

Clinical evidence for homeopathy

Brief

Homeopathic remedies are included in the NHS England document published in July 2017: Items which should not routinely be prescribed in primary care: a consultation on guidance for CCGs. These items are classified as being of low clinical effectiveness, where there is a lack of robust evidence of clinical effectiveness or there are significant safety concerns. This evidence review has been prepared in response to concerns raised by the British Homeopathic Association (BHA) regarding inclusion of homeopathic remedies in the NHS England document. This review aims to focus on the literature available and will assess the quality of this literature.

Summary of clinical evidence

- The principles on which homeopathy is based are very different to conventional medical beliefs. Two theories central to homeopathy are;
 - Like cures like: A substance, that could in conventional doses cause an undesirable effect, is used, in very dilute amounts, to treat that symptom.
 - The more dilute a preparation is the more potent it is. Homeopathic remedies are prepared by repeated dilutions of a base substance. The dilution process is known as potentisation, implying that each subsequent dilution and succussion increases the potency of the preparation.
- In 2015, the Australian National Health and Medical Research Council (NHMRC) conducted a systematic evidence review summarising the evidence from systematic reviews regarding the effectiveness of homeopathy as a treatment for any clinical condition in humans. The review included 57 systematic reviews for a total of 68 clinical conditions.
- The Australian NHMRC concluded overall that there was no condition for which there was a high level of confidence (LOC) in the body of evidence. One condition was associated with a moderate LOC (post-operative ileus). The remainder were associated with a moderate-low, low or very low LOC. They concluded that the available evidence is not compelling and fails to demonstrate that homeopathy is an effective treatment for any of the reported clinical conditions in humans.
- A literature search for systematic reviews published subsequent to the Australian search has identified a further 8 reviews. Seven of these have been scored using the AMSTAR tool for assessing methodological quality of systematic reviews and summarised below. One could not be obtained within the timeframe.
- The BHA, in their submission to NHS England, included a summary of clinical evidence. We identified three review papers that were not considered by the Australian review; the remaining papers within the BHA submission were either included in the Australian review or had been rejected by the review process as being of insufficient quality or the wrong type of evidence.

Place in national/ International guidance

- We have not identified any NICE guidance which recommends the use of homeopathy for any clinical condition. NICE specifically recommend against the use of homeopathy for the treatment of otitis media with effusion, induction of labour or treatment of lower urinary tract symptoms (LUTS) in men.
- The Australian NHMRC concluded that homeopathy should not be used to treat health conditions that are chronic, serious, or could become serious. People who choose homeopathy may put their health at risk if they reject or delay treatments for which there is good evidence for safety and effectiveness. People who are considering whether to use homeopathy should first get advice from a registered health practitioner. Those who use homeopathy should tell their health practitioner and should keep taking any prescribed treatments.
- The UK Science and Technology Committee report into homeopathy in 2010 concluded that the systematic reviews and meta-analyses conclusively demonstrate that homeopathic products perform no better than placebos. They recommended that by providing homeopathy on the NHS and allowing MHRA licensing of products, the Government runs the risk of endorsing homeopathy as an efficacious system of medicine. To maintain patient trust, choice and safety, the Government should not endorse the use of placebo treatments, including homeopathy. Their overall recommendation was that homeopathy should not be funded on the NHS and the MHRA should stop licensing homeopathic products.
- The government response noted that there remains some controversy, since there are peer-reviewed reports that suggest there may be limited evidence of efficacy of homeopathy in certain circumstances. They reasserted the government position on the use of homeopathy within the NHS was that the local NHS and clinicians, rather than Whitehall, are best placed to make decisions on what treatment is appropriate for their patients - including complementary or alternative treatments such as homeopathy - and provide accordingly for those treatments. They further noted that in order for the public to make informed choices, it is vitally important that the scientific evidence base for homeopathy is clearly explained and available.

- In the US, the Federal Trade Commission (FTC) issued a policy statement in 2016 to the effect that the FTC will hold efficacy and safety claims for OTC homeopathic drugs to the same standard as other products making similar claims. That is, companies must have competent and reliable scientific evidence for health-related claims, including claims that a product can treat specific conditions.

Systematic reviews

Process:

1. The Australian NHMRC review was considered a robust, comprehensive systematic review of the evidence published around homeopathy up to January 2013.
2. A comprehensive literature search was therefore undertaken to identify any further systematic reviews published subsequent to the NHMRC document (see appendix for search strategy). We concentrated on literature published from 2013 to date. Eight systematic reviews were identified, of which one could not be accessed within the available time frame. We have not considered lower-quality evidence- for example case studies or surveys.
3. For completeness, we also reviewed the BHA submission, concentrating on their summary of clinical trial data. Any systematic reviews cited in the BHA submission that were not considered by the NHMRC document were also sourced and reviewed. Two systematic reviews and one review of three trials were identified.
4. In total, 10 systematic reviews were identified (of which 9 were appraised and summarised below), in addition to the NHMRC review.
5. We used the AMSTAR tool for scoring methodological quality of systematic reviews. This scores a systematic review on a scale 0-11. We considered a score of 8-11 as a high quality systematic review; 4-7 moderate quality and 0-3 a low quality systematic review.

Systematic reviews published subsequent to NHMRC document:

Summary: A summary of the main findings from each of the systematic reviews or meta-analysis published subsequent to the NHMRC document are included below; whilst the systematic reviews conducted appear to be of moderate to good quality when scored using the AMSTAR tool, the quality of the trials included within most of the reviews are variable thus this new data does not change the conclusion of the NHMRC review conducted in 2015

Mathie et al 2014

A systematic review and meta-analysis of trials of individualised homeopathic treatments. In individualised homeopathy, the homeopath matches all the person's symptoms to a single homeopathic medicine, rather than treating the person for a particular health condition using one or more homeopathic medicines. Individualised homeopathy typically involves a long interview between the practitioner and the patient. The review included 32 eligible trials covering 24 different medical conditions and patient numbers completing the trials ranging from 3 to 199. Twenty-two trials were included in a meta-analysis. From this the odds ratio in favour of individualised homeopathy was 1.53 (95%CI 1.22 to 1.91). However the authors found that 29 of the 32 trials had unclear or high risk of bias and concluded that the finding should be interpreted with caution.

The systematic review was considered high quality (AMSTAR score 9/11).

Boehm et al 2014

A systematic review and meta-analysis of homeopathy in the treatment of fibromyalgia. The authors identified 6 controlled trials suitable for inclusion in the meta-analysis. Patient numbers ranged from 20-62. The homeopathic treatments used differed between the trials. Meta-analysis found in favour of homeopathy for three measures – tender point count, pain intensity and fatigue. Measures for sensory or affective pain or depression showed no difference to placebo. Overall quality of trial reporting and methodology in the included trials was considered low.

The systematic review was considered moderate quality (AMSTAR score 7/11).

Mathie et al 2015

A Cochrane review of homeopathic Oscillocochinum® for the prevention or treatment of influenza and influenza-like illness (ILI). This was an update of a previous Cochrane systematic review; this update limited the search to trials of the branded product. Oscillocochinum® is made from a serial dilution of a solution of wild duck heart and liver extract, which may be reservoirs and vectors of influenza vaccine. The authors found that the overall standard of trial reporting was poor. The authors concluded that there is insufficient good evidence to enable robust conclusions to be made about Oscillocochinum® in the prevention or treatment of influenza and ILI. There was no evidence of efficacy in the prevention of influenza or ILI. They did not rule out the possibility that Oscillocochinum®

could have a clinically useful treatment effect but, given the low quality of the eligible studies, the evidence is not compelling. There was no evidence of clinically important harms due to *Oscillocochinum*®. The systematic review was considered high quality (AMSTAR score 10/11).

Stub et al 2016

This meta-analysis concentrates on the reporting of adverse effects and homeopathy aggravation in clinical trials. Homeopathy aggravations are thought to be the temporary appearance of new symptoms, or a temporary intensification of existing symptoms, following a dose of a homeopathic remedy. The meta-analysis conducted was of high quality as rated utilising the AMSTAR tool (8/11). Adverse effects data from 39 RCTs were included in the meta-analysis with a total of 5902 subjects. The conclusions from the meta-analysis note that the proportion of patients experiencing adverse effects to be similar for patients randomized to homeopathic treatment compared to patients randomized to control such as placebo and conventional medicine. They also note that for the concept of 'homeopathic aggravations' the evidence was not strong enough to provide support for the existence of aggravations.

Mathie et al 2017

This systematic review and meta-analysis included RCTs of non-individualised homeopathy for any medical condition, and aimed to test the null hypothesis that non-individualised homeopathy is not distinguishable from placebo. The review was of high quality (AMSTAR score 9/11). Included trials (n=75, 54 of which could be included in the meta-analysis) were found to have high heterogeneity, and there was evidence of publication bias towards trials favouring homeopathy. Meta-analysis of all 54 trials found a small effect size in favour of homeopathy (standardised mean difference [SMD] -0.33, 95% CI -0.44 to -0.21, p<0.001).

An additional analysis was performed, taking into account the risk of bias of each individual trial, as assessed using the Cochrane risk-of-bias appraisal tool. Trials with a high (n=28) or uncertain risk of bias (n=23) retained a small effect size in favour of homeopathy (high risk of bias, SMD -0.38, 95% CI -0.50 to -0.26, p<0.001; uncertain risk of bias, SMD -0.31, 95% CI -0.51 to -0.11, p=0.002). The trials with the lowest risk of bias (n=3) found no significant effect size (SMD = -0.18, 95% CI -0.46 to 0.09, p=0.165). No significant difference was found between these three effect estimates (p=0.417). The authors concluded that the evidence did not support rejection of the null hypothesis.

Shaddel et al 2014

A systematic review of trials of homeopathy in people with intellectual disabilities included trials which enrolled patients with attention deficit hyperactivity disorder (ADHD), autism, dyslexia, and speech and social development in people with cerebral palsy.

The review was of moderate quality (AMSTAR score 5/11). Included trials (n=12) were of variable quality with Jadad scores ranging to 1 to 5 (on a possible scale of 0 to 5). No meta-analysis was performed and no trial results were presented; trial outcomes were simply presented as +, -, or ±.

There were eight trials in people with ADHD, including five which were of good quality. Three of these (total sample size 187 patients, average 24 weeks follow-up) found in favour of homeopathy while two (sample size 63, average follow-up 11 weeks) found against. Two good quality trials found no significant clinical effect of homeopathic treatment in patients with speech difficulties. All other trials were of low quality. The authors concluded that evidence is conflicting on the evidence for homeopathy for treatment of ADHD, and that there is no evidence to support the use of homeopathy for autism or speech difficulties.

Saha et al 2013

This review and meta-analysis included prospective, double-blind, randomised trials of individualised homeopathy in patients with headache and migraine. The review was of moderate quality (AMSTAR score 6/11). Included trials (n=4) had Jadad scores which ranged from 3 to 5 and were found to have significant heterogeneity. There was evidence of significant publication bias in favour of trials with significant results and positive effects. Meta-analysis found no significant difference between homeopathy and placebo (risk ratio 1.58, 95% CI 0.8 to 3.1, p=0.187). Adjustment for publication bias reduced the risk ratio to 0.98 (95% CI 0.5 to 1.9). Only one of the four included trials found a significant benefit of homeopathy compared to; this trial also had the poorest quality of the four.

The authors concluded that, due to the quality and quantity of the literature, there is no clear evidence that homeopathy is superior to placebo for treatment of headache and migraine.

Reviews cited by the BHA but not considered by the NHMRC

Summary: The reviews cited by the BHA but not considered by the NHMRC review are summarised below, however all three were scored as being of low quality using the AMSTAR tool for assessing systematic reviews.

Bellavite P et al 2006

A systematic review of homeopathy for common upper respiratory tract infections and otorhinolaryngologic conditions. Twenty-four studies were included covering eleven clinical conditions. A narrative summary of each study was provided. No attempt was made in the paper to provide a summarised overview of the evidence. Nine trials compared homeopathy against placebo, eight against conventional therapy and seven were uncontrolled. No statistical data were reported thus it is not possible to verify the statistical significance of the results. The systematic review was considered low quality (AMSTAR score 2/11).

Bergemann 2011

A systematic review assessing homeopathy for upper respiratory tract infections and allergic conditions. Twenty nine studies were identified as suitable for inclusion covering 11 clinical conditions. A total of 5062 patients were included with study size ranging from 1 to 1479. Sixteen studies were placebo controlled; in the remainder homeopathy was compared against conventional management or no control. Of the sixteen placebo-controlled studies, the author concluded that eight showed results in favour of homeopathy, however details are limited and most trials appear to have significant methodological limitations. No statistical details were provided. The systematic review was considered low quality (AMSTAR score 2/11).

Other reviews

The BHA submission included a paper summarising the results of three randomised, placebo-controlled, double blind trials of homeopathic arnica therapy in patients receiving knee surgery. A total of 343 patients having arthroscopy, artificial knee joint implantation or cruciate ligament reconstruction. No difference was seen between arnica and placebo in percentage change in knee circumference (the primary measure) in patients having arthroscopy or artificial knee joint implantation. Patients having cruciate ligament reconstruction receiving arnica showed statistically significantly less percentage increase in knee circumference than placebo. Secondary outcome measures (including pain on days 1 and 2, number of punctures and total drainage of fluid), showed no statistically significant difference between arnica and placebo for any indication other than a borderline statistically significantly less pain with arnica in patients having cruciate ligament reconstruction. There were no statistically significant differences in adverse events between arnica and placebo.

References

- UKMi Medicines Q&A Considerations when addressing questions about potential for adverse effects and drug interactions with homeopathic remedies 27 June 2017 (Available from www.sps.nhs.uk Accessed 3/11/2017)
- Australian Government National Health and Medical Research Council NHMRC Statement on Homeopathy and NHMRC Information Paper - Evidence on the effectiveness of homeopathy for treating health conditions (Available from <https://www.nhmrc.gov.au/guidelines-publications/cam02> , accessed 1/11/2017)
- Government Response to the Science and Technology Committee report 'Evidence Check 2: Homeopathy' July 2010 (Available from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216053/dh_117811.pdf , accessed 3/1/2017)
- Federal Trade Commission Enforcement Policy Statement on Marketing Claims for Over-the-Counter Homeopathic Drugs December 2016 (Available from <https://www.ftc.gov/policy/federal-register-notices/federal-trade-commission-enforcement-policy-statement-marketing> accessed 3/11/2017)
- Mathie RT, Lloyd SM, Legg LA et al. Randomised placebo-controlled trials of individualised homeopathic treatment: systematic review and meta-analysis *Systematic Reviews* 2014, 3:142
- Boehm K, Raak C, Cramer H et al Homeopathy in the treatment of fibromyalgia—A comprehensive literature-review and meta-analysis *Complementary Therapies in Medicine* (2014) 22, 731—742
- Mathie RT, Frye J, Fisher P. Homeopathic Oscillococinum® for preventing and treating influenza and influenza-like illness. *Cochrane Database of Systematic Reviews* 2015, Issue 1. Art. No.: CD001957. DOI: 10.1002/14651858.CD001957.pub6.
- Stub T, Musial F, Kristoffersen A et al Adverse effects of homeopathy, what do we know? A systematic review and meta-analysis of randomized controlled trials *Complementary Therapies in Medicine* 26 (2016) 146–163
- Mathie RT, Ramparsad N, Legg LA, Clausen J, Moss S, Davidson JR, Messow CM, McConnachie A. Randomised, double-blind, placebo-controlled trials of non-individualised homeopathic treatment: systematic review and meta-analysis. *Syst Rev*. 2017 Mar 24;6(1):63. doi: 10.1186/s13643-017-0445-3.
- Shaddel F, Ghazirad M, Bryant M. What is the best available evidence for using homeopathy in patients with intellectual disabilities? *Iran J Pediatr*. 2014 Aug;24(4):339-44.
- Saha S, Koley M. Homeopathic treatment of headaches & migraine: a meta-analysis of the randomized controlled trials. *Asian Journal of Pharmaceutical and Clinical Research*. 2013 Aug; 6(suppl 3):194-199

Bellavite P, Ortolani R, Pontarollo F, et al. Immunology and homeopathy. 4. Clinical studies – Part 1. Evidence-based Complementary and Alternative Medicine: eCAM, 2006; 3: 293–301.

Bergemann SM, Bornhöft, Bloch D, et al, Clinical Studies on the Effectiveness of Homeopathy for URTI/A (Upper Respiratory Tract Infections and Allergic Reactions). In Bornhöft G, Matthiessen PF (eds), Homeopathy in Healthcare – Effectiveness, Appropriateness, Safety, Costs. Springer, Berlin 2011.

Brinkhaus B, Wilkens JM, Lüdtker R, et al. Homeopathic arnica therapy in patients receiving knee surgery: Results of three randomized double-blind trials. Complementary Therapies in Medicine, 2006; 14: 237–246

Written by Trent Medicines Information, Leicester and Regional Drug & Therapeutic Centre, Newcastle
Contact: rtdc.rxsupp@nuth.nhs.uk
October 2017.

Appendix: search strategy

Database: EMBASE.

1	"NETWORK META-ANALYSIS"/	482
2	"META ANALYSIS"/	136068
3	"SYSTEMATIC REVIEW"/	153257
4	("meta analysis").ti,ab	132872
5	("systematic review").ti,ab	123143
6	("pooled analysis").ti,ab	10380
7	REVIEW/	2276720
8	(review).ti,ab	1585192
9	(systemat* OR pool*).ti,ab	635821
10	(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9)	3666855
11	HOMEOPATHY/	8926
12	(homeopath*).ti,ab	5859
13	(homoeopath*).ti,ab	969
14	(11 OR 12 OR 13)	10616
15	(10 AND 14)	2122
16	15 [DT FROM 2013] [English language]	395