest methodological scoring, both as per Jadad scale and bias minimisation, was obtained conjointly by the studies by van Haselen et al.28 and Widrig et al.21. The studies by Birnesser et al.29 and Strösser et al.32 were of the poorest methodological qualities. None tried individualised homoeopathy; instead various ‘complexes’ and ‘combination formulae’ against placebo, conventional oral drugs, topical gels or intra-articular injections are used. The studies recruited a total of 1,444 patients, and six of those studied OA knee, one studied both OA knee and hip and one studied OA hand. Randomisation was used in seven of the eight studies (one study not mentioning and describing randomisation properly) and double blinding by six studies. One study was single blind20 and one was open label30. Only a single study used cross-over design25. The study by Birnesser et al.26 was a prospective cohort study. Study duration ranged between 3 and 10 weeks (Table 1).

Discussion
Summary of evidence
A total of eight clinical trials on OA were included in our systematic review. Individualised (‘classical’) homoeopathy has not been tested in any of the trials identified. The study by Strösser et al. yielded the most positive results favouring homoeopathy, and the study by Shipley et al. showed the poorest, in fact, negative result. Claims have been made that studies with better methodological quality tend to yield less positive results in favour of homoeopathy34; but our analysis generated conflicting evidence. Studies with the highest methodological qualities, that is, those done by van Haselen et al. and Widrig et al., produced significantly positive results, suggesting an advantage of using homoeopathic therapy over conventional therapies. Finally, it can be concluded that evidences have been generated to support the use of ‘complex homoeopathy’ over placebo and almost in equivalence to conventional therapies for managing OA.

Strengths and limitations
As we identified varying trials in terms of using homoeopathic (not truly ‘homoeopathic’) treatment in a single disease (OA) using different end-points (both dichotomous and continuous) like global improvement in the number of patients in either group, reduction in visual analogue scales measuring pain on movement and during rest, stiffness and loss of function, WOMAC indices of OA etc., the assumption of a common underlying treatment effect size seems to be inappropriate. Thus, heterogeneity existed in terms of using differing outcome measures, differing intervention and comparators (either placebo or conventional therapies; differing in dosage, duration, mode of intervention), differing study design (randomised/non-randomised/quasi-randomised; open/single blind/double blind etc.) and differing statistical tests applied. Therefore, a combination of significance levels (sum of logs, sum of Z, weighted sum of Z, sum of t, mean Z, mean P, count test and logit procedure) may be been chosen as a more appropriate statistical approach to perform a meta-analysis. The rationale for this choice was that all the trials explored the same broad question, that is, ‘Is homoeopathic treatment efficacious at all in a clinical condition like OA?’ If the results are interpreted with sufficient caution and prudence (least optimistic results), this approach may provide a way to combine results from very dissimilar trials with differing outcomes and statistical tests.

Reviews that include only published studies like ours might be at risk of overestimating the treatment effect. Including data from unpublished studies (or unpublished outcomes) is therefore important in minimising bias. However, this can be time-consuming, and the original data may no longer be available. Although those performing individual patient data meta-analyses have generally been successful in obtaining data from the authors of unpublished studies, the same may not be true of other types of reviews.

The practical difficulties of locating and obtaining information from unpublished studies may, for example, make the ideal of including relevant unpublished studies unachievable in the timescales available for many commissioned reviews. When information from unpublished studies is obtained, the published and unpublished material should be subjected to the same methodological evaluation.

This study is restricted by chances of potential flaw or premature negative bias of making any conclusion from the limited quantity of trials currently available in peer-reviewed literature, especially in the context of absence of any single trial testing individualised homoeopathy, the ‘classical’ form of homoeopathy. However, the obvious advantage of not using individualised homoeopathy was the absence of some inherent debatable issues like ‘empathy’ or ‘consultation biases’, and ambiguity regarding selection of the correct individualised medicine for a given condition. Inadequate reporting has also inadvertently introduced a source of error into the trials. While the standard practice is to report the 95% confidence limits and two-tailed P-values, these were missing in many studies.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Interventions and comparator</th>
<th>Outcomes (homoeopathy vs. control)</th>
<th>Methods</th>
<th>Jadad score (maximum = 5), risk of bias minimisation score (maximum = 10)</th>
<th>Overall result (P-value)</th>
</tr>
</thead>
</table>
| Shipley25  | 1. 36/33  
2. OA hip and knee  
3. 6.7% female; mean age 65 years  
4. London | 1. Rhus tox 6 × five drops eight hourly  
2. Two capsules of Fenoprofen (each containing 300 mg) eight hourly and placebo | 1. Rhus tox 6 × and placebo did not differ significantly; patients' preference was for Fenoprofen  
2. ? | 1. Randomised, cross-over  
2. Double blind, double dummy  
3. ?  
4. Likely  
5. 6 weeks, 2 weeks for each treatment regime | 4, 6 | Negative; P-value not reported |
| Nahler26   | 1. 121/114  
2. OA knee  
3. Male : female = 1 : 1; mean age 67 years  
4. Germany, Austria | 1. Zeel® compositum (Rhus tox, Amica montana, Solanum dulcamara, Sanguinaria canadensis, sulphur) two 2 mL IA injections per week over 5 weeks  
2. 5 injections of Hyalart® one 2 mL IA injection per week over 5 weeks | 1. Similar significant improvement in both groups; difference insignificant (P = 0.4298)  
2. Pain relief during movement: Zeel® 55/57; Hyalart® 57/57 | 1. Randomised  
2. Single blind  
3. ?  
4. Likely  
5. 5 weeks | 3, 8 | Positive; P-value not reported; but no significant group difference (P = 0.4298) |
| Shealy27   | 1. 65/65  
2. OA knee  
3. Male : female = 30 : 35; age 34–85 years  
4. Missouri, USA | 1. 10 drops of homeopathic preparation consisting of equal parts of Rhus tox 12 x, Causticum 12 x, Lac vaccinum 30 x, 6 hourly for 1 month  
2. Acetaminophen 2,600 mg 24 hourly for 1 month | 1. Slight advantage, though non-significant (P = 0.47), of homoeopathy over acetaminophen  
2. 40% or greater pain relief: homoeopathy 24/43 (55%); acetaminophen 8/22 (38%); patients preferred to continue homoeopathy | 1. Randomised (probably; not stated clearly)  
2. Double blind, double dummy  
3. Coded drugs  
4. Unlikely  
5. 1 month | 3, 8 | Positive, but no significance (P = 0.47) |
| van Haselen28 | 1. 184/184  
2. OA knee  
3. 7.4% female; mean age 64 years  
4. London, UK | 1. SRL® gel containing Symphytum officinale, Rhus tox and Ledum palustre, 8 hourly for 4 weeks  
2. Feldene® gel containing 0.5% piroxicam, 8 hourly for 4 weeks | 1. Mean pain reduction: 16.5 mm VAS in SRL® group and 8.1 mm in Feldene® group; though better in homoeopathy, statistically non-significant (P = 0.67)  
2. SRL® group 55/92; Feldene® group 48/92 | 1. Randomised  
2. Double blind  
3. Coded drugs  
4. Unlikely  
5. 4 weeks | 5, 10 | Positive and significant (P = 0.036) |
Table 1 (Continued)

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Maronna²⁰</td>
<td>1. 121/121  2. OA knee  3. ?  4. Germany</td>
<td>1. Zeel® comp. tablets 24 hourly for 10 weeks  2. Diclofenac 25 mg tablets; 24 hourly for 10 weeks</td>
<td>1. WOMAC indices: statistically significant improvement in both groups, but difference non-significant  2. Zeel® comp. group 47%; Diclofenac group 51%</td>
<td>1. Randomised  2. Double blind  3. ?  4. Likely  5. 10 weeks</td>
<td>3, 6</td>
<td>Positive; P-value not reported (claimed to be statistically significant!)</td>
</tr>
<tr>
<td>Bimesser²⁰</td>
<td>1. 592/592  2. OA knee stages I and II (Richter’s classification)  3. ?  4. Germany</td>
<td>1. Zeel® comp. N tablets containing Arnica montana, Sanguinaria canadensis, Rhus tox, Solanum dulcamara and sulphur; one tablet three to five times a day for 10 weeks  2. COX-2 inhibitors Celebrex® (Celecoxib 100 or 200 mg) capsules and Vioxx® (Rofecoxib 12.5 or 25 mg) tablets</td>
<td>1. Zeel® comp. N was not less effective than COX-2 inhibitors; tolerability higher in homoeopathy group  2. 255/323 (79%); 231/269 (86%); difference between groups non-significant (P = 0.16)</td>
<td>1. Non-randomised  2. Open  3. None  4. Very likely  5. 10 weeks</td>
<td>0, 5</td>
<td>Positive; P-value not reported (claimed to be statistically significant!)</td>
</tr>
<tr>
<td>Widrig²¹</td>
<td>1. 204/198  2. OA hand  3. Mean age 64 years; female 74%  4. Switzerland</td>
<td>1. A. Vogel® Arnica Gel (arnica tincture 50 gm / 100 gm gel; drug-to-extract ratio of the tincture 1:20); 8 hourly for 3 weeks  2. Optifem® Gel (ibuprofen gel 5%; 8 hourly for 3 weeks</td>
<td>1. Pain VAS reduced significantly in both groups; difference in reduction non-significant  2. 71/89 (80%); 64/85 (75%)</td>
<td>1. Randomised  2. Double-blind  3. Coded drugs  4. Unlikely  5. 3 weeks</td>
<td>5, 10</td>
<td>Negative; P-value not reported</td>
</tr>
<tr>
<td>Strösser²²</td>
<td>1. 121/114  2. OA knee, mild to moderate  3. ?  4. Germany</td>
<td>1. Zeel® comp tablet; 1 tablet 8 hourly for 10 weeks  2. Diclofenac 25 mg tablet; 1 tablet 8 hourly for 10 weeks</td>
<td>1. Mobility and functionality of joints and WOMAC score improved significantly in both groups; difference statistically non-significant  2. 7/53; 7/61</td>
<td>1. Randomised  2. Double blind  3. ?  4. Likely  5. 10 weeks</td>
<td>0, 4</td>
<td>Positive (P-value not reported)</td>
</tr>
</tbody>
</table>

'?' Data not available.
Another clear shortcoming is that extraction and assessments were made by the reviewers manually. Disagreements were resolved by discussion with involvement of a third reviewer as and when necessary. Instead, the quality assessments and the results of this qualitative systematic review should be interpreted with caution. The methodological assessment, though explicit, involved subjective judgements. These quality scoring methods are useful in evaluating the robustness of results of a review when corrected for possible sources of bias. However, for a more in-depth assessment, these scores are too crude, too formal and depend too much on reporting. To date, and given the often insufficient detail in reporting, a valid and reliable assessment of methodological quality remains elusive. In particular, the reliability of data collection can hardly be assessed unless it is guaranteed that good clinical practice (GCP) guidelines have been followed. With these shortcomings in mind, the results of this qualitative analysis should only be seen as a crude indicator of the trend of the results in the single trials.

Conclusion
In spite of the insufficient quantity of research literature and insufficient trial reporting, this review concludes that there is clear evidence that homoeopathic complexes and combination formulae play a considerable role in treatment of OA; however, immediate uptake of trials testing individualised homoeopathy followed by further confirmatory independent replications is warranted, provided the trials are rigorous and systematic.

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Abbreviation list
OA, osteoarthritis.

References


