Effectiveness of Homeopathy for Clinical Conditions: Evaluation of the Evidence

Review of Literature from Public Submissions

Prepared for the National Health and Medical Research Council Homeopathy Working Committee

by ARCH

November 2014

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List of Abbreviations

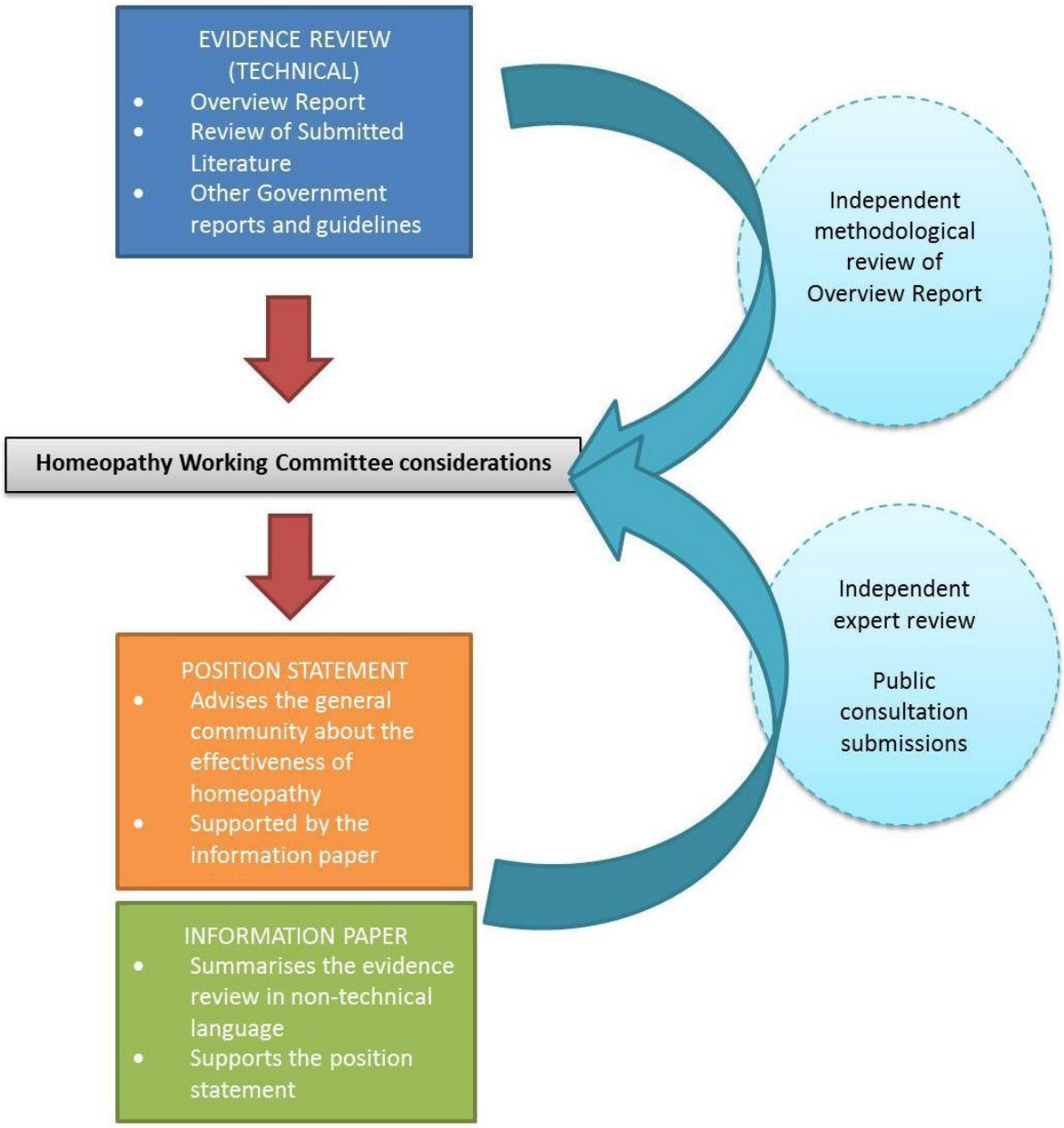
ARCH	Australian Research Centre for Health of Women and Babies
HWC	Homeopathy Working Committee
NHMRC	National Health and Medical Research Council

1 Introduction

The purpose of this *Review of Literature from Public Submissions* was to review and evaluate the individual studies submitted to the National Health and Medical Research Council (NHMRC) as potential evidence of the clinical effectiveness of homeopathy for any clinical condition. The literature was submitted by members of the public. This report accompanies the *Overview Report* and the *Review of Submitted Literature on the effectiveness of homeopathy for any clinical condition* (for which literature was submitted by the Australian Homeopathy Association, the Australian Medical Fellowship of Homeopathy and members of the public). Both the *Overview Report* and *Review of Submitted Literature* were prepared by Health Technology Analysts Pty Ltd (trading as Optum), in conjunction with the Homeopathy Working Committee (HWC).

This *Review of Literature from Public Submissions* was prepared by Adelaide Research and Innovative Pty Ltd (the evidence reviewer, Australian Research Centre for Health of Women and Babies (ARCH)), in conjunction with the HWC. The three reports will be considered in the development of an Information Paper to summarise the evidence on the effectiveness of homeopathy for the treatment of clinical conditions. They will also be considered in the development of a Position Statement to declare NHMRC's position on homeopathy as a treatment for clinical conditions, including the rationale for that position (**Figure 1)**.

Figure 1 Effectiveness of homeopathy for clinical conditions: project flow chart



2 Review of literature from public submissions

2.1 Methodology

2.1.1 Study eligibility

All of the submitted literature was assessed and categorised as either 'in scope' or 'out of scope'. 'In scope' literature included articles that addressed the primary clinical research question:

- For patients with a specific clinical condition, is homeopathy an effective treatment, compared with no homeopathy/other treatments?

For the purpose of this evaluation, literature addressing the following topics was considered 'out of scope' and was not considered any further in the evaluation:

- Homeopathy for preventative/prophylactic use
- Homeopathy used in conjunction with other therapies, where the design of the study confounds the results (i.e. where the specific effect of homeopathy cannot be determined)

All 'in scope' literature was graded according to NHMRC's levels of evidence (NHMRC, 2009). The following *a priori* exclusion criteria were applied to the 'in scope' literature:

- Systematic review already included in the *Overview Report*
- Systematic review had been considered, but subsequently excluded from the *Overview Report* for reasons such as wrong intervention, wrong outcomes, study not published in the English language and superseded systematic review by the same authors
- Study already included within a systematic review in the *Overview Report* or already included in the *Review of Submitted Literature*
- *Wrong research type or publication type.* Studies that were not systematic reviews, meta-analyses or prospectively designed and controlled studies (including randomised controlled trials, pseudo-randomised controlled trials, non-randomised controlled trials and prospective cohort studies) were excluded. Editorials, comments, book chapters, animal studies, correspondence, and news items were excluded. Studies were also excluded if they were not reported in full (e.g. research or systematic review protocols, conference proceedings, articles published in abstract form)
- *Wrong intervention*. Study did not investigate the effect of homeopathy
- *Wrong outcomes*. Study did not include outcomes relevant to the primary research question
- Study not published in the English language

The excluded articles are documented, with their level of evidence (where it could be assigned) and reasons for exclusion in **Appendix A.**

2.1.2 Critical appraisal and data extraction

Full citation details for the final list of included studies are provided in **Appendix B**. Each included study from the submitted literature was graded according to NHMRC's levels of evidence (NHMRC, 2009) and then quality appraised and the data extracted.

Quality appraisal of the included Level II/III-1 studies (randomised and pseudo randomised controlled trials) was carried out using the Cochrane Collaboration's Risk of Bias tool (Higgins and Green, 2011). This tool consists of six domains and assesses five specific biases (and other potential sources of bias), shown in **Table 1**. For Level III-2 studies (non-randomised studies, such as prospective cohort studies) as guided by the Cochrane Handbook, the general structure of the Risk of Bias tool (shown in **Table 1**) was followed. We also referred to the Newcastle-Ottawa Scale for additional guidance on the assessment of the methodological quality of non-randomised studies (Wells et al. 2014)

We have made explicit judgements about whether studies were thought to be at an overall low, moderate or high risk of bias according to the criteria given in the Cochrane Handbook (Higgins and Green, 2011), considering the likely magnitude of bias (assessed across the six domains) and whether it was likely to impact on the findings. The quality assessment forms for the included studies are presented in **Appendix C**.

Table 1 The Cochrane Collaboration's tool for assessing risk of bias (Higgins and Green 2011)

Domain	Description	Review authors' judgement
Sequence generation ***(selection bias)***	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment ***(selection bias)***	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors ***(performance and detection bias)***	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data ***(attrition bias)***	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting ***(reporting bias)***	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of	State any important concerns about bias not	Was the study

bias	addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	apparently free of other problems that could put it at a high risk of bias?

Data extraction forms and evidence summary tables were used to capture information relevant to the review of the effectiveness of homeopathy in accordance with NHMRC standards. Extracted information included:

- General study details (citation, study design, evidence level, country and setting)
- Affiliations/sources of funds and conflicts of interest
- Internal and external validity considerations
- Participant details, including key demographic characteristics
- Primary, secondary and other study outcome results

The data were extracted by one evidence reviewer, and discussed with a second reviewer as necessary. Data extraction forms for all of the included studies are presented in **Appendix C**.

2.2 Results of the review of evidence from public submissions

2.2.1 Overview of the submitted literature

A total of 153 articles/citations were submitted to NHMRC during public consultation. A review of the 153 titles (and abstracts if available and appropriate) found that a large majority of the citations (64 articles) were of the wrong research or publication type. A further 16 articles had already been included in the *Overview Report* or *Review of Submitted Literature* (13 primary studies, three systematic reviews). Eight articles were excluded as they covered the wrong intervention (two articles), outcomes (two articles) or were not published in the English language (four articles); six were excluded as they assessed homeopathy for prophylaxis/preventative use (**Table 2**).

Table 2 Summary of the application of the exclusion criteria to evidence from public submissions based on title/abstract only

Review of evidence from public submissions	**Total number of articles**
Total number of submitted articles /citations	**153**
Wrong research type or publication type	64
Primary study already included in the *Overview Report* or the *Review of Submitted Literature*	13
Systematic review already included in the *Overview Report*	3
Wrong intervention	2
Wrong outcomes	2
Not in English	4
Out of scope: homeopathy for prophylactic use	6
Citations excluded after title/abstract review[a]	**94**
Number of articles reviewed in full text	**59**

[a]Excluded articles are documented, with their reasons for exclusion, in **Appendix A.**

This resulted in 59 potentially relevant articles that were not included in the *Overview Report* or *Review of Submitted Literature*. Upon full text review of these 59 articles, four articles were excluded as they were the wrong research type or publication type. Two articles were excluded as they were meta-analyses of primary studies already included in the *Overview Report* or the *Review of Submitted Literature*. Seven articles were excluded as they covered the wrong intervention (three articles), outcomes (three articles), or the full text was not published in English (one article); three additional articles were excluded as they examined homeopathy used in conjunction with other therapies, where the design of the study confounds the results and the specific effect of homeopathy cannot be determined, and one was excluded as it assessed homeopathy for prophylactic use. Three articles were submitted during public consultation that represented a single study (Maronna 2000, Porcher-Spark 2000, Strosser 2000). This resulted in a final total of 40 included studies (*42 articles*) – 36 Level II/III-1 studies and four Level III-2 studies (**Table 3**).

Table 3 Summary of the application of the exclusion criteria to evidence from public submissions based on full text review

Review of evidence from public submissions	**Total number of articles**
Number of articles reviewed in full text	**59**
Wrong research type or publication type	4
Meta-analysis of primary studies already included in the *Overview Report* or the *Review of Submitted Literature*	2
Wrong intervention	3
Wrong outcomes	3
Not in English	1
Out of scope: homeopathy used in conjunction with other therapies, where the design of the study confounds the results and the specific effect of homeopathy cannot be determined	3
Out of scope: homeopathy for prophylactic use	1
Articles excluded after full text review[a]	**17**
Final number of included studies	*42 articles, referring to* **40 studies**

[a]Excluded articles are documented, with their reasons for exclusion, in **Appendix A.**

The included studies assessed the effectiveness of homeopathy for the treatment of patients with a total of 35 different clinical conditions, compared with no homeopathy/other treatments. For 14 of the conditions, reported in 16 studies, (rheumatoid arthritis, influenza-like illness (ILI), menopausal hot flushes, rhinosinusitis, oral dryness, psychophysiological onset insomnia, stress, dermatological reactions (radiotherapy), warts, chronic low back pain, upper respiratory tract infection (URTI), otitis media, ankle sprain, and osteoarthritis of the knee) the same or similar clinical conditions were examined in the *Overview Report*. The remaining clinical conditions were not evaluated in the *Overview Report*, often as there were no relevant systematic reviews.

The majority of the 16 included studies assessing homeopathy for the treatment of clinical conditions already considered in the *Overview Report* contained limitations that should be considered in the evaluation of the evidence. In general, the evidence base for homeopathy was not of high quality and many of the individual studies were poorly designed, conducted and/or reported. In addition, many of the studies were small in size; some were insufficiently powered to detect differences in clinically important outcomes, and many based conclusions on subjectively measured outcomes. Furthermore, some studies investigated individualised homeopathy (where the treatment plan is developed specifically for the patient), increasing the complexity of determining the efficacy of specific remedies/regimens.

For the majority of studies (15/16) some benefits with homeopathy were reported compared with placebo or no treatment (or no difference compared with an active control). However, it is possible, and in many cases likely, that the conclusions will change in light of further studies. Of the 16 studies, Pach et al. 2011 was considered to be of the highest methodological quality (low risk of bias overall). The trial showed that verum injections were superior to no treatment injections, but not to placebo injections for the treatment of chronic low back pain. The only other trial to observe no improvements with homeopathy (Brien et al. 2011; low risk of bias overall) reported benefits associated with the homeopathic consultation process (rather than the remedies themselves) for rheumatoid arthritis. Summaries of the results from these 16 trials are given below (**Table 4**).

The remaining 24 included studies assessing homeopathy for the treatment of clinical conditions not considered in the *Overview Report* similarly contained limitations that should be considered in the evaluation of the evidence. Largely, the evidence base was not of high quality; similar to the trials assessing conditions already included in the *Overview Report*, many of these studies were small in size, poorly designed, conducted and/or reported. Furthermore, it is important to highlight that these articles were not identified using a systematic methodology (and no systematic reviews of these clinical conditions were included in the *Overview Report*), increasing the potential for bias within this dataset.

For the majority of these studies (22/24) some benefits with homeopathy were reported compared with placebo, no treatment, or standard care (or no difference compared with an active control). In the trial considered to be of the highest methodological quality in this group of studies (Dean et al. 2012; low risk of bias overall), no difference was shown between Kali phos (homeopathy) and placebo in the treatment of mental fatigue. One further trial (Sencer et al. 2012; moderate risk of bias overall) reported no benefits from Traumeel (homeopathy) in the treatment of mucositis in children undergoing haematopoietic stem cell therapy. Summaries of the results from these 24 studies are given below (**Table 5**).

Table 4 Summary of results from included studies (N=16) assessing conditions already considered in the Overview Report

Study ID	Condition, N*	Intervention and comparison	Results	ROB**
Brien 2011	Rheumatoid arthritis, N=83 randomised; N=77 analysed	Consultation and IH vs. consultation and homeopathic complex vs. consultation and placebo vs. homeopathic complex vs. placebo	No significant improvements with homeopathy (IH/complex) vs. placebo for primary outcomes (ACR 20% improvement and 35% improvement in global assessment) or secondary outcomes; clinically relevant benefits seen with, and attributed to homeopathic consultations not remedies **SUMMARY: No significant improvement**	Low
Chakraborty 2013b	Influenza-like illness, N=447	LM potency IH vs. centesimal potency IH vs. placebo	Significantly earlier improvements in subjectively measured symptom scores with IH LM/centesimal potency (i.e. day 2 vs. day 5); fewer complications/sequel with IH **SUMMARY: Significant improvement**	Moderate to high
Colau 2012	Menopausal hot flashes, N=108 randomised; N=101 analysed	BRN-01 tablets vs. placebo	Significantly lower AUC for 12 week global HFS (primary outcome) with homeopathy; no significant differences for other outcomes (i.e. symptom severity; QOL; adverse events) **SUMMARY: Significant improvement only for HFS AUC**	Moderate
Relton 2012	Menopausal hot flushes, N=48 randomised; 44 analysed	'Offer' of homeopathy vs. no offer	Mean change in HFFSS favoured the 'offer' of homeopathy group; majority of secondary outcomes (medication use; quality of life; GCS (menopausal symptoms); MYMOP primary symptom score) favoured offer group at 36 week follow up; MYMOP wellbeing score favoured no offer group **SUMMARY: Improvement, significance not reported**	Moderate
Friese 2007	Acute rhinosinusitis, N=144	Homeopathic complex vs. placebo	Significantly lower sum of symptom scores with homeopathy at 7 days (primary outcome); benefits for secondary outcomes (significance not reported) (i.e. symptoms; improvement noted; complete recovery in 7 days; satisfaction; tolerability) **SUMMARY: Significant improvement**	High
Haila 2005	Oral dryness, N=29 randomised; N=28 analysed	IH vs. placebo	Significantly higher VAS scores with IH for subjective symptoms (dryness while eating, need to sip liquid for swallowing, need to drink during night, amount of salivation); no clear differences for unstimulated/stimulated salivary flow **SUMMARY: Significant improvement for subjective symptoms**	Moderate to high

Harrison 2013	Psychophysiological onset insomnia (males), N=34 randomised; N=28 analysed	Homeopathic complex vs. placebo	Significant difference in favour of homeopathy for bedtime somatic and cognitive arousal (measured by PSAS), and sleep onset latency at day 28 (sleep diary) **SUMMARY: Significant improvement**	Moderate to high
Hellhammer 2013	Stress (women), N=40	dysto-loges S tablets (verum) vs. placebo	No significant differences in primary outcome (cortisol) or other physiological or psychological parameters in response to TSST (day 15) between groups, except for lower NE in verum group; no differences in psychological parameters concerning sleep and life quality, except improved sleep quality with verum (not seen with placebo) **SUMMARY: Significant improvement in NE and sleep quality only (mainly no improvement)**	Low to moderate
Kulkarni 1998	Dermatological reactions to radiotherapy, N=82	Cobaltum 30 vs. Causticum 30 vs. placebo	Significantly lower average grade of radiation reactions overall with homeopathy (and lower average grades for reactions on the head and neck; thorax; pelvis) **SUMMARY: Significant improvement**	High
Manchanda 1997	Warts, N=124 randomised; N=104 analysed	Homeopathy (thuja, ruta, calcarea carb and causticum) vs. placebo	Higher proportion *"improved"* with homeopathy **SUMMARY: Improvement, significance not reported**	High
Pach 2011	Chronic low back pain, N=150 randomised; N=142 analysed	Disci/Rhus toxicodendron compositum (verum) vs. placebo vs. no treatment	Significantly lower back pain (VAS) at 8 weeks (primary outcome) with verum vs. no treatment; no difference between verum and placebo; few other differences between groups shown (SES; PDI, HFAQ; SF-36 QoL scores; adverse effects) and only between verum vs. no treatment **SUMMARY: Significant improvement vs. no treatment, not vs. placebo**	Low
Steinsbekk 2005	URTI (children), N=169 randomised; N=142 analysed	IH vs. waiting list control	Significantly lower total symptom score (primary outcome) and fewer days with URTI symptoms in IH group; no significant differences for other outcomes (antibiotics, analgesics, antipyretics, visits to a doctor, days with other illness, and parents with work absence) **SUMMARY: Significant improvement in symptoms (scores/days) but not for other outcomes**	Moderate to high
Zanasi 2014	Acute cough in URTI (adults), N=80	Homeopathic syrup vs. placebo syrup	Significantly lower VCD cough score (primary outcome) at 4 and 7 days for homeopathy group (not at 2 and 14 days), and fewer participants in homeopathy group with VCD score > 2 at 4 and 7 days (not at 2 and 14 days); significantly lower sputum viscosity at day 4; no difference in patients' subjective evaluation or absolute improvement in sputum viscosity	Low

			SUMMARY: Significant improvement in cough severity (days 4 and 7 only) and sputum viscosity at day 4; no improvement at day 2/14 or for patients' evaluation	
Taylor 2011	AOM (children), N=120 randomised; N=94 analysed (primary outcomes)	Homeopathic ear drops vs. standard care	No significant difference in ETG-5 scores (primary outcome) at assessments 1 and 4-10; significantly lower scores for homeopathy group at assessment 2 and 3. No differences for majority of outcomes (AOM-FS scores, FSIIR scores, return visits to doctor/prescriptions filled; adverse events) (expect homeopathy group less likely to have diarrhoea and have 'hyper' behaviour; and had less symptomatic medication use on day 3) **SUMMARY: Significant improvement in symptoms in early period but not sustained and not for majority of other outcomes**	Moderate to high
González de Vega 2013	Acute ankle sprain, N=449 randomised; N=420 analysed	Traumeel gel vs. Traumeel ointment vs. diclofenac gel	No significant differences between groups for primary outcomes (percentage reduction in pain (VAS) and improvement in FAAM ADL at 7 days); no significant differences for all secondary outcomes at day 14/42 **SUMMARY**: **No significant difference shown**	Moderate to high
Maronna 2000	Osteoarthritis of knee, N=121 randomised; N=114 analysed	Zeel comp. vs. diclofenac	No significant difference between groups after 6 weeks for primary outcome (WOMAC Osteoarthritis Index: pain, stiffness, functionality); no differences in patient assessment of efficacy and tolerance **SUMMARY: No significant difference shown**	Moderate to high

Abbreviations: ACR: American College of Rheumatology; AOM: Acute Otitis Media; AOM-FS: Acute Otitis Media Faces Scale; AUC: areas under the curve; ETG-5: Ear Treatment Group-5 Symptom; FAAM ADL: Foot and Ankle Ability Measure Activity of Daily Living; FSIIR: Functional Status II-Revised; GCS: Greene Climacteric Scale HFAQ; Hannover Functional Ability Questionnaire; HFFSS: hot flush frequency and severity scale; HFS: Hot Flash Score; IH: individualised homeopathy; MYMOP: Measure Your Medical Outcome Profile; N: number; NE: norepinephrine; PDI: Pain Disability Index Scale; PSAS: Pre-sleep Arousal Scale; QA: quality assessment; QoL: quality of life; SES: Pain Perception Scale; SF-36: quality of life (Medical Outcome Study-Short Form 36); TSST: Trier Social Stress Test; URTI: upper respiratory tract infections; VAS: visual analogue scale; VCD: verbal category descriptive; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index. *N: number of participants; **ROB: Risk of Bias according to criteria outlined in the Cochrane Handbook of Systematic Reviews.

Table 5 Summary of results from included studies (N=24) assessing conditions not considered in the Overview Report

Study ID	Condition, N*	Intervention and comparison	Results	ROB**
Bell 2011	Coffee-related insomnia, N=70 enrolled; N=59 received treatment; N=54 analysed	Combined remedies, Nux Vomica, Coffea Cruda vs. placebo	Significant increase in total sleep time and other sleep parameters (NREM, stage 2 sleep, SWS) with the homeopathic remedies combined and individually; significant increase in awakenings and type 2 arousals, with homeopathy, though lower POMS fatigue ratings with homeopathy; no difference in PSQI **SUMMARY: Significant increase in sleep time and other sleep parameters; increase in awakenings/disruption, though lower fatigue ratings**	Moderate to high
Belon 2007	Arsenic toxicity, N=39 randomised; N=25 analysed	Arsenicum Album-30 vs. placebo	Significant reduction in arsenic content in blood but not urine at 2 months in favour of homeopathy; significant improvements in PCV, neutrophil, eosinophil, ALT, LPO, GGT readings with homeopathy at 2 months; no significant differences for Hb, ESR, triglycerides, creatinine, GSH, AST or G6PD readings **SUMMARY: Significant improvement in some biochemical/pathophysiological parameters but not others; reduction in arsenic in blood, not urine**	High
Khuda-Bukhsh 2011	Arsenic toxicity, N=28 randomised; N=14 analysed	Arsenicum Album LM 0/3 vs. placebo	No significant differences for arsenic content in blood or urine at 2 months, for biochemical parameters (AcP; AlkP; ALT; AST; LPO; GSH; GGT; G6PD) or pathophysiological parameters (blood glucose; Hb; ESR; cholesterol; HDL-C; LDL-C; triacylglycerol; creatinine; PCV; ANA titre) except for lymphocyte viability which was significantly improved with homeopathy **SUMMARY: No significant improvements**	High
Bignamini 1991	Anal fissures, N=31	Nitricum acidum 9CH vs. placebo	No significant differences seen for rectal pain (proctodynia), bleeding, itching or lesions but significant improvements for burning sensation and subjective opinion of treatment for the homeopathy group **SUMMARY: Significant improvements for burning sensation and opinion of treatment efficacy; not for other outcomes**	High
Chakraborty 2013a	Haemorrhoids, N=279 randomised; N=278 analysed	IH vs. placebo	Significant improvements in AUC for bleeding, pain, heaviness and itching (but not discharge) at 90 days (primary outcomes) with homeopathy; significant improvements for all secondary outcomes (all except QOL social domain) **SUMMARY: Significant improvement**	Moderate
Chand 2014	Multidrug resistant tuberculosis,	IH and standard drug regimens vs. placebo and standard drug	No significant differences in sputum and culture conversion rates (or other outcomes: weight gain, ESR reduction, Hb increase, symptom score); significantly more patients with chest x-ray improvement with homeopathy. For culture positive patients, improvements in weight gain,	Moderate

	N=120	regimens	ESR, Hb increase **Significant improvement in chest x-ray, but not sputum/culture conversion or other outcomes; further significant improvements for culture positive patients**	
Clark 2000	Plantar fasciitis, N=18 randomised; N=14 analysed	Ruta graveolens vs. placebo	Significantly faster resolution of pain in the homeopathy group **SUMMARY: Significant improvement**	High
Dean 2012	Mental fatigue, N=86 (crossover trial)	Kali phos vs. placebo	No significant differences seen for primary outcomes (Stroop Colour-Word test or mental fatigue scores) **SUMMARY: No significant differences shown**	Low
Derasse 2005	Acute febrile infections in children, N=198	Viburcol vs. acetaminophen	Treatment and tolerability were significantly more likely to be rated excellent by carers with homeopathy; no significant/clear differences seen for individual symptoms or other outcomes **SUMMARY: Significantly more likely to be rated excellent by carers; no differences in other outcomes**	High
Ernst 1990	Varicose veins, N=61 (122 legs)	Poikiven vs. placebo	Venous filling time significantly improved at 24 days with homeopathy (but not at 12 days, and not leg volume, calf circumference, haematocrit, plasma or blood viscosity); all symptoms were significantly improved with homeopathy **SUMMARY: Significant improvement**	High
Issing 2005	Vertigo, N=170 randomised; N=154 analysed	Vertigoheel vs. Ginkgo biloba	No significant differences for dizziness questionnaire score, frequency, duration and intensity of vertigo (primary outcomes) or for other outcomes except for the 'combined test' which was significantly in favour of homeopathy **SUMMARY: No significant differences, except for 'combined test'**	Moderate to high
Weiser 1998	Vertigo, N=119 randomised; N=105 analysed	Vertigoheel and placebo vs. betahistine hydrochloride and placebo	No significant differences shown for primary outcomes (frequency, duration and intensity of vertigo attacks) or for any secondary outcomes (QOL scores; vertigo-specific questionnaire scores; global assessment of efficacy and tolerability) **SUMMARY: No significant difference shown**	Moderate
Wolschner 2001	Vertigo, N=774	Vertigoheel vs. dimenhydrinate	No clear differences seen for number, intensity or duration of vertigo attacks, or other outcomes (i.e. symptoms; improvement; compliance; adverse effects; tolerability) **SUMMARY: No differences shown; significance not reported**	High
Mourão 2013	Chronic periodontitis,	Homeopathy and non-surgical	Significant improvement seen with homeopathy (not control) for CAL (main outcome), but no differences seen for other outcomes (BOP, PI, PD or serological parameters; except for a	Moderate to high

	N=40	periodontal therapy vs. non-surgical periodontal therapy	significant reduction in HDL-C with homeopathy) **SUMMARY: Significant improvement for CAL, but not for other outcomes**	
Naidoo 2013	Cat allergy, N=30	Cat saliva 9cH and Histaminum 9cH vs. placebo	Significant improvements in wheal diameter score (primary outcome), flare reaction scale and itchiness with homeopathy **SUMMARY: Significant improvement**	Moderate to high
Pellow 2013	Diaper dermatitis, N=40 randomised; N=37 analysed	Homeopathic-medicated milking cream vs. non-medicated milking cream	No significant improvements for genital region or right inner thigh (percentage area affected and rash severity); significant improvements for left inner thigh, right buttock and left buttock **SUMMARY: Significant improvements for some regions, not others**	Moderate to high
Pomposelli 2009	Diabetic polyneuropathy, N=77	IH vs. conventional therapy	Significant improvement in DNS score at 6 months for homeopathy group (not control group) but no significant difference at 12 months (primary outcome); no significant differences in other outcomes (i.e. electrophysiological conductivity; weight; glucose; blood pressure) except for some improvements in QOL components with homeopathy **SUMMARY: Significant improvement in DNS at 6 months (not 12 months), and some QOL components**	High
Robertson 2007	Post-tonsillectomy pain, N=190 randomised; N=111 analysed	Arnica montana vs. placebo	No significant difference for primary outcome (pain on VAS) at days 1-9, 12 and 13; significant improvement for homeopathy group on days 10, 11 and 14, and significantly larger 'drop' in score from day 1-14; no significant difference for other outcomes (i.e. analgesia consumption; return to work; return to swallowing; visits to GP; antibiotic use) **SUMMARY: Significant difference in pain score at day 14 (but not before day 9); no differences for other outcomes**	Moderate
Saha 2013	Essential hypertension, N=150 randomised; N=132 analysed	IH vs. placebo	Significant improvements in blood pressure with homeopathy (primary outcome) (SBP and DBP at 3 and 6 months) **SUMMARY: Significant improvements**	Moderate to high
Saruggia 1992	End-stage renal failure, N=35 (crossover trial)	China ruba 9CH vs. placebo	Significant improvements for headache, lethargy and asthenia with homeopathy, but no significant improvements for nausea and vomiting **SUMMARY: Significant improvements for some symptoms, not others**	High
Schmidt 1996	Subcutaneous	Arnica 1X vs. Arnica	Better injury scores reported for the homeopathy groups compared with placebo	High

	mechanical injury, N=337; N=141 analysed	6C vs. placebo (petroleum jelly)	**SUMMARY: Improvement, significance not reported**	
Sencer 2012	Mucositis in stem cell therapy, N=195 randomised; N=190 analysed	Traumeel vs. placebo	No significant difference for AUC of Walsh score to day 20 (primary outcome); no significant differences for other outcomes (i.e. WHO oral mucositis score; morphine doses; parental nutrition; nasogastric feeding; mortality; adverse events) **SUMMARY: No significant improvement**	Moderate
Totonchi 2007	Post-rhinoplasty ecchymosis and oedema, N=48	Arnica vs. corticosteroids (intravenous and oral tapering) vs. no treatment	No significant difference in ecchymosis extent or intensity at day 2 (oedema significantly less in homeopathy and corticosteroid groups vs. no treatment group at day 2); extent and intensity of ecchymosis significantly lower/less at day 8 in homeopathy and no treatment groups vs. corticosteroid group **SUMMARY: No significant improvement with homeopathy compared with no treatment for extent and intensity of ecchymosis (except for less oedema on day 2)**	Moderate to high
Villanueva 2001	Malnutrition in children, N=99	Homeopathic complex vs. no treatment	Significantly more children recovered to normal weight in homeopathy group; significant improvement for children aged 1-14 years, but not 15-19 years **SUMMARY: Significant improvement for children aged 1-14 (not 15-19)**	High

Abbreviations: AcP: acid phosphatase; AlkP: alkaline phosphatase; ALT: alanine aminotransferase; ANA: anti-nuclear antibody; AST: aspartate aminotransferase; AUC: area under the curve; BOP: bleeding on probing; CAL: clinical attachment level; DBP: diastolic blood pressure; DNS: diabetic neuropathy symptom; ESR: erythrocyte sedimentation rate; GGT: gamma glutamyl transferase; GP: general practitioner; GSH: reduced glutathione; G6PD: glucose-6-phosphate dehydrogenase; Hb: haemoglobin; HDL-C: high-density lipoprotein cholesterol; IH: individualised homeopathy; LDL-C: low-density lipoprotein cholesterol; N: number; LPO: lipid peroxidase; NREM: non rapid eye movement sleep; PCV: packed call volume; number; PD: probing depth; PI: plaque index; POMS; profile of mood states scale; PSQI: Pittsburgh sleep quality index; QOL: quality of life; SBP: systolic blood pressure; SWS: slow wave sleep; VAS: visual analogue scale; WHO: World Health Organization. *N: number of participants; **ROB: Risk of Bias according to criteria outlined in the Cochrane Handbook of Systematic Reviews.

Conditions already considered in the Overview Report

2.2.2 Rheumatoid arthritis

One randomised controlled trial (Level II) was identified that assessed whether any benefits from adjunctive homeopathic intervention in patients with rheumatoid arthritis were due to homeopathic consultation, homeopathic remedies, or both (Brien et al. 2011) (**Table 6**). The trial randomised 83 adult patients with a diagnosis of rheumatoid arthritis for more than two years, to either homeopathic consultation or no consultation; patients in the consultation group were further randomised to individualised homeopathy, rheumatoid complex or placebo; the no consultation group was further randomised to rheumatoid complex or placebo. This trial was judged to be at a low risk of bias overall. Adequate methods were used to generate the random sequence (computer-generated) and to conceal allocation (sequentially ordered sealed envelopes) in this trial. While patients and study staff were aware of the consultation allocation (due to the nature of that intervention), a placebo was used to blind treatment allocation (homeopathy vs. placebo); and blinding was evaluated and considered 'secure' for the study nurse, participants and the homeopaths. The risk of attrition bias was judged to be low, with six (7%) of study participants dropping out before receiving treatment, and therefore not included in the intention-to-treat analyses. While there was no access to a published trial protocol, the risk of reporting bias was considered low, with the published report clearly pre-specifying (and reporting on) primary and secondary outcomes, which were those documented in the online trial registration.

In Brien et al. (2011), no significant improvements for patients receiving homeopathic remedies (individualised homeopathy/rheumatoid complex) were observed for the co-primary outcomes: patients achieving American College of Rheumatology (ACR) 20% improvement criteria, and patients achieving 35% improvement in global assessment (GA) (on a visual analogue scale (VAS)). No clear differences between the individualised homeopathy/rheumatoid complex groups and placebo groups were shown for other outcomes, including: 28-joint Disease Activity Score (DAS), tender and swollen joint count, pain, patient and physician GA, inflammatory markers, positive and negative mood, and adverse effects. However, the study reported that patients receiving a placebo, compared with individualised homeopathy, had significantly improved mean patient GA (P=0.008). A number of differences were seen for secondary outcomes between the consultation and no consultation groups. The authors concluded that *"Homeopathic consultations but not homeopathic remedies are associated with clinically relevant benefits for patients with active but relatively stable RA."*

Table 6 Evidence summary table of Brien et al. (2007) on the effectiveness of homeopathy for the treatment of rheumatoid arthritis

Study ID	Brien 2011
Level of evidence	Level II
Risk of bias	Low risk of bias
N	83 randomised, 77 analysed
Patient population	Patients aged > 18 years; diagnosis of RA for > 2 years [1987 ACR guidelines]; current disease activity minimum DAS-28 score > 2.6; patient GA score ≥ 30 mm; stable medication for > 3 months
Intervention	1) Consultation and individualised homeopathy 2) Consultation and rheumatoid complex

	4) No consultation and rheumatoid complex
Comparator	3) Consultation and placebo 5) No consultation and placebo
Outcomes	**Results**
Achieved ACR20 (N, %)	No significant differences
Achieved 35% patient GA (N, %)	No significant differences
Rheumatological measures (mean, SD)	
DAS-28	No significant differences, except significant improvement with consultation vs. no consultation
Swollen joint count	No significant differences, except significant reduction with consultation vs. no consultation
Tender joint count	No significant differences
Current pain (VAS)	No significant differences, except significant reduction with consultation vs. no consultation
CRP (mg/L)	No significant differences
ESR (mm/hour)	No significant differences
HAQ	No significant differences
Patient GA	No significant differences
Physician GA	No significant differences
Other measures (mean, SD)	No significant differences
Positive mood (PANAS)	No significant differences
Negative mood (PANAS)	No significant differences, except significant improvement with consultation vs. no consultation
MYMOP	No significant differences
Weekly pain scores (VAS)	No significant differences, except significant reduction with consultation vs. no consultation
Weekly GA	No significant differences, except significant improvement with placebo vs. individualised homeopathy; and consultation vs. no consultation
Adverse events (serious, non-serious and patient attribution) (N, %)	No significant differences

Abbreviations: ACR: American College of Rheumatology; ACR20: American College of Rheumatology 20% improvement criteria; CRP: c-reactive protein; DAS-28: Disease Activity Score 28; ESR: erythrocyte sedimentation rate; GA: global assessment; HAQ: Health Assessment Questionnaire; mg/L: milligrams per litre; mm/hour: millimitres per hour; MYMOP: Measure Yourself Medical Outcome Profile; N: number; PANAS: Positive and Negative Affect Schedule; RA: rheumatoid arthritis; SD: standard deviation; VAS: visual analogue scale

2.2.3 Influenza-like illness

One randomised controlled trial (Level II) was identified that assessed individualised homeopathy (LM potency and centesimal potency) for the treatment of ILI (Chakraborty et al. 2013b) (**Table 7**). The trial randomised 447 participants aged 12 to 60 years, who had presented within 36 hours of onset of ILI (characterised by abrupt onset of fever, with at least one respiratory symptom and one 'constitutional symptom') to the three groups (LM potency individualised homeopathy; centesimal potency individualised homeopathy; or placebo). This trial was judged to be at a moderate to high risk of bias overall. While adequate methods were used to generate the random sequence

(computer-generated), the methods for concealing allocation were not detailed, and thus the risk of selection bias was judged as unclear. While a placebo was used, the trial was described as *"single blind,"* (no further details provided) and thus the risk of performance bias was judged to be unclear, and the risk of detection bias was judged to be high. The risk of attrition bias was judged to be unclear, with some suggestion that there were more 'drop outs' in the placebo group (with more patients being *"referred due to persistent high fever"*: nine in placebo group vs. five in LM group vs. two in Centesimal group); data were replaced with the using last-observation-carried-forward method, and the impact that this may have had on the results is not clear. The risk of reporting bias was judged to be high, with data for the placebo group incompletely reported (and reported in the Discussion not Results); similarly data comparing the two homeopathy groups was not reported in sufficient detail: *"there was no statistically significant difference of treatment outcome between LM and Centesimal treatment groups."* The authors noted that as paracetamol was able to be used in the homeopathy groups where temperature did not *"come down,"* that the result seen for the earlier improvement in fever may not be a *"pure effect of homeopathic treatment on reducing the temperature."*

In Chakraborty et al. (2013b) it was reported that both treatment groups (LM and Centesimal) had improvements in complaints (fever, headache, myalgia, malaise, sore throat, fatigue, nasal complaints, chill, sweat, cough) significantly earlier than the placebo group (i.e. second day of follow up versus fifth day for most complaints). The authors also reported that the treatment groups required less paracetamol (for persisting fever), and that the complication/sequel rate (bronchitis, sinusitis, asthma, and tracheobronchitis) was significantly lower in the intervention groups. The authors concluded that *"The study revealed the significant effect of individualized homoeopathic treatment in the patients suffering from ILI with no significant difference between LM and Centesimal groups."*

Table 7 Evidence summary table of Chakraborty et al. (2013b) on the effectiveness of homeopathy for the treatment of influenza-like illness

Study ID	Chakraborty 2013b
Level of evidence	Level II
Risk of bias	Moderate to high risk of bias
N	447
Patient population	Patients of either sex, 12 to 60 years, presenting within 36 hours of onset of ILI characterised by abrupt onset of fever (≥ 100.4°F or 38°C body temperature) with at least one respiratory symptom (cough, sore throat, or nasal symptom) and at least one constitutional symptom (headache, malaise, myalgia, sweats, chills, or fatigue)
Intervention	Individualised homeopathy **LM potency:** Patients had treatment initiated with 0/1 potency, followed by next higher potency as per need. **Centesimal potency:** Patients had treatment initiated in 30C potency. The indicated medicines were repeated every few minutes to hours depending upon the requirement of the patient.
Comparator	Placebo: globules impregnated with non‑succussed dispensing alcohol
Outcomes	**Results**
Day of significant improvement for:	Significantly earlier improvement in LM and Centesimal

fever, headache, myalgia, malaise, sore throat, fatigue, nasal complaints, chills, sweat, cough (median, IQR)	groups compared with placebo, except for nasal complaints which was significant in the LM group only
Paracetamol requirement (N, %)	Less required in LM and Centesimal groups compared with placebo (significance not reported)
Complications/sequel of influenza (bronchitis, sinusitis, bronchial asthma, tracheobronchitis) (N, %)	Significantly fewer in LM and Centesimal groups compared with placebo

Abbreviations: ILI: influenza-like illness; IQR: interquartile range; N: number

2.2.4 Menopausal hot flashes/flushes

Two Level II studies were identified assessing the effects of homeopathy on the treatment of menopausal hot flashes/flushes (Colau et al. 2012 and Relton et al. 2012)

Colau et al. (2012) was a multi-centre randomised controlled trial that assessed the effects of 12 weeks of treatment with BRN-01 tablets (a registered homeopathic medicine) on menopausal hot flashes (**Table 8**). The trial randomised 108 women aged at least 50 years (with at least five hot flashes a day causing significant negative life effect, socially or professionally), to either BRN-01 tablets or placebo tablets. This trial was judged to be at a moderate risk of bias overall. Adequate methods were used to generate the random sequence (computer-generated) and conceal allocation, and thus the risk of selection bias was judged as low. Women and study personnel were blinded with the use of an identical placebo, however, compliance was significantly lower in the placebo group; thus the risks of performance and detection bias were judged to be unclear. The risk of attrition bias was judged to be low with few exclusions post-randomisation (and similar numbers and reasons across the two groups). The risk of reporting bias, however, was judged to be high, as for two outcomes (reduction in distress in patients' professional and/or social life, and number of night sweats between week 1 and 12), it was reported that: *"A similar reduction was also found (data not shown)."*

In Colau et al. (2012) the primary outcome was the global hot flash score (HFS) over 12 weeks, and this was assessed as the area under the curve. The global HFS (AUC) was shown to be significantly lower in the BRN-01 group than the placebo group; on adjustment for baseline values, this result remained significant. In contrast however, no significance difference was observed for the outcome: time to 'clinically relevant' decrease of 3 points in HFS (weeks). No differences were seen for: Hot Flash Related Daily Interference Scale (HFRDIS) score for quality of life, reduction in severity of symptoms (Menopause Rating Scale (MRS)), reduction in distress in personal/professional life, and the number of night sweats. The frequency of adverse effects was similar between groups, and no serious adverse events were directly attributable to treatment.

Relton et al. (2012) was a pilot 'cohort multiple randomised controlled trial', with a number of objectives (relating to evaluating the acceptability of the study design), which included assessing the effects of treatment by a homeopath for women with menopausal hot flushes (Relton et al. 2012) (**Table 8**). The trial randomised 48 women, aged 45 to 65 years, who reported 14 or more menopausal hot flushes/night sweats per week, to either the 'offer' of treatment by a homeopath, or to no offer. The trial was judged to be at a moderate risk of bias overall. The risk of selection bias was judged to be low, with the use of a random number sheet generated by a statistician using block randomisation; allocation was concealed with the use of sealed, numbered envelopes. Due to the

nature of the intervention, there was no blinding; thus the risks of performance and detection bias were judged to be high. While some outcome data were available for 100% of women in the no offer group, some data were available for only 83% of the offer group (and for some outcomes, outcome data were not available for 25% of women); thus the risk of attrition bias was unclear. There was insufficient information to determine risk of reporting bias (for example, with no access to a trial registration/protocol). Of the 24 women randomised to the 'offer' group, 17 (71%) accepted the offer, and had one or more consultations with a homeopath (between one and five appointments); thus not all women allocated to this group received homeopathy.

In Relton et al. (2012) the primary outcome measure of clinical effectiveness was the Hot Flush Frequency and Severity Scale (HFFSS) (mean change from baseline at 36 weeks). The trial reported that HFFSS mean change favoured the 'offer' of homeopathy group. For secondary outcomes, it was reported that all outcomes (all medication; prescribed medication; self-prescribed medication; the EQ-5D score (to measure generic quality of life); the Greene Climacteric Scale (GCS) (relating to 21 menopausal symptoms); the Measure Your Medical Outcome Profile (MYMOP) primary symptom score) at 36 weeks, adjusted for baseline values, favoured the offer group. The MYMOP wellbeing score, adjusted for baseline values, however favoured no offer group. Given that this was a pilot trial (with a small number of participants), and that no formal power calculations had been carried out, the study investigators did not conduct any tests of significance to compare the two groups.

Table 8 Evidence summary table of Colau et al. (2012) and Relton et al. (2010) on the effectiveness of homeopathy for the treatment of menopausal hot flashes/flushes

Study ID	Colau 2012
Level of evidence	Level II
Risk of bias	Moderate risk of bias
N	108 randomised, 101 analysed
Patient population	Menopausal women ≥ 50 years of age, with menopause < 24 months, and ≥ 5 hot flashes a day causing negative effects on social/professional life
Intervention	BRN-01 tablets (registered homeopathic medicine. Oral treatment (2 tablets per day) was started on day 3 after study enrolment and was continued for 12 weeks. Women were able to take up to 4 tablets a day if required (for severity of vasomotor symptoms)
Comparator	Identical placebo tablets
Outcomes	**Results**
Global HFS over 12 weeks of treatment (using AUC) (mean, SD)	Significantly lower in homeopathy group
Adjusted global HFS over 12 weeks of treatment (using AUC) (mean, SD)	Significantly lower in homeopathy group
'Clinically relevant' decrease of 3 points in HFS (weeks) (mean, SD)	No significant difference
HFRDIS score for QoL at 12 weeks (mean, SD)	No significant difference
Reduction in HFRDIS score for QoL at week 12 (mean, SD)	No significant difference
Reduction in MRS score at week 12 (mean, SD)	No significant difference
Reduction in distress in patients'	*"A similar reduction"* (data not reported)

professional and/or personal life	
Number of night sweats between week 1 and 12 (using a VAS)	*"A similar reduction"* (data not reported)
Morisky-Green scores for compliance (N, %)	Significantly poorer compliance in placebo group
Number of unused tablets returned by patients (mean, SD)	No significant difference
Adverse events (including severe adverse events) (N, %)	No significant difference
Study ID	Relton 2012
Level of evidence	Level II
Risk of bias	Moderate risk of bias
N	48 randomised, 44 analysed
Patient population	Women aged 45 to 65, who reported 14 or more menopausal hot flushes/night sweats per week
Intervention	Offer of homeopathic treatment (by one of 2 study homeopaths)
Comparator	No offer of treatment
Outcomes	**Results**
HFFSS (difference between 36 week and baseline score) (mean, SD)	Favoured the offer group (significance not reported)
GCS total score (0-63) (difference between 36 week and baseline score) (mean, SD)	Favoured the offer group (significance not reported)
MYMOP primary symptom score (0-6) (difference between 36 week and baseline score) (mean, SD)	Favoured the offer group (significance not reported)
MYMOP wellbeing score (0-6) (difference between 36 week and baseline score) (mean, SD)	Favoured the no offer group (significance not reported)
EQ-5D quality of life (0-1) (difference between 36 week and baseline score) (mean, SD)	Favoured the offer group (significance not reported)
All medication (difference between 36 week and baseline score) (mean, SD)	Favoured the offer group (significance not reported)
Prescribed medication (difference between 36 week and baseline score) (mean, SD)	Favoured the offer group (significance not reported)
Self-prescribed medication (difference between 36 week and baseline score) (mean, SD)	Favoured the offer group (significance not reported)

Abbreviations: AUC: area under the curve; GCS: Greene Climacteric Scale; EQ-5D: generic quality of life measure; HFRDIS: Hot Flash Related Daily Interference Scale; HFFSS: hot flush frequency and severity score; HFS: hot flash score; MRS: Menopause Rating Scale; MYMOP: Measure Your Medical Outcome Profile; N: number; QoL: quality of life; SD: standard deviation; VAS: visual analogue scale

2.2.5 Rhinosinusitis

One randomised controlled trial (Level II) was identified that assessed the effects of homeopathy in acute rhinosinusitis (Friese and Zabalotnyi 2007) (**Table 9**). The information relating to the study by Friese and Zabalotnyi (2007) was taken from a published translation (*"Translated from German by Dr R Lorenz"*). The trial randomised 144 adult patients (from 10 centres in Ukraine) with sinusitis (confirmed on x-ray), to either a homeopathic complex (taken hourly until improvement began (up to 12 tablets per day), followed by two tablets three times a day as maintenance) or to a placebo, and patients were examined at seven, 14 and 21 days. This trial was judged to be at a high risk of bias overall (based on the information available in the published translation). The methods for sequence generation and allocation concealment were not reported, and thus the trial was judged to be at an unclear risk of selection bias. While a placebo was used, no information was provided on blinded outcome assessment, and thus the risk of detection bias was unclear. Furthermore, the risk of attrition bias was judged to be high, with a rate of drop-out for the placebo group of 88% (vs. 2% in the homeopathy group) (54 participants dropped out after seven days, and a further nine after 14 days); the integrity of blinding was thus questioned, and accordingly the risk of performance bias was judged as unclear. The risk of reporting bias was unclear, with insufficient information to determine risk; however for most outcomes, results of tests of significance were not reported in the translation. The risk of other bias was also judged as unclear, with insufficient information available to assess other sources of bias.

In Friese and Zabalotnyi (2007) the primary outcome was the sum of symptom scores, and a significantly lower mean sum of symptom scores at seven days was reported for the homeopathy group compared with the placebo group. While a lower mean score was also reported at day 21, this was not considered valid (by the evidence reviewer), given the large and differential loss to follow up in the placebo group, and use of the last-observation-carried-forward method. Differences in favour of the homeopathy group were shown for a number of other outcomes (individual symptoms at seven days (headache, maxillary sinus pressure pain, nasal obstruction, nasal secretion, 'post nasal' secretion), 'improvement noted within the first seven days', 'complete recovery in seven days', 'no improvement at 7 days', 'worsening at 7 days', satisfaction and tolerability). It was reported that *"Only one patient (Pg) complained of side effects, being coughing for 2 weeks,"* and compliance was reported as over 95% in both groups. The frequency of application of supportive measures (salt water rinsing, paracetamol) was similar across groups (over 70%).

Table 9 Evidence summary table of Friese and Zabalotnyi (2007) on the effectiveness of homeopathy for the treatment of acute rhinosinusitis

Study ID	Friese 2007
Level of evidence	Level II
Risk of bias	Unclear/High risk of bias
N	144
Patient population	Patients aged 18 to 65 with acute sinusitis (confirmed with a PA x-ray – thickening of upper lateral rim of the maxillary sinus mucous membrane of at least 5 mm, or shading of the sinus, or presence of a fluid level); sum of scores for 5 sinusitis symptoms (0 [no symptoms] to 4 [severe symptoms]) had to be between 8 and 20 points
Intervention	Homoeopathic complex. Medication was taken hourly until improvement, up to 12 tablets a day, followed by 2 tablets 3 times a day as maintenance (examined after 7, 14 and 21

	days)
Comparator	Placebo
Outcomes	**Results**
Sum of symptom scores after 7 days (mean, SD)	Significantly lower in homeopathy group
Sum of symptom scores after 21 days (mean, SD)	Lower in homeopathy group (significance not reported)
Improvement in individual symptoms (headache; maxillary sinus pressure pain; nasal obstruction; nasal secretion; 'post nasal' secretion) at 7 days (N, %)	More frequent in homeopathy group (significance not reported)
Improvement within first 7 days (N, %)	More frequent in homeopathy group (significance not reported)
Complete recovery at 7 days (N, %)	More frequent in homeopathy group (significance not reported)
No improvement at 7 days (N, %)	Less frequent in homeopathy group (significance not reported)
Worsening of symptoms (N, %)	Less frequent in homeopathy group (significance not reported)
Compliance (N, %)	No difference between groups (significance not reported)
Use of supportive measures up to day 7 (N, %)	No difference between groups (significance not reported)
Use of paracetamol (N, %)	No difference between groups (significance not reported)
Tolerability (very good or good) (N, %)	More frequent in homeopathy group (significance not reported)
Side effects (coughing for two weeks) (N, %)	No difference between groups (significance not reported)
Satisfaction (very satisfied or satisfied) (N, %)	More frequent in homeopathy group (significance not reported)
Inflammatory markers: ESR at 7 days, leukocyte counts	Not clearly reported

Abbreviations: ESR: erythrocyte sedimentation rate; N: number; PA: posterior to anterior; SD: standard deviation

2.2.6 Oral dryness

One randomised controlled trial (Level II) was identified that assessed the effects of individualised homeopathic treatment on salivary flow rate and subjective symptoms in patients with oral dryness (Haila et al. 2005) (**Table 10**). The trial randomised 29 patients with symptoms of dry mouth (15 with Sjogren's syndrome and 10 with rheumatoid arthritis) to either individualised homeopathy (three granules of D12 potency daily, four granules twice a week of D30 potency, or five granules of D200 potency once a week) or to a placebo for six weeks; the patients were followed up for a further 12 weeks (however at six weeks, all participants in the placebo group were also given homeopathy, and thus results have only been presented for the first six weeks in this report). This trial was judged to be at a moderate to high risk of bias overall. While adequate methods were used to generate the random sequence (coin-toss), no methods for concealing allocation were detailed, and thus the risk

of selection bias was judged as unclear. While participants were reported to be blind, with the use of a placebo, the study personnel were not blinded (including those who took the salivary samples); thus the risk of performance bias was judged as unclear, and the risk of detection bias was judged as high. The risk of attrition bias was judged to be low, with only one exclusion from the placebo group, and no losses to follow up. There was insufficient information available to confidently assess reporting bias.

In Haila et al. (2005), at six weeks, it was reported that the homeopathy group had significantly higher patient reported visual analogue scale (VAS) scores for subjective symptoms including dryness while eating, need to sip liquid to aid swallowing, need to drink during the night, amount of salivation, when compared with placebo (10 cm VAS scale, with 10 indicating the best situation). These results however, were not supported by clear differences between groups in unstimulated and stimulated salivary flow rates.

Table 10 Evidence summary table of Haila et al. (2005) on the effectiveness of homeopathy for the treatment of oral dryness

Study ID	Haila 2005
Level of evidence	Level II
Risk of bias	Moderate to high risk of bias
N	29 randomised, 28 analysed
Patient population	Patients with symptoms of dry mouth (15 with Sjogren's syndrome and 10 with rheumatoid arthritis).
Intervention	Individualised homeopathic treatments (3 granules daily of the D12 (12x) potency or 4 granules twice a week of the D30 (30x) or 5 granules of D200 (200x) once a week, for 6 weeks
Comparator	Placebo (sugar granules)
Outcomes	**Results**
Unstimulated flow rate increased during 6 week period (N, %)	No clear difference (significance not reported)
Stimulated flow rate increased during 6 week period (N, %)	No clear difference (significance not reported)
Dryness while eating (VAS* score) at 6 weeks (mean, 95% CI)	Significantly higher score (better) in homeopathy group
Need to sip liquid to aid swallowing (VAS* score) at 6 weeks (mean, 95% CI)	Significantly higher score (better) in homeopathy group
Need to drink during the night (VAS* score) at 6 weeks (mean, 95% CI)	Significantly higher score (better) in homeopathy group
Amount of salivation (VAS* score) at 6 weeks (mean, 95% CI)	Significantly higher score (better) in homeopathy group

*VAS questions were: (a) severe mouth dryness while eating a meal – 0; no mouth dryness while eating a meal - 10, (b) I need a lot of liquids to aid swallowing – 0; I do not need liquids to aid swallowing - 10, (c) I often need to sip water at night – 0; I do not need water at night - 10 (d) salivation feels scanty – 0; salivation feels normal – 10.

Abbreviations: CI: confidence interval; N: number; VAS: visual analogue score

2.2.7 Psychophysiological onset insomnia

One randomised controlled trial (Level II) was identified that assessed the effectiveness of a homeopathic complex on psychophysiological onset insomnia in males (Harrison et al. 2013) (**Table 11**). The trial randomised 34 men aged 18 to 40 years with chronic primary insomnia to a homeopathic complex (five drops of the medication under the tongue in the evening before supper and again before bed) or to a placebo. This trial was judged to be at a moderate to high risk of bias overall. Adequate methods were used to generate the random sequence (computer-generated), and to conceal allocation, and thus the risk of selection bias was judged to be low. Participants and study personnel were blinded to group allocation with the use of an identical placebo; thus the risks of performance and detection bias were also judged to be low. The risk of attrition bias was however judged to be high; in an already small sample size (N=34), there was a 22% drop-out rate in the homeopathy group and 12.5% in the placebo group, with drop-outs due to differing reasons. The risk of reporting bias was also judged to be high; measures of variance were not reported for the two main subjective outcomes presented (bedtime arousal levels and sleep onset latency), and adverse effects were mentioned in the Discussion only. The risk of 'other' bias was also judged as high, with differences between groups at baseline apparent (for example, participants in the homeopathy group were older, less likely to sleep alone and more likely to be affected by nightly arousals).

In Harrison et al. (2013) a significant difference in favour of homeopathy for bedtime arousal levels at day 28 was reported (measured using a Pre-sleep Arousal Scale (PSAS)); along with significantly shorter median sleep onset latency at day 28 (measured using a Sleep Diary (SD)). Harrison et al. (2013) reported that reductions over time in somatic and cognitive arousal (PSAS) and improvement in sleep onset latency (SD) were significant for the homeopathy group across the duration of the study, but no significant changes were observed for the placebo group. In their Discussion, the authors noted that there were no adverse effects in the study.

Table 11 Evidence summary table of Harrison et al. (2013) on the effectiveness of homeopathy for the treatment of psychophysiological onset insomnia

Study ID	Harrison 2013
Level of evidence	Level II
Risk of bias	Moderate to high risk of bias
N	34 randomised, 28 analysed
Patient population	Males between 18 and 40 years with chronic PI, who had insomnia at least 3 days per week for a minimum of 1 month, and for not more than 10 years
Intervention	Homeopathic complex: 5 drops of the medication under the tongue in the evening before supper, and again before going to bed.
Comparator	Placebo formula
Outcomes	**Results**
Arousal levels at day 28 (PSAS) (median)	Significantly lower in homeopathy group
Sleep onset latency at day 28 (sleep diary) (median) (minutes)	Significantly lower in homeopathy group
Reduction over time in somatic and cognitive arousals (PSAS*)	Significant reduction for homeopathy group No significant change for placebo group
Improvement in sleep onset latency (sleep diary) (mean)	Significant improvement for homeopathy group No significant change for placebo group

Adverse effects	None reported

*PSAS: The scale has 16 questions organised into 2 subscales for cognitive and somatic arousal. Each question has 5 varying degrees of severity 1 (not at all) to 5 (extremely); PSAS score ranges from 16 to 80, with elevated scores indicating the presence and severity of PI.

Abbreviations: N: number; PI: psychophysiological onset insomnia, PSAS: Pre-sleep Arousal Scale

2.2.8 Stress

One randomised controlled trial (Level II) was identified that investigated the effectiveness of dystologes S tablets ('verum'), three tablets per day for 14 days (and six tablets on day 15), for the treatment of stress (Hellhammer et al. 2013) (**Table 12**). The trial randomised 40 women aged 30 to 50 years who experienced physical symptoms without organic findings when stressed to either verum or placebo, and measured women's responses to the Trier Social Stress Test (TSST). This trial was judged to be at a low to moderate risk of bias overall. The trial was considered to be at a low risk of selection bias, with adequate methods used for sequence generation and allocation concealment. Similarly, the trial was judged to be at low risks of performance and detection bias, with the use of an identical placebo. Only one participant in the verum group dropped out (5%), and all women were included in the intention-to-treat analyses; thus the risk of attrition bias was judged to be low. There was insufficient information to confidently assess selective reporting. While there were no clear differences between groups in the baseline characteristics reported, the authors themselves acknowledged the limitations associated with having not assessed norepinephrine (NE) concentrations before the treatment period; *"one cannot exclude that NE levels in the treatment group were lower even before substance intake."*

In Hellhammer et al. (2013) the primary outcome was salivary cortisol response to the stress test (TSST). In regards to physiological and psychological parameters, both groups had increases in response to the TSST in all variables measured (cortisol; catecholamines; adrenocorticotrophic hormone (ACTH); heart rate; State-Trait-Anxiety Questionnaire (STAI); Multidimensional Mood States Questionnaire (MDBF)-positive mood; MDBF-alertness; MDBF-calmness; visual analogue scale (VAS)-stress; VAS-anxiety; VAS-insecurity), and no group differences were seen, except for significantly lower norepinephrine (NE) concentrations before and after the TSST for the verum group compared with the placebo group. Across the 14 day study, both groups reported improvements in psychological parameters concerning sleep and life quality (Perceived stress (PSS); visual analogue scale for sleep quality (VIS)-stress symptoms; VIS-easefulness; VIS-concentration; VIS-time falling asleep; VIS-waking up at night; VIS-good night), with no significant group differences seen. Women in the verum group were shown to have significantly improved sleep quality after the treatment period; an improvement not reported for the placebo group; however the between group comparison was not significant. No adverse effects were reported in either group.

Table 12 Evidence summary table of Hellhammer et al. (2013) on the effectiveness of homeopathy for the treatment of stress

Study ID	Hellhammer 2013
Level of evidence	Level II
Risk of bias	Low to moderate risk of bias
N	40
Patient population	Women aged 30 to 50 years who were employed full-time who regularly experienced physical symptoms without

	organic findings when stressed. Symptoms included uneasiness, nervousness, attention deficit, tension, fatigue, sleep disorders, headaches, lack of concentration, and gastro-intestinal disorders.
Intervention	dysto-loges S tablets ('verum'); 3 tablets daily for 14 days, one tablet before each meal; on day 15, participants took three tablets before breakfast and an additional three tablets upon arrival at the study site
Comparator	Placebo tablets
Outcomes	**Results**
Primary outcome	
Salivary cortisol in response to TSST (mmol/L) (mean, 95% CI)	No significant difference
Secondary biological outcomes in response to stress test (TSST)	
Plasma cortisol (nmol/L) (mean, 95% CI)	No significant difference
ACTH (pg/mL) (mean, 95% CI)	No significant difference
Epinephrine (pg/mL) (mean, 95% CI)	No significant difference
Heart rate (bpm) (mean, 95% CI)	No significant difference
Noreinephrine (pg/mL) (mean, 95% CI)	Significantly lower in verum group before and after the TSST vs. placebo
Secondary psychological outcomes in response to stress test (TSST)	
State anxiety (STAI) (mean, 95% CI)	No significant difference
Positive mood (MDBF) (mean, 95% CI)	No significant difference
Alertness (MDBF) (mean, 95% CI)	No significant difference
Calmness (MDBF) (mean, 95% CI)	No significant difference
Stress perception (VAS) (mm) (mean, 95% CI)	No significant difference
Anxiety (VAS) (mm) (mean, 95% CI)	No significant difference
Insecurity (VAS) (mm) (mean, 95% CI)	No significant difference
Secondary psychological outcomes concerning sleep and life quality	
Perceived stress (PSS) (mean, 95% CI)	No significant difference
No. stress symptoms (VIS) (mean, 95% CI)	No significant difference
Concentration (VIS) (mm) (mean, 95% CI)	No significant difference
Easefulness (VIS) (mm) (mean, 95% CI)	No significant difference
Time falling asleep (VIS) (min) (mean, 95% CI)	No significant difference
Waking up at night (VIS) (mean, 95% CI)	No significant difference
Having a good night (VIS) (mm) (mean, 95% CI)	No significant difference
Sleep quality	Significantly improved in verum group from baseline to end of treatment; no difference for placebo group
Adverse events	None occurred in either group

Compliance	*"very good"*

Abbreviations: ACTH: adrenocorticotrophic hormone; bpm: beats per minute; CI: confidence interval; L: litre; MDBF: Multidimensional Mood States; mL: millilitres; mm: millimetres; N: number; NE: norepinephrine; nmol: nanomole; pg: pictograms; STAI: State-Trait-Anxiety Questionnaire; TSST: Trier Social Stress Test; VAS: visual analogue scales; VIS: visual analogue scales for sleep quality

2.2.9 Dermatological reactions (radiotherapy)

One randomised controlled trial (Level II) was identified that investigated the use of homeopathic medicines for the prevention of dermatological reactions to radiotherapy (Kulkarni et al. 1988) (**Table 13**). The trial randomised 82 patients undergoing radiotherapy to Cobaltum 30, Causticum 30 or placebo (patients were instructed to take 3 pills from the given bottle, once every morning on an empty stomach, throughout the entire course of their radiotherapy). This trial was judged to be at a high risk of bias overall. While the trial was described as *"randomised"*, no detail was provided regarding sequence generation or allocation concealment, and thus the risk of selection bias was judged to be unclear. While a placebo was used, and thus the risk of performance bias was judged to be low, it was unclear whether outcome assessors were blind; thus the risk of detection bias was unclear. The risk of attrition bias was also judged to be unclear, with no information provided on missing data (losses/exclusions). As only averages were presented for the grading of radiation reactions (with no measures of group variation, or tests of significance reported), the risk of reporting bias was judged to be high. Furthermore, in the conclusion, the authors noted that "*We did not observe any significant reduction of tumour regression rates in the patients on homeopathic medicines,"* however no data relating to tumour regression were presented in the results.

In Kulkarni et al. (1988) the only outcomes with reported data were: average grading of radiation reactions, and average region wise grading of radiation reactions (head and neck, thorax, pelvis); for each outcome, the average was lower in the two homeopathy groups than the placebo group. The authors reported there was *"about 30% overall reduction in the degree of radiation reaction"* and in their conclusion they stated that *"homeopathic medicines i.e. Cobaltum and Causticum significantly reduce the degree of radiation reactions."*

Table 13 Evidence summary table of Kulkarni et al. (1988) on the effectiveness of homeopathy for the prevention of dermatological reactions to radiotherapy

Study ID	Kulkarni 1988
Level of evidence	Level II
Risk of bias	High risk of bias
N	82
Patient population	Patients undergoing radiotherapy.
Intervention	Two groups: Cobaltum 30 and Causticum 30. Patients were instructed to take 3 pills from the give bottle, once every morning on an empty stomach, throughout the entire course of their radiotherapy.
Comparator	Placebo
Outcomes	**Results**
Grading of radiation reactions overall (and averages of the head and neck; thorax; pelvis) (average)	Lower with homeopathy (in conclusion *"homeopathic medicines… significantly reduce the degree of radiation reactions*")

Tumour regression rates	No significant reduction for homeopathy group (reported in conclusion)

Abbreviations: N: number

2.2.10 Warts/molluscum contagiosum

One randomised controlled trial (Level II) was identified that investigated the effectiveness of a variety of homeopathic drugs (thuja, ruta, calcarea carb and causticum) for the treatment of warts and molluscum contagiosum compared with placebo (Manchanda et al. 1997) (**Table 14**). The trial 'registered' 124 people in the study, who received either homeopathy (drugs of 30 potency given three times daily; 200 potency twice daily and 1 M potency, once daily; all for 15 days) or placebo. This trial was judged to be at a high risk of bias overall. No details were provided on the methods used for sequence generation and allocation concealment, and thus the risk of selection bias was unclear. The authors state that a placebo was used, and the trial was *"double blind"* and thus the risk of performance bias was judged to be low; no further details were provided regarding blinding of outcome assessment, and thus the risk of detection bias was judged to be unclear. The risk of attrition bias was also judged to be unclear, as while 16% (20/124) of participants *"dropped out",* the reasons for dropping out were not reported, nor were the numbers per group. The only outcome for which data were reported was *"improvement result"* (and total numbers in each group were not clear); therefore the risk of reporting bias was judged to be high.

In Manchanda et al. (1997), the authors reported that 81% of participants improved in the homeopathy group, while only 19% improved in the placebo group: *"The results of active drug group are far better than the placebo group."*

Table 14 Evidence summary table of Manchanda et al. (1997) on the effectiveness of homeopathy for the treatment of warts and molluscum contagiosum

Study ID	Manchanda 1997
Level of evidence	Level II
Risk of bias	High risk of bias
N	124 randomised, 104 analysed
Patient population	People with warts (verruca vulgaris, verruca plana, verruca filiformis, verruca plantaris, verruca genitalis) or molluscum contagiosum of any age
Intervention	Thuja, ruta, calcarea carb and causticum for 15 days
Comparator	Placebo
Outcomes	**Results**
'Improved'	81% homeopathy group vs. 19% in placebo group (significance not reported)

Abbreviations: N: number

2.2.11 Chronic low back pain

One randomised controlled trial (Level II) was identified that investigated the efficacy of subcutaneous injections with Disci/Rhus toxicodendron compositum (verum) for the treatment of chronic low back pain, (Pach et al. 2011) (**Table 15**). The trial randomised 150 participants from nine outpatient clinics (aged 30 to 75 years, with low back pain for at least 12 months) to either 10 mL Disci/Rhus toxicodendron compositum (verum) injections subcutaneously (12 sessions within 8 weeks), placebo (according to same regiment), or no treatment (1:1:1 ratio). The trial was judged to be at a low risk of bias overall. The trial was considered to be at a low risk of selection bias, using appropriate methods for sequence generation (computer-generated sequence), and allocation concealment (opaque, sequentially numbered and sealed envelopes). The trial was at a low risk of performance and detection bias, with identical placebo injections used to blind participants, study personnel and statisticians (patients and physicians did not identify treatment allocation more often than expected by chance when questioned at eight weeks). It was not possible, however, to blind allocation to the 'no treatment group.' The trial was judged to be at a low risk of attrition bias, with a relatively low rate of loss to follow up, similar reasons for losses/exclusions across groups, and intention-to-treat analyses performed (additional per protocol analyses were performed). The trial reported on pre-specified outcomes (as outlined in the accompanying trial protocol); thus the risk of reporting bias was low. While most baseline characteristics were comparable between groups at baseline, differences in gender, height, and two scales of the quality of life Medical Outcome Study-Short Form 36 (SF-36) were present.

In Pach et al. (2011), the primary outcome was the average low back pain intensity over the last seven days on a visual analogue scale (VAS) (0-100mm; 0 = no pain; 100 = worst imaginable pain) after eight weeks of treatment. Average low back pain after eight weeks was shown to be significantly lower in the verum group than the no treatment group (for unadjusted and adjusted analyses); however no difference was shown between the verum and placebo groups. Similarly, at 26 week follow up, no differences were shown between groups for average low back pain. Few other differences between groups were shown for outcomes including scores on the pain perception scale (SES), pain disability index scale (PDI), back function (Hannover Functional Ability Questionnaire (HFAQ)), and most SF-36 quality of life component scores (except for fewer days with rescue medication at weeks 1-8, lower pain disability index at 26 weeks, higher bodily pain score at 8 weeks, and lower mental health score at 8 weeks – all in the verum group compared with no treatment group). No differences were shown in the risk of adverse effects. The authors concluded that *"The homeopathic preparation was not superior to placebo. Compared to no treatment injections [verum] resulted in significant and clinical relevant chronic back pain relief."*

Table 15 Evidence summary table of Pach et al. (2011) on the effectiveness of homeopathy for the treatment of chronic low back pain

Study ID	Pach 2011
Level of evidence	Level II
Risk of bias	Low risk of bias
N	150 randomised, 142 analysed
Patient population	People aged 30 to 75 years, male or female, with low back pain for at least 12 months (chronic), who had already received standard therapy, with average back pain intensity of at least 40 mm on VAS (0-100 mm) in last seven days at baseline, with no other treatment except oral NSAIDs and muscle relaxants within four weeks prior to study entry
Intervention	10 mL Disci/Rhus toxicodendron compositum (verum)

	injections subcutaneously (12 sessions within 8 weeks)
Comparator	Placebo No treatment
Outcomes	**Results**
Primary	
Pain intensity in last 7 days at 8 week follow up (on VAS, 0-100) adjusted and unadjusted (mean, 95% CI)	Significantly lower in verum vs. no treatment No significant difference between verum vs. placebo
Secondary	
Pain intensity in last 7 days at 26 week follow up (on VAS, 0-100) adjusted (mean, 95% CI)	No significant differences
Days with rescue medication (weeks 1-4; 5-8; 1-8) (mean, 95% CI)	Significantly fewer in verum vs. no treatment No significant difference between verum vs. placebo
Affective pain at 8 and 26 weeks (SES) (mean, 95% CI)	No significant differences
Sensory pain at 8 and 26 weeks (SES) (mean, 95% CI)	No significant differences
PDI at 8 and 26 weeks (mean, 95% CI)	No significant differences at 8 weeks Significantly lower in verum vs. no treatment at 26 weeks
Back function (HFAQ) at 8 and 26 weeks (mean, 95% CI)	No significant differences
Physical component score at 8 and 26 weeks (SF-36) (mean, 95% CI)	No significant differences
Mental component score at 8 and 26 weeks (SF-36) (mean, 95% CI)	No significant differences
Physical functioning at 8 and 26 weeks (SF-36) (mean, 95% CI)	No significant differences
Role physical at 8 and 26 weeks (SF-36) (mean, 95% CI)	No significant differences
Bodily pain at 8 and 36 weeks (SF-36) (mean, 95% CI)	Significantly higher in verum vs. no treatment at 8 weeks No significant differences at 26 weeks
General health perception at 8 and 26 weeks (SF-36) (mean, 95% CI)	No significant differences
Vitality at 8 and 26 weeks (SF-36) (mean, 95% CI)	No significant differences
Social functioning at 8 and 26 weeks (SF-36) (mean, 95% CI)	No significant differences
Role emotional at 8 and 26 weeks (SF-36) (mean, 95% CI)	No significant differences
Mental health at 8 and 26 weeks (SF-36) (mean, 95% CI)	Significantly lower in verum vs. no treatment at 8 weeks No significant differences at 26 weeks
Adverse events: any; haematoma at injection site; common cold; pain (N, %)	No significant differences

Abbreviations: CI: confidence interval; HFAQ: Hannover Functional Ability Questionnaire; N: number; NSAID: non-steroidal anti-inflammatory drug; PDI: pain disability index; SES: pain perception scale; SF-36: quality of life (Medical Outcome Study-Short Form 36); VAS: visual analogue scale

2.2.12 Upper respiratory tract infection

Two Level II studies (Steinsbekk et al. 2005; Zanasi et al. 2014) were identified that examined the effectiveness of homeopathy for treating URTI, specifically for the prevention of recurrent URTI in children (Steinsbekk et al. 2005) and for treating acute cough in URTI in adults (Zanasi et al. 2014) (**Table 16**).

Steinsbekk et al. (2005) randomised 169 children who had been to a doctor with an URTI, to either individualised homeopathy treatment by (one of five) homeopaths for treating upper respiratory tract infection, or to a 'waiting list control', in which children were told they would get an appointment after filling out their symptom diary for 12 weeks. This trial was judged to be at a moderate to high risk of bias overall. The trial had appropriate methods of randomisation and allocation concealment, however, due to the nature of the intervention, there was no blinding of participants/study personnel, and thus (with only subjectively measured outcomes), the trial was judged to be at a high risk of both performance and detection bias. The risk of attrition bias was unclear; 27 (16%) children did not return any data or withdrew after randomisation (14/82 (17%) in the homeopathic group and 13/87 (15%) in the control group) a further nine children in the homeopathic care group and two in the control group were lost to follow up and the authors noted that *"those lost to follow-up in both groups tended to have higher symptom scores and more days with URTI than those who completed the study",* although suggested no change to overall results when missing values were imputed for the period they had participated. There was insufficient information to confidently assess the risk of reporting bias. While the groups were comparable at baseline, it was noted that children could have *"any other treatment of choice",* except for any form of homeopathic medication. Furthermore, with the use of individualised homeopathy, there was great variation in the treatment received by children in the homeopathy group, making interpretation difficult; 22 different medicines were prescribed to the 68 children; the length and number of consultations varied; 18 children had their prescription changed; 12 had two medicines at the same time; seven had a second medicine to use during acute episodes.

In Steinsbekk et al. (2005) the primary outcome was the median total symptom score, which was shown to be significantly lower in the homeopathic care group. Children in this group also had significantly fewer days with URTI symptoms. No significant differences were shown for the other outcomes in the study (related to use of, and days with, antibiotics and analgesics/antipyretics; visits to a medical doctor; days with other illness; and parents having work absence due to child's illness); 22% of children in the homeopathic care group reported mild and transient side effects.

Zanasi et al. (2014) randomised 80 participants over 18 years to either homeopathic syrup (15 mL four times per day for 7 days; with follow up at day 14) or placebo syrup for the treatment of acute cough induced by URTI. This trial was judged to be at a low risk of bias overall. Adequate methods were used to generate the random sequence (computer-generated) and to conceal allocation (sequentially numbered drug containers of identical appearance), and thus the trial was judged to be at a low risk of selection bias. Similarly, the trial was judged to be at a low risk performance and detection bias, with the use of an identical placebo. There was low risk of attrition bias, with no loss to follow up, and intention-to-treat analyses were performed, though of note is that sputum

viscosity measurements were available for only 53/80 patients (where a sufficient amount of mucus had been collected). Without access to a trial protocol, it was not possible to confidently assess selective reporting; however no obvious risk was identified. The trial was judged to be at an unclear risk of other bias, with gender and age being the only baseline characteristics reported, and the homeopathic group was, on average, older.

In Zanasi et al. (2014) the primary outcome was the mean verbal category descriptive (VCD) cough score, which was shown not to differ between groups at two and 14 days, however was shown to be significantly lower at four and seven days in the homeopathy group. Similarly, the proportion of patients with a VCD score of more than 2 at two and 14 days did not differ between groups; at four and seven days however, there were significantly fewer participants with a score over 2 in the homeopathy group. While the sputum in the homeopathy group was significantly less viscous at four days, no difference was shown in the absolute improvement in sputum viscosity, or in patients' subjective evaluation of mucus. Two patients in the homeopathy group and three in the placebo group had side effects *"unrelated to treatment."*

Table 16 Evidence summary table of Steinsbekk et al. (2005) and Zanasi et al. (2014) on the effectiveness of homeopathy for the treatment of upper respiratory tract infection

Study ID	Steinsbekk 2005
Level of evidence	Level II
Risk of bias	Moderate to high risk of bias
N	169 randomised, 142 analysed
Patient population	Children less than 10 years of age who had been to a medical doctor for URTI. URTI was defined as having a health problem to which the consulting doctor gave an International Classification of Primary Care code of H01 (ear pain), H71 (acute otitis media), H72 (glue ear), H74 (chronic otitis media), R72 (streptococcal infection), R74 (URTI), R75 (sinusitis) or R76 (tonsillitis).
Intervention	Pragmatic, individualised homeopathic care (from one of five homeopaths) for 12 weeks
Comparator	Waiting list control
Outcomes	
Total symptom score (median, 95% CI)	Significantly lower in homeopathic care group
Days with URTI (median, 95% CI)	Significantly fewer in homeopathic care group
Days with antibiotic (median, 95% CI)	No significant difference
Days with analgesic/antipyretic (median, 95% CI)	No significant difference
Visits to medical doctor (median, 95% CI)	No significant difference
Days with other illness (median, 95% CI)	No significant difference
Days with noises from chest (median, 95% CI)	No significant difference
Days with work absence due to ill child (median, 95% CI)	No significant difference
Had days with URTI (N, %)	Significantly fewer in homeopathic care group
Had days with other illness (N, %)	No significant difference

Used antibiotics (N, %)	No significant difference
Used analgesic/antipyretic (N, %)	No significant difference
Consulted a medical doctor (N, %)	No significant difference
Had parents with work absence when ill (N, %)	No significant difference
Adverse effects (N, %)	22.1% of the homeopathic care group (mild, transient)
Study ID	Zanasi 2014
Level of evidence	Level II
Risk of bias	Low risk of bias
N	80
Patient population	People of at least 18 years of age with cough induced by URTI lasting from 3 to 5 days.
Intervention	Homeopathic syrup: 15 mL four times a day for 7 days
Comparator	Placebo syrup
Outcomes	**Results**
VCD cough score of 2 or more at 2 days and 14 days (mean, SD)	No significant difference
VCD cough score of 2 or more at 4 days and 7 days (mean, SD)	Significantly lower in homeopathy group
VCD cough score of 2 or more at 2 days and 14 days (N, %)	No significant difference
VCD cough score of 2 or more at 4 days and 7 days (N, %)	Significantly fewer participants in homeopathy group
Cough present at 14 day (N, %)	No clear difference (significance not reported)
Sputum viscosity at day 4 (mean, SD)	Significantly lower in homeopathy group
Absolute improvement in sputum viscosity (N m) (mean, SD)	No significant difference
Subjective evaluation of mucus	No significant difference
Adverse events directly related to treatment (N, %)	None in either group
Side effects unrelated to treatment (N, %)	No clear difference (significance not reported)

Abbreviations: CI: confidence interval; N: number; N m: newton metres; SD: standard deviation; URTI: upper respiratory tract infection; VCD: verbal category descriptive

2.2.13 Otitis media

One randomised controlled trial (Level II) was identified that investigated the use of homeopathic ear drops as an adjunct to standard care, in children with acute otitis media (Taylor and Jacobs 2011) (**Table 17**). The trial randomised 120 children six months to 11 years of age to standard care alone, or to the addition of homeopathic ear drops (3-4 drops up to 3 times/day as needed for relief of symptoms for a maximum of 5 days). This trial was judged to be at a moderate to high risk of bias overall. While adequate methods were used to generate the random sequence (computer-generated), no methods for concealing allocation were detailed, and thus the risk of selection bias was judged as unclear. There was no blinding of participants and personnel (with no placebo used), and the majority of outcomes were subjective, reported by the parents, and thus there was potential for both performance and detection bias. The risk of attrition bias was judged to be

unclear, as while symptom diaries were received for 75% of the homeopathy group and 83% of the standard care group, the numbers who completed the ear treatment group symptom questionnaire (ETG-5) at each of the 10 assessment time points (8am and 8pm for the first five days after enrolment) was not clear (reported as total numbers across the two groups). Additionally, children whose parents returned diaries were significantly less likely to live in a household with a cigarette smoker and more likely to have a mother who was a college graduate. For ETG-5 scores, AOM-FS scores and FSII scores, only means (no standard deviations) were reported for groups; and for symptomatic medication use, the data were only reported for day 3 only, where a significant difference was observed (for days 1-2,4-5 *"no other statistically significant differences were noted"*). The risk of reporting bias was thus judged as high.

In Taylor and Jacobs (2011) the primary outcomes were mean ETG-5 scores at assessments 1-10 and adverse events. No significant differences were reported for ETG-5 scores at assessments 1 and 4-10, however differences were shown in favour of the homeopathy group (lower scores) at assessments 2 and 3. While there were no significant differences for vomiting, rash, headache, lethargy, or 'other symptoms', children receiving homeopathy were reported to be significantly more likely to have diarrhoea or 'hyper' behaviour. No significant differences were seen between groups in the parent assessed faces scale (AOM-FS) scores at assessments 1-10, in the function status (FSIIR) scores at 12-15 day follow up, in return visits to health care providers, or prescriptions filled at 12-15 day follow up. The homeopathic ear drop group used significantly fewer symptomatic medications on day 3, however no differences were seen at days 1-2 and 4-5.

Table 17 Evidence summary table of Taylor and Jacobs (2011) on the effectiveness of homeopathy for the treatment of acute otitis media in children

Study ID	Taylor 2011
Level of evidence	Level II
Risk of bias	Moderate to high risk of bias
N	120 randomised, 94 analysed for primary outcomes
Patient population	Children 6 months to 11 years old diagnosed with AOM; with distinctly abnormal tympanic membrane(s), significant discomfort related to AOM, an otoscopy scale score of ≥ 4; with parents who indicated that the symptom severity on the AOM-FS was 4 or greater (corresponding to a 'moderate problem' or more)
Intervention	Homeopathic ear drops administered 3-4 drops up to 3 times/day as needed for relief of symptoms for a maximum of 5 days
Comparator	Standard care
Outcomes	**Results**
ETG-5 scores at assessment 1, 4-10 (mean)	No significant differences
ETG-5 scores at assessments 2 and 3 (mean)	Significantly lower in homeopathy group
Adverse events – vomiting, rash, headache, lethargy, other symptoms (N, %)	No significant differences
Adverse events – diarrhoea and 'hyper' behaviour (N, %)	Significantly lower in homeopathy group
AOM-FS scores at assessments 1-10	No significant differences

(mean)	
FSIIR scores at 12-15 day follow up (mean)	No significant differences
Use of symptomatic medications at day 3 (N, %)	Significantly lower in homeopathy group
Use of symptomatic medications at days 1-2, 4-5 (N, %)	No significant differences
One or more return visits to health care provider at 12-15 day follow up (N, %)	No significant differences
Prescriptions filled a at 12-15 day follow up (N, %)	No significant differences
Side effects (pain, crying, irritability, itchiness, redness, diarrhoea) (N, %)	18% of children in homeopathy group

Abbreviations: AOM: acute otitis media; AOM-FS: Acute Otitis Media-Faces Scale*;* ETG-5: ear treatment group symptom questionnaire; FSIIR: functional status II revised scale; N: number

2.2.14 Ankle sprain

One randomised controlled trial (Level II) was identified that assessed the 'non-inferiority' of the homeopathic medication Traumeel, compared with diclofenac (a non-steroidal anti-inflammatory drug, as an active control) in patients following acute ankle sprain (González de Vega et al. 2013) (**Table 18**). In this multi-centre study, conducted in 15 outpatients centres in Spain, 449 physically active adults with acute unilateral ankle sprain of the lateral ligaments in the past 24 hours (with moderate/severe pain) were randomised to either 2 grams of Traumeel ointment (T-O group), 2 grams of Traumeel gel (T-G group), or 2 grams of diclofenac gel (D-G group), all applied topically three times a day for 14 days, with six week follow up. The trial was judged to be at a moderate to high risk of bias overall. Adequate methods were used to generate the random sequence (computer-generated) and conceal allocation (central randomisation), and thus the risk of selection bias was judged as low. Performance and detection bias were however judged as unclear, as while it was possible to blind the T-G and D-G groups, due to the consistency of the ointment, participants/ investigators were not blind to allocation to the T-O group. Exclusions from the intention-to treat analysis were 6% in the T-O group, 5% in the T-G group and 7% in the placebo group (mainly due to 'early recovery' and 'administrative reasons' – the numbers and reasons similar across group). Exclusions from the per-protocol analysis, however, appeared to be higher in the T-O group in particular (with more exclusions due to non-compliance); and thus the risk of attrition bias was judged as unclear. While p values were reported for primary outcomes, for the majority of secondary outcomes, no results of tests of significance were reported, and for many outcomes only means/medians were reported (with no accompanying measures of variation); thus the risk of reporting bias was judged as high. In this trial, there was insufficient justification for the absence of an active control group: the *"study did not include a placebo-control arm, which may have had some relevance to the assessment of an injury that usually resolved without treatment."* Furthermore, there was a lack of detail provided regarding clinical judgement and statistical reasoning to justify the defined non-inferiority margin.

González de Vega et al. (2013) reported for the primary outcomes (percentage reduction in pain (100 mm VAS) on day 7; improvement in Foot and Ankle Ability Measure (FAAM) Activity of Daily Living (ADL) subscale score on day 7) that *"the confidence intervals were above the predefined lower*

equivalence margin (0.40), demonstrating non-inferiority of T-O and T-G vs. D-G for the treatment of pain and for the improvement of ankle function." The study reported that the T-O and T-G groups were 'non-inferior' to the D-G group on all secondary outcome variables (predominately at 14 day follow up); with no significant group differences seen in pain reduction; FAAM Sport and ADL subscales; ankle swelling; normal function/activity; global assessment of treatment efficacy; tolerability; rescue paracetamol use; non-compliance; need for concomitant medication. Adverse events 'possibly' or 'probably' related to treatment occurred in 3.3% of the T-O group, and 2.0% of the T-G and D-G groups.

Table 18 Evidence summary table of González de Vega et al. (2013) on the effectiveness of homeopathy for the treatment pain and improving mobility after acute ankle sprain

Study ID	González de Vega 2013
Level of evidence	Level II
Risk of bias	Moderate to high risk of bias
N	449 randomised, 420 analysed
Patient population	Physically active adults, aged 18 to 40 years, with acute unilateral ankle sprain of the lateral ligaments in the past 24 hours; with moderate to severe pain on weight bearing and be unable to perform their usual training/sports activities.
Intervention	2 g Traumeel ointment (T-O) or gel (T-G) administered topically to the ankle three times a day for 14 days
Comparator	2 g diclofenac gel (D-G) (NSAID) administered topically to the ankle three times a day for 14 days.
Outcomes	**Results**
	"At all visits in the main treatment period, the confidence intervals were above the predefined lower equivalence margin (0.40), demonstrating non-inferiority of T-O and T-G vs. D-G for the treatment of pain and for the improvement of ankle function."
Ankle pain (VAS) score change from baseline on day 7 (median) (%)	No significant differences between T-O and D-G or T-G and D-G
FAAM ADL subscale score change from baseline on day 7 (median) (points)	No significant differences between T-O and D-G or T-G and D-G
Ankle pain (VAS) score change from baseline on day 14 (median) (%)	No significant differences between T-O and D-G or T-G and D-
Ankle pain (VAS) score change from baseline on day 42 (median) (%)	No significant differences between T-O and D-G or T-G and D-
FAAM ADL subscale score change from baseline on day 14 (median) (points)	No significant differences between T-O and D-G or T-G and D-
FAAM ADL subscale score change from baseline on day 42 (median) (points)	No significant differences between T-O and D-G or T-G and D-
FAAM Sports subscale score change from baseline on day 14 (median) (points)	*"T-O and T-G were non-inferior to D-G on all secondary outcome variables"*
Ankle swelling, figure of eight change from baseline on day 14 (median)	As above.

(cm)	
Global assessment of treatment efficacy on day 14 (mean) (5-point scale)	As above.
Global assessment of treatment efficacy on day 14 (reporting 'very good' or 'good') (N, %)	As above.
Normal function/activity (patients reporting scores of 0 or 1) at day 14 (N, %)	As above.
Total pain relief at day 7 (N, %)	No clear differences (significance not reported)
Compliance below 80% (non-compliance) (N, %)	No significant difference
Concomitant medications for participants with adverse effects (N, %)	*"No significant difference"*
Rescue medication (paracetamol) tablets per participant (mean)	*"No significant difference"*
Rescue medication (paracetamol) in treatment and follow-up period (N, %)	*"No significant difference"*
Adverse events (N, %)	No significant difference
Adverse events 'possibly' or 'probably' related to treatment (N, %)	No significant difference

Abbreviations: ADL: Activity of Daily Living; FAAM: Foot and Ankle Disability Measure; N: number; NSAID: non-steroidal anti-inflammatory drug; VAS: visual analogue scale

2.2.15 Osteoarthritis

One randomised controlled trial (Level II) was identified that assessed the 'equivalence' of the homeopathic medication Zeel comp., compared with diclofenac (a non-steroidal anti-inflammatory drug) in patients with mild to moderate osteoarthritis of the knee (Maronna et al. 2000) (**Table 19**). The information about this trial has been extracted from two articles submitted during the public consultation, a published summary (translation) by Porcher-Spark (2000) and a paper by Strosser et al. (2000). The trial randomised 121 men and women suffering from mild to moderate osteoarthritis of the knee for at least six months to either one tablet of Zeel comp. (homeopathic complex preparation) (and a diclofenac placebo), or to one tablet of diclofenac 25 mg (and a Zeel comp. placebo tablet) three times per day for 10 weeks. This trial was judged to be at a moderate to high risk of bias overall (based on information available). While the trial was discussed as being randomised, the methods used for sequence generation and allocation concealment were not described in the translation, and thus the risk of selection bias was unclear. Blinding of participants and study personnel was considered possible, in view of the use of the placebos given to both groups and the outcomes were subjectively assessed by patients; thus the risks of performance and detection bias have been judged as low. There was a low rate of post-randomisation exclusion (7/121 (6%) in the study, however all were in the Zeel comp. group); thus the risk of attrition bias was unclear. There was insufficient information to confidently assess reporting bias. The evidence reviewer notes the inability to confidently assess methodological quality due to the use of a summarised translation of the Maronna et al. (2000) study (including detail regarding choice of non-

inferiority margin, sample size estimation and statistical analysis); however notes that the claims of equivalence (below) are not substantiated by the data presented.

Maronna et al. (2000) measured the primary outcome using a validated questionnaire for use in patient self-assessment (WOMAC Osteoarthritis Index); the study reported that while after two and four weeks, a marked improvement was first observed for the diclofenac group, after six weeks *"statistical analysis of the data showed the therapeutic equivalence of the two test medications"* (including parameters: pain, stiffness and functionality). At the end of the study no clear differences in patients' assessment of efficacy ('very good' and 'good') or tolerance ('very good' and 'good') were shown.

Table 19 Evidence summary table of Maronna et al. (2000) on the effectiveness of homeopathy for the treatment of osteoarthritis

Study ID	Maronna 2000
Level of evidence	Level II
Risk of bias	Moderate to high risk of bias
N	121 randomised, 114 analysed
Patient population	Men and women suffering from mild to moderate osteoarthritis of the knee for at least six months; diagnosis confirmed either clinically or radiologically according to criteria established by Altman or Kellgren; scoring at least 5 and not more than 16 on Lequesne's index of pain and functionality
Intervention	One tablet of Zeel comp. (homeopathic complex preparation) and a diclofenac placebo three times per day for 10 weeks
Comparator	One tablet of diclofenac 25 mg and a Zeel comp. placebo tablet three times per day for 10 weeks
Outcomes	**Results**
WOMAC Osteoarthritis Index (average)	After 2 and 4 weeks, a marked improvement was first observed in the diclofenac group; after 6 weeks *"statistical analysis of the data showed the therapeutic equivalence of the two test medications."*
Total index, pain index, stiffness index, functionality index: reduction after 2 weeks, 4 weeks, 6 weeks, 10 weeks (average)	*"At the latest, equivalence was established between the two groups after six weeks."*
Patient assessment of efficacy at end of study ('very good' or 'good') (N, %)	No clear difference (significance not reported)
Patient assessment of tolerance ('very good' or 'good') (%)	No clear difference (significance not reported)

Abbreviations: N: number; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Conditions not considered in the Overview Report

2.2.16 Coffee-related insomnia

One non-randomised prospective study (Level III-2) was identified that investigated the effect of homeopathic remedies on sleep characteristics of young adults with coffee-related insomnia (Bell et al. 2011) (**Table 20**). The study enrolled individuals aged 18 to 31 years (70 enrolled; 59 received treatment; 54 analysed), who all received placebo pellets on night eight, and homeopathy pellets (either Nux Vomica or Coffea Cruda) on night 22 of a four week study. The study was judged to be at a moderate to high risk of bias overall. The risk of selection bias was judged to be high (for the allocation to placebo and homeopathy), with all patients receiving the placebo first, followed by the homeopathy second; *"dynamic allocation"* was however utilised to randomise participants to one of two homeopathic remedies on night 22. The study was described as *"single-blind"*, with participants blinded through the use of an identical placebo, and study personnel not blind. There was no description of blinded outcome assessment, and thus the risks of performance and detection bias were judged to be unclear. The risk of attrition bias was judged to be high, with a large number of post 'enrolment' exclusions/losses, and a high proportion of the polysomnography recordings unavailable for analysis (missing data were imputed by linear interpolation or last value carried forward). Primary and secondary outcomes were not pre-specified, with the study aiming to test feasibility more so than outcomes such as insomnia; with no access to a trial protocol, the risk of reporting bias was judged as unclear.

In Bell et al. (2011), the homeopathic remedies (Nux Vomica and Coffea Cruda) significantly increased total sleep time and other sleep parameters (non rapid eye movement (NREM) sleep including more minutes in stage 2 and increased slow wave sleep (SWS)) compared with placebo. The homeopathic remedies were however associated with significantly more sleep disruptions after sleep onset, with more awakenings, number of stage changes, and more type 2 arousals compared with placebo. Only Nux Vomica was associated with a significant increase on the arousal index. For subjective measures, there was no significant difference seen for ratings of global sleep quality (PSQI: Pittsburgh sleep quality index) with homeopathy, and despite the increase in sleep disruption observed with homeopathy, participants reported lower profile of mood states (POMS) fatigue ratings with homeopathy.

Table 20 Evidence summary table of Bell et al. (2011) on the effectiveness of homeopathy for the treatment of coffee-related insomnia

Study ID	Bell 2011
Level of evidence	Level III-2
Risk of bias	Moderate to high risk of bias
N	70 enrolled, 59 received treatment, 54 analysed
Patient population	Young adults aged 18 to 31 years (male and female) with coffee-related insomnia
Intervention	Combined remedies, Nux Vomica, Coffea Cruda
Comparator	Placebo
Outcomes	**Results**
Total sleep time	Significantly increased with combined and single remedies
Stage 2	Significantly increased with combined and single remedies
NREM	Significantly increased with combined and single remedies
SWS	Significantly increased with combined and single remedies
Awakenings	Significantly increased with combined and single remedies
Arousal index	Significantly increased with Nux Vomica only

Type 2 arousals	Significantly increased with combined remedies and Nux Vomica
POMS-fatigue	Significantly increased with combined remedies only
Weekly PSQI global score	No significant differences

Abbreviations: N: number; NREM: non rapid eye movement sleep; POMS; profile of mood states scale; PSQI: Pittsburgh sleep quality index; SWS: slow wave sleep (stages 3 and 4 mins)

2.2.17 Arsenic toxicity

Two randomised controlled trials (Level II) were identified assessing the effects of homeopathy for the treatment of arsenic toxicity (Belon et al. 2007 and Khuda-Bukhsh et al. 2011).

Belon et al. (2007) investigated the effects of homeopathy on individuals living in an arsenic-contaminated area showing symptoms of arsenic poisoning (**Table 21**). The trial randomised 39 individuals to homeopathy (Arsenicum Album-30) or placebo over a two month study period. This trial was judged to be at a high risk of bias overall. Verum and placebo bottles were coded, with participants asked to choose a bottle from a tray. Thus allocation concealment was judged to be at high risk of bias, further reinforced by an imbalance in numbers randomised to verum and to placebo and a later large differential loss to follow-up between verum and placebo at two months, making the risk of attrition bias high. Selective outcome reporting bias was also judged to be high, with incomplete reporting of results and no specification of primary and secondary outcomes.

In Belon et al. (2007), packed cell volume, neutrophil, eosinophil and lipid peroxidation readings and some liver function tests showed significant improvement for verum compared with placebo, but a range of tests did not show significant differences. While arsenic concentration in blood samples showed a significant reduction for verum compared with placebo, urine samples did not. Improvements in health outcomes were reported narratively and rather vaguely.

A second randomised controlled trial (Khuda-Bukhsh et al. 2011) assessed the effects of a lower, millesimal potency homeopathic remedy (Arsenicum Album LNM 0/3) also for ameliorating arsenic toxicity (**Table 21**). This trial randomised 24 individuals with initial signs or symptoms of arsenic poisoning, to a homeopathic remedy (Arsenicum Album LM 0/3) or a placebo for two months. The trial was also judged to be at a high risk of bias overall. The risk of selection bias was judged to be high, with no method for random sequence generation reported, and allocation concealment judged to be at a high risk of bias (25 *"similar"* bottles containing the homeopathy remedy, and 25 containing placebo were marked with *"numerical codes"* and kept on a tray; subjects could take a bottle of their choice). The risks of performance bias and detection bias were judged to be unclear – while a placebo was used, the high and differential loss to follow up suggest that participants may not have been successfully blinded; blinding of outcome assessors was not stated. The trial was at a high risk of attrition bias, with 50% loss to follow up (14/28 participants randomised were analysed; exact losses to follow-up per group were not clear, with numbers randomised to the two groups not reported). The risk of reporting bias was judged to be high – for some outcomes, results presented in text and tables do not seem to correspond, and for some outcomes, statements such *as "not statistically significant"* or *"similar"* are made.

In Khuda-Bukhsh et al. (2011) there were no significant differences between groups in the mean arsenic content in blood or urine at follow up. Similarly, for all 'biochemical parameters' assessed at two months there did not appear to be any clear differences between groups. For the 'pathophysiological parameters' assessed, there were no significant differences between groups,

except for mean lymphocyte viability, which was reported to be significantly higher in the homeopathy group compared with the placebo group at two month follow up. No significant differences between groups were shown in anti-nuclear antibody titre, and while a *"slight lowering of matrix metalloproteinase activity"* was reported for the homeopathy group, this difference was not significant.

Table 21 Evidence summary table of Belon et al. (2007) and Khuda-Bukhsh et al. (2011) on the effectiveness of homeopathy for the treatment of arsenic toxicity

Study ID	Belon 2007
Level of evidence	Level II
Risk of bias	High risk of bias
N	39 randomised, results available for 25
Patient population	Participants with symptoms of arsenic poisoning
Intervention	Arsenicum Album-30
Comparator	Placebo (sugar infused with alcohol)
Outcomes	**Results**
PCV at 2 months (%)	Significant difference in favour of homeopathy
Hb at 2 months (g/dL)	No significant difference
ESR at 2 months (mm/hour)	No significant difference
Triglycerides at 2 months (units unknown)	No significant difference
Creatinine at 2 months (*"amount"*)	No significant difference
Neutrophil at 2 months (%)	Significant difference in favour of homeopathy
Eosinophil at 2 months (%)	Significant difference in favour of homeopathy
GSH at 2 months (nM/mL)	No significant difference
AST at 2 months (nM/100 mg protein/min)	No significant difference
ALT at 2 months (nM/100 mg protein/min)	Significant difference in favour of homeopathy
LPO at 2 months (nM/MDA/mL)	Significant difference in favour of homeopathy
G6PD at 2 months (IU/L)	No significant difference
GGT at 2 months (IU/L)	Significant difference in favour of homeopathy
Arsenic concentration in urine at 2 months (ppb)	No significant difference
Arsenic concentration in blood at 2 months (ppb)	Significant difference in favour of homeopathy
Study ID	Khuda-Bukhsh 2011
Level of evidence	Level II
Risk of bias	High risk of bias
N	28 randomised, results available for 14
Patient population	People with initial signs or symptoms or arsenic poisoning.
Intervention	Arsenicum Album LM 0/3, 10 drops of the remedy twice daily for 2 months.
Comparator	Placebo (as above)
Outcomes	**Results**
Arsenic content in urine and blood at 2 months (µg/mL) (mean, SD)	No significant differences
Biochemical parameters at 2	Unclear – but appears no significant differences

months (AcP (nmol/(g protein.min)); AlkP (nmol/(g protein.min)); ALT (nmol/(g protein.min)); AST (nmol/(g protein.min)); LPO (nmol MDA/mL sample); GSH (nmol/mL sample); GGT (IU/L); G6PD (IU/L)) (mean, SD)	
Pathophysiological parameters at 2 months (blood glucose (mg/L); Hb (g/L); ESR (mm/h); total cholesterol (mg/L); HDL-C (mg/L); LDL-C (mg/L); triacylglycerol (mg/L); creatinine (mg/L); PCV (%); lymphocyte viability (%))(mean, SD)	No significant differences except for lymphocyte viability which was significantly higher in the homeopathy group compared with placebo group
Matrix metalloproteinase at 2 months	Band intensities *"Slightly lower"* in homeopathy group (assumed no significant differences)
ANA titre at 2 months (titre positive, negative or in borderline) (N, %)	No significant difference

Abbreviations: AcP: acid phosphatase; AlkP: alkaline phosphatase; ALT: alanine aminotransferase; ANA: anti-nuclear antibody; AST: aspartate aminotransferase; ESR: erythrocyte sedimentation rate; g: grams; GGT: gamma glutamyl transferase; GSH: reduced glutathione; G6PD: glucose-6-phosphate dehydrogenase; Hb: haemoglobin; HDL-C: high-density lipoprotein cholesterol; IU: international unit; L: litre; LDL-C: low-density lipoprotein cholesterol; LPO: lipid peroxidase; MDA: malonaldehyde; mg: milligrams; mm: millimetres; N: number; nmol: nanomole; PCV: packed cell volume; SD: standard deviation; µg: micrograms

2.2.18 Anal fissures

One randomised controlled trial (Level II) was identified assessing the homeopathic treatment of anal fissures (Bignamini et al. 1991) (**Table 22**). The trial randomised 31 patients with anal fissure symptomatology to either Nitricum acidum 9 CH (five granules dissolved sublingually, each morning for 15 days) or to a placebo. The trial was judged to be at a high risk of bias overall (based on information available). No details were provided regarding sequence generation or allocation concealment methods, and thus the risk of selection bias was unclear. While the authors stated that a placebo was used, no details were provided regarding its characteristics, and no details were provided regarding blinding of study personnel or *"objective"* outcome assessors; thus the risks of performance and detection bias were also judged to be unclear. There was no information provided on whether there were any losses or exclusions and thus the risk of attrition bias was unclear. The risk of reporting bias was judged to be high, as for four of the six outcomes, the p value was presented only as *"n.s."*

In Bignamini et al. (1991), no significant differences between groups were reported for proctodynia (pain during and after defecation), proctorrhagia (bleeding from the anus), itching, or the objective appearance of the lesion. Significantly fewer participants in the homeopathy group reported a burning sensation, and there was a difference in subjective opinion of treatment efficacy in favour of

homeopathy (with more participants in the homeopathy group reported being 'healed' and fewer reported having 'exacerbated').

Table 22 Evidence summary table of Bignamini et al. (1991) on the effectiveness of homeopathy for the treatment of anal fissures

Study ID	Bignamini 1991
Level of evidence	Level II
Risk of bias	High risk of bias
N	31
Patient population	Patients with anal fissure symptomatology
Intervention	Nitricum acidum 9 CH (five granules dissolved sublingually, each morning for 15 days)
Comparator	Placebo
Outcomes	**Results**
Proctodynia (N, %)	No significant difference
Proctorrhagia (N, %)	No significant difference
Itching (N, %)	No significant difference
Burning sensation (N, %)	Significantly fewer participants in homeopathy group
Lesions (N, %)	No significant difference
Subjective opinion of treatment efficacy (N, %)	Significantly different between groups (fewer 'unchanged' in homeopathy group; fewer 'healed' in placebo group; more 'exacerbated' in placebo group)

Abbreviations: N: number

2.2.19 Haemorrhoidal disease

One multi-centre randomised controlled trial (Level II) was identified that assessed the use of homeopathy for acute haemorrhoids (Chakraborty et al. 2013) (**Table 23**). The trial randomised 279 patients to receive either individualised homeopathic treatment or placebo for 90 days. The trial was judged to be at a moderate risk of bias overall. Considering the risk of selection bias, a computer-generated sequence of random numbers was used; however the methods used to conceal allocation were not reported. Participants were blinded with the use of an identical placebo, however due to the need for the study investigators to individualise the homeopathic treatment, they were not blinded; thus the risk of performance bias was judged to be unclear. The blinding of outcome assessors was not stated, and thus the risk of detection bias was unclear. Losses to follow up were counted in the group to which they were originally allocated, and the risk of attrition bias was judged as low (138/139 participants were analysed on an intention to treat basis). Similarly, the risk of reporting bias was low, with data reported for expected outcomes.

In Chakraborty et al. (2013), the primary outcomes were changes in haemorrhoidal symptoms; the trial reported that after 90 days of treatment, there was a significant difference in favour of homeopathy in the mean area under the curve (AUC) for bleeding, pain, heaviness and itching, however no significant difference was seen for discharge. Considering secondary outcomes, it was reported that significant differences in favour of homeopathy were found in the World Health Organization Quality of Life-BREF physical, psychological and environmental domains; however no differences was observed for the social domain. The proportions of patients with improvements in

symptoms (bleeding, pain, heaviness and itching) were also reported to be significantly higher in the homeopathy group compared with the placebo group at the end of treatment.

Table 23 Evidence summary table of Chakraborty et al. (2013a) on the effectiveness of homeopathy for the treatment of haemorrhoidal disease

Study ID	Chakraborty 2013a
Level of evidence	Level II
Risk of bias	Moderate risk of bias
N	279 randomised, 278 analysed
Patient population	Patients aged 25 to 60 years with haemorrhoids
Intervention	Individualised homeopathic treatments
Comparator	Placebo
Outcomes	**Results**
Bleeding after 90 days (median AUC, 95% CI)	Significant difference in favour of homeopathy
Pain after 90 days (median AUC, 95% CI)	Significant difference in favour of homeopathy
Heaviness after 90 days (median AUC, 95% CI)	Significant difference in favour of homeopathy
Itching after 90 days (median AUC, 95% CI)	Significant difference in favour of homeopathy
Discharge after 90 days (median AUC, 95% CI)	No significant difference
Anitis after 90 days (median AUC, 95% CI)	Significant difference in favour of homeopathy
WHOQOL-BREF physical domain (median, 95% CI)	Significant difference in favour of homeopathy
WHOQOL-BREF psychological domain (median, 95% CI)	Significant difference in favour of homeopathy
WHOQOL-BREF social domain (median, 95% CI)	No significant difference
WHOQOL-BREF environmental domain (median, 95% CI)	Significant difference in favour of homeopathy
Bleeding improvement at day 90 (N, %)	Significant difference in favour of homeopathy
Pain improvement at day 90 (N, %)	Significant difference in favour of homeopathy
Heaviness improvement at day 90 (N, %)	Significant difference in favour of homeopathy
Itching improvement at day 90 (N, %)	Significant difference in favour of homeopathy
Discharge improvement at day 90 (N, %)	Significant difference in favour of homeopathy
Bleeding clearance time (median) (days)	Significant difference in favour of homeopathy
Pain clearance time (median) (days)	Significant difference in favour of homeopathy

Abbreviations: AUC: area under the curve; CI: confidence interval; N: number; WHOQOL-BREF: World Health Organization Quality of Life-BREF

2.2.20 Pulmonary tuberculosis

One randomised controlled trial (Level II) was identified that investigated the use of homeopathic preparations and standard drug regimens for treating people with multidrug resistant tuberculosis (Chand et al. 2014) (**Table 24**). The trial randomised 120 patients of all age groups, diagnosed with chronic tuberculosis to homeopathy and standard drug regimens or to placebo and standard drug regimens over a 24 month period. This trial was judged to be at a moderate risk of bias overall. While adequate methods were used to generate the random sequence, it was not clear how the individualised homeopathic treatment was allocated in a concealed manner. The treating physicians, pharmacist and the patients remained blinded throughout the study so the risk of performance and detection was judged to be low. However if allocation concealment was not adequate, blinding of participants and personnel may have been compromised, particularly for subjective outcomes. The risk of attrition bias was judged to be unclear, with over 18% of participants having missing data in each group and the last observation carried forward method used for intention-to-treat analyses. Risk of selective outcome reporting bias was judged to be unclear; no other major sources of bias were evident.

In Chand et al. (2014) neither sputum or culture conversions were significantly different between the homeopathy and standard drug regimen (SR) group and the placebo and SR group after 24 months of treatment. Significantly more patients in the homeopathy and SR group showed improvements on chest x-ray compared with patients in the placebo and SR group. No significant differences between relapse after completion of treatment (there were no relapses), weight gain, erythrocyte sedimentation rate, haemoglobin or symptom score. Chand et al. (2014) also analysed results separately for the subgroup of culture positive patients, and found that significantly more patients in the homeopathy and SR group showed improvements on chest x-ray compared with patients in the placebo and SR group; significant positive changes in weight, haemoglobin and erythrocyte sedimentation rate were also seen for this subgroup of patients.

Table 24 Evidence summary table of Chand et al. (2014) on the effectiveness of homeopathy for the treatment of multi-drug resistant pulmonary tuberculosis

Study ID	Chand 2014
Level of evidence	Level II
Risk of bias	Moderate risk of bias
N	120
Patient population	Multidrug resistant tuberculosis patients (both culture positive and culture negative)
Intervention	Individualised homeopathy and SR
Comparator	Placebo and standard regimen
Outcomes	**Results**
Sputum conversion (N, %)	No significant difference
Culture conversion (N, %)	No significant difference
Chest x-ray improvement (N, %)	Significantly more patients in the homeopathy and SR group
Chest x-ray deterioration (N, %)	Significantly fewer patients in the homeopathy and SR group
Compliance (N, %)	No clear difference (significance not reported)
Relapse after treatment completed (N, %)	No cases in either group
Weight gain (kg) (mean, SD)	No significant difference

ESR reduction (mm) (mean, SD)	No significant difference
Hb increase, g% (mean, SD)	No significant difference
Symptom score (mean, SD)	No significant difference
Culture positive subgroup of patients	
Sputum conversion (N, %)	No significant difference
Chest x-ray improvement (N, %)	Significantly more patients in the homeopathy and SR group
Chest x-ray deterioration (N, %)	Significantly fewer patients in the homeopathy and SR group
Weight gain (kg) (mean, SD)	Significantly higher in the homeopathy and SR group
ESR reduction (mm) (mean, SD)	Significantly greater in the homeopathy and SR group
Hb increase, g% (mean, SD)	Significantly higher in the homeopathy and SR group
Symptom score (mean, SD)	No significant difference

Abbreviations: ESR: erythrocyte sedimentation rate; g: grams; Hb: haemoglobin; kg: kilograms; mm: millimetres; N: number; SD: standard deviation; SR: standard drug regimen

2.2.21 Plantar fasciitis

One randomised controlled trial (Level II) was identified that investigated the use of homeopathy for the treatment of plantar fasciitis (Clark and Percivall 2000) (**Table 25**). The trial randomised 18 patients aged 16 to 70 years with plantar fasciitis, to either the tablets containing the homeopathic remedy Ruta graveolens or to placebo tablets (two tablets, three times a day for 14 days). The trial was judged to be at a high risk of bias overall. While it was reported that randomly numbered bottles were used to conceal allocation, no method for generating the random sequence was reported; thus the risk of selection bias was judged to be unclear. The trial was *"double blind"* with the use of an identical placebo; thus the risks of performance and detection bias were judged to be low. Of the 18 participants, four were excluded (22.2%) for varying reasons; it was not clearly reported from which groups they were excluded and thus the risk of attrition bias was judged to be unclear. The risk of reporting bias was judged to be high, with pain (on a visual analogue scale) being the only reported outcome; side effects were mentioned in the Discussion only *("negligible"*). The risk of other bias was judged to be high; with no baseline characteristics reported by group, and in the Discussion the authors note variation in the patients' activity levels prior to and during the study.

In Clark and Percivall (2000) mean pain was reported per group for days 1-14 on a visual analogue scale. The authors report that *"The results show a significant ($p<0.05$) difference in the means by day 4;"* and also reported that the gradient for the homeopathic treatment was *"greater than that of the placebo (significant at 95% Confidence Level) indicating a faster resolution of pain level over the same time period."*

Table 25 Evidence summary table of Clark and Percivall (2000) on the effectiveness of homeopathy for the treatment of plantar fasciitis

Study ID	Clark 2000
Level of evidence	Level II
Risk of bias	High risk of bias
N	18 assumed to be randomised, 14 analysed
Patient population	Patients with plantar fasciitis aged 16 to 70 years.
Intervention	Ruta graveolens (2 drops of 30C strength with sugar tablets); 2 tablets, 3 times a day for 14 days.

Comparator	Placebo (sugar tablets).
Outcomes	**Results**
Pain from day 1 to day 14 (100 mm VAS) (mean, SD): linear regression analysis	Significantly greater gradient (faster resolution) for the homeopathy group than the placebo group (significantly better for the homeopathy group by day 4)

Abbreviations: mm: millimetres; N: number; SD: standard deviation; VAS: Visual Analogue Scale

2.2.22 Mental fatigue

One randomised controlled trial (Level II) with a crossover design was identified that investigated the use of homeopathy (Kali phos) in university staff and students with self-reported mental fatigue (Dean et al. 2012) (**Table 26**). The trial randomised 86 participants to homeopathy first and placebo second (after a seven day wash-out period); and vice versa. This trial was judged to be at a low risk of bias overall. Adequate methods were used to generate the random sequence (computer-generated), and also for concealment of allocation (pharmacy preparation). The trial was placebo-controlled and identity of powders was not revealed by the pharmacy until after completion of the analysis, so risk of performance and detection bias was judged to be low. Only two outcomes were reported but we were unable to assess if this constituted selective outcome reporting bias (with no access to a trial protocol). The risk of attrition bias was judged to be low.

In Dean et al. (2012) the primary outcomes were accuracy on the Stroop Colour-Word test and mental fatigue scores (Chalder). No other outcomes were reported. No significant differences were seen between groups for these two outcomes. Limitations on how the Stroop Colour-Word test was administered meant that the test was not sufficiently challenging and therefore not sufficiently sensitive, giving a 'ceiling effect'.

Table 26 Evidence summary table of Dean et al. (2012) on the effectiveness of homeopathy for the treatment of mental fatigue

Study ID	Dean 2012
Level of evidence	Level II
Risk of bias	Low risk of bias
N	86 (crossover design)
Patient population	University staff and students with self-reported mental fatigue
Intervention	Homeopathy (Kali phos) (then placebo)
Comparator	Placebo (then homeopathy: Kali phos)
Outcomes	**Results**
Stroop Colour-Word test (mean, 95% CI)	No significant difference
Mental fatigue scores (Chalder) (mean, 95% CI)	No significant difference

Abbreviations: CI: confidence interval; N: number

2.2.23 Acute febrile infections

One prospective cohort study (Level III-2) was identified that investigated the use of homeopathic drops in children with infectious fever (Derasse et al. 2005) (**Table 27**). The study compared viburcol drops with acetaminophen in 198 children less than 12 years of age with acute infections accompanied by fevers. This study was judged to be at a high risk of bias overall. There was no randomisation (the choice of treatment was left to the practitioner's discretion) and therefore selection bias was judged as high. There was no blinding of participants and personnel, with most outcomes subjective, so performance and detection bias were also judged to be high. The risk of attrition bias was judged to be unclear, with over 20% of children discontinuing treatment early *"for reasons of symptom disappearance".* Selective outcome reporting bias was unclear with actual data and p values not always reported, as was the risk of 'other bias', due to unequal numbers in intervention and comparison groups.

In Derasse et al. (2005) most of the outcomes related to symptoms (fever, cramps, distress, crying and temperature) were within the predefined non-inferiority margin. Disturbed sleep was less frequent with acetaminophen, while total symptom score, eating/drinking difficulties, and overall severity of infection showed improvement with viburcol. Significantly more carers rated the treatment and its tolerability as excellent for viburcol compared with acetaminophen, while compliance did not differ significantly between groups. No adverse events were reported.

Table 27 Evidence summary table of Derasse et al. (2005) on the effectiveness of homeopathy for the treatment of acute febrile infections

Study ID	Derasse 2005
Level of evidence	Level III-2
Risk of bias	High risk of bias
N	198
Patient population	Children (aged less than 12 years) with infectious fever (e.g. rhinitis, bronchitis, otitis media, tonsillitis)
Intervention	Complex homeopathic medicine (viburcol)
Comparator	Acetaminophen
Outcomes	**Results**
Treatment rated as excellent (N, %)	Significantly better for viburcol
Global evaluation of moderate or lower (N, %)	No clear difference (significance not reported)
Tolerability rated as excellent (N, %)	Significantly better for viburcol
Compliance rated as excellent (N, %)	No clear difference (significance not reported)
Adverse events (N, %)	No difference (none reported for either group)
Temperature (change from baseline) (mean, SD)	No clear difference (significance not reported)
Fever score (final) (mean, SD)	No clear difference (significance not reported)
Time to symptomatic improvement (24 hours, 48 hours, 72 hours) (N, %)	No significant difference
Fever, cramps, distress, crying, temperature, disturbed sleep, total score, eating/drinking difficulties, overall severity of infection scores (non-inferiority analysis)	Viburcol non-inferior to acetaminophen on all variables

Abbreviations: N: number; SD: standard deviation

2.2.24 Varicose veins

One randomised controlled trial (Level II) was identified that investigated the use of homeopathic Poikiven versus placebo in patients with primary varicose veins (Ernst et al. 1990) (**Table 28**). The trial randomised 61 patients: 31 patients (62 legs) to the Poikiven group and 30 patients (60 legs) to placebo. This trial was judged to be at a high risk of bias overall. While many aspects of the methodology were not reported and therefore judged as unclear risk of bias, the baseline imbalance may indicate a 'failure' of randomisation. In addition the objective outcome measures were not adjusted for within-patient factors (i.e. two legs per patient). No losses to follow-up were reported. Reporting of outcomes was incomplete and both primary and secondary outcomes were not pre-specified, therefore reporting bias was judged to be high.

In Ernst et al. (1990), none of the objective outcomes, except venous filling time at 24 days, showed significant differences between groups; venous filling time was significantly increased in the Poikiven group. In contrast, all of the subjective outcomes regarding symptoms (cramps, itching, leg heaviness, pain on prolonged standing, and need for leg elevation) were reported by patients to be significantly improved in the Poikiven group compared with the placebo group.

Table 28 Evidence summary table of Ernst et al. (1990) on the effectiveness of homeopathy for the treatment of varicose veins

Study ID	Ernst 1990
Level of evidence	Level II
Risk of bias	High risk of bias
N	61
Patient population	Individuals with primary varicose veins
Intervention	Poikiven
Comparator	Placebo
Outcomes	**Results**
Leg volume, venous filling time, calf circumference, haematocrit, plasma viscosity and blood viscosity (mean, SEM)	No significant differences between groups, except for venous filling time at day 24 (significantly increased in homeopathy group)
Subjective symptoms (patient reported): cramps, itching, leg heaviness, pain on prolonged standing, reduced need for leg elevation	All were rated as significantly improved in the Poikiven group compared with the placebo group

Abbreviations: N: number; SEM: standard error of the mean

2.2.25 Vertigo

Two Level II studies and one Level III-2 study were identified assessing the effects of homeopathy on the treatment of vertigo (Issing et al. 2005; Weiser et al. 1998; Wolschner et al. 2001).

Issing et al. (2005) was a randomised controlled trial that investigated the use of the homeopathic preparation Vertigoheel for treating vertigo in an older population 60 to 80 years (**Table 29**). The

trial randomised 170 patients to Vertigoheel or to Ginkgo biloba for eight weeks. This trial was judged to be at a moderate to high risk of bias overall. Methods of randomisation (sequence generation and allocation concealment) were not reported and thus the risk of selection bias was judged as unclear. Participants and personnel were blinded, although, differences between tablets were not explained. Most outcomes were of a subjective nature. The risk of attrition bias was judged to be unclear, with an intention-to-treat analysis not fully conducted. Reporting of outcomes was incomplete leading to a judgment of unclear for selective outcome reporting bias. Other bias was also judged to be unclear, with some baseline imbalance.

In Issing et al. (2005) the primary outcomes were scores on a dizziness questionnaire and frequency, duration and intensity of episodes of dizziness. None of these showed significant differences between Vertigoheel and Ginkgo biloba. The 'combined test' met the pre-specified criteria for demonstrating that Vertigoheel was not inferior to Ginkgo biloba. Other secondary outcomes such line walking, global assessments (patient and doctor), tolerability and compliance did not show clear differences between groups (significance not reported). Three adverse events with a suspected relation to the study medication were reported – one case of abdominal pain and nausea for Vertigoheel and two cases for Ginkgo biloba (abdominal pain and flatulence).

Weiser et al. (1998) was a *"confirmative equivalence"* randomised controlled trial (Level II) also comparing the use of the homeopathic preparation Vertigoheel to conventional treatment in patients with vertigo (**Table 29**). The trial randomised 119 individuals with acute or chronic vertigo symptoms of various origins, to Vertigoheel, 15 drops, 3 times a day, plus a placebo, or to a conventional treatment – betahistine hydrochloride (18 mg per day in 3 daily doses) plus a placebo for six weeks. Overall, the trial was judged to be at a moderate risk of bias. The trial used adequate methods to generate the random sequence (computer generated list), however methods for allocation concealment were not clearly detailed. Blinding of participants, personnel and outcome assessors was achieved through the use of placebos for both groups. The risk of attrition bias was judged to be unclear – 2/119 participants were excluded with as their data was *"inconsistent and not comprehensible";* a further 12/119 participants were excluded for reasons such as lack of compliance and loss to follow up. The risk of reporting bias was also unclear; while data were reported clearly in tables for the primary and a number of secondary outcomes, for some outcomes, general statements were made (and no data provided) such as: *"Mean relevant changes from baseline were not observed in either treatment group…."*

In Weiser et al. (1998) the primary outcomes were the frequency, duration and intensity of vertigo attacks, and no significant differences between the homeopathy and betahistine groups were shown for these outcomes. Similarly for the range of secondary outcomes reported – including mean change from baseline vertigo-specific questionnaire scores, quality of life scores (across all physical health and mental health domains), and global assessment of efficacy and tolerance by participants and investigators – no significant differences between groups were reported. For adverse effects, it was reported that 31 patients experienced 29 adverse events in the homeopathic group and 28 in the betahistine group (numbers of adverse events per group, and not patients per group reported). The authors concluded that *"Concerning the main efficacy variable, therapeutic equivalence between the homeopathic remedy and betahistine could be shown with statistical significance (confirmative analysis)."*

Wolschner et al. (2011) was a prospective cohort study (Level III-2) that compared Vertigoheel to dimenhydrinate for the treatment of vertigo (**Table 29**). The study included 774 individuals suffering from either vestibular or non-vestibular vertigo, who received either Vertigoheel or dimenhydrinate tablets – the dosage and duration of treatment was left to the discretion of the physician, with

treatment lasting for a maximum of eight weeks. The study was judged to be at a high risk of bias overall. The processes for selection of the exposed (homeopathy) and un-exposed (dimenhydrinate) groups were not clear; the study detailed that 159 physicians participated, however it was not detailed whether all physicians could prescribe both treatments, or whether specific physicians prescribed homeopathy/dimenhydrinate. With lack of randomisation, the risk of selection bias was judged to be high. In regards to comparability of the two groups, the authors discuss some baseline differences (such as concomitant illness), however no potential confounders were controlled for in the analyses, with the results presented as summary statistics (such as percentages) only. There was no blinding of participants or study personnel, and outcome assessment was not conducted blind, with outcomes largely assessed by the prescribing physicians or the patients themselves; therefore the risks of performance and detection bias were judged as high. It was not detailed and unclear as to whether there were any losses to follow up, and thus the risk of attrition bias was judged to be unclear. There was insufficient information available to confidently assess risk of reporting bias.

In Wolschner et al. (2011), both groups were reported to have a statistically significant reduction in the average number of vertigo attacks, average score of intensity of vertigo, and average daily duration of vertigo symptoms from baseline to the end of treatment; there was no clear difference between groups (significance not reported). Similarly, the study reported significant reductions in symptom severity across the study duration for both groups, with no apparent difference between groups in effect. In regards to improvement of vertigo symptoms in the first week of therapy, 49% of patients in the homeopathy group had improvement vs. 59% in the dimenhydrinate group. The physicians rated the effect of the medication as good or very good for 88% of patients in the homeopathy group and 87% in the dimenhydrinate group; and compliance was rated as good or very good in 96% of the homeopathy group and 93% in the dimenhydrinate group. Premature termination of therapy occurred in 1.4% of the homeopathy group compared with 4.3% of the dimenhydrinate group. Overall, the physicians rated the tolerance as good or very good for 99% of the homeopathy group and 98% of the dimenhydrinate group. The authors concluded that: *The study confirms that Vertigoheel is a safe and effective treatment option for vertigo of varying etiology and is therapeutically equivalent to medications containing dimenhydrinate."*

Table 29 Evidence summary table of Issing et al. (2005), Weiser et al. (1998) and Wolschner et al. (2011) on the effectiveness of homeopathy for the treatment of vertigo

Study ID	Issing 2005
Level of evidence	Level II
Risk of bias	Moderate to high risk of bias
N	170 randomised, 154 analysed
Patient population	Patients aged 60 to 80 years with atherosclerosis-related vertigo
Intervention	Vertigoheel
Comparator	Ginkgo biloba
Outcomes	**Results**
Dizziness questionnaire (mean, SD)	No significant difference
Frequency, duration and intensity of vertigo (mean, SD)	No significant difference
Line walking (mean, SD)	No clear difference (significance not reported)
Unterberger's stepping test and rotation (mean, SD)	No clear difference (significance not reported)
Combined test (mean, SD)	In favour of Vertigoheel (p = 0.05)
Psychological or physical symptoms of	No clear difference (significance not reported)

dizziness (N, %)	
Compliance (mean, SD)	No clear difference (significance not reported)
Global assessments (patients and doctors) (N, %)	*"no noteworthy differences"*
Tolerability (patients and doctors) (N, %)	No clear difference (significance not reported)
Adverse events with suspected relationship to study medication (N, %)	Vertigoheel: 1; Ginkgo biloba: 2
Study ID	Weiser 1998
Level of evidence	Level II
Risk of bias	Moderate risk of bias
N	119 randomised, 105 analysed
Patient population	Individuals with acute or chronic vertigo symptoms of various origins, with a minimum of 3 vertigo attacks during the week before the study began, and an assessment of intensity of vertigo attacks by the patient between 2 and 4 on a 5-point rating scale.
Intervention	Homeopathic preparation (Vertigoheel), 15 drops, 3 times a day, plus a placebo for 42 consecutive days.
Comparator	Betahistine hydrochloride (18 mg per day) and placebo (as above).
Outcomes	**Results**
Frequency of vertigo attacks (5-point rating scale)^ (mean, SD)	No significant difference
Duration of vertigo attacks (5-point rating scale)^ (mean, SD)	No significant difference
Intensity of vertigo attacks (5-point rating scale)^ (mean, SD)	No significant difference
Vertigo-specific questionnaire scores* (mean, SD)	No significant differences
Quality of life physical health scores (physical functioning, role limitations attributed to physical problems, bodily pain, general health)^ (mean, SD)	No significant differences
Quality of life mental health scores (vitality, role limitations attributed to emotional problems, social functioning, mental health)^ (mean, SD)	No significant differences
Global assessment of efficacy by investigators and patients	No significant difference
Global tolerance assessments of the investigators and patients	No significant difference
Adverse events	No clear difference (29 in the homeopathic group; 28 in the betahistine group among 31 patients)
Study ID	Wolschner 2001
Level of evidence	Level III-2

Risk of bias	High risk of bias
N	774
Patient population	Patient suffering either vestibular or non-vestibular vertigo.
Intervention	Vertigoheel tablets, the dosage and duration of treatment was left to the discretion of the physician, up to a maximum of 8 weeks. (In most cases the prescribed dose was 2-3 tablets three times a day).
Comparator	Dimenhydrinate (50 mg tablets), (as above). (The standard dose (59% patients) of dimenhydrinate was 50 mg 2-3 times per day)
Outcomes	**Results**
Number of vertigo attacks at 'exit examination'** (mean)	No clear difference (significance not reported)
Intensity of vertigo at 'exit examination' score (scale 0-4)** (mean)	No clear difference (significance not reported)
Duration of vertigo symptoms at 'exit examination' score (scale 0-5)** (mean)	No clear difference (significance not reported)
Degree of severity of nausea; vomiting; perspiration scores at 'exit examination' (scale 0-3)** (mean)	No clear difference (significance not reported)
Improvement of vertigo symptoms in the first week of therapy; no improvement during treatment (N, %)	No clear difference (significance not reported)
Good or very good effect of medication; fair effect; no success (physician rated) (N, %)	No clear difference (significance not reported)
Good or very good compliance (physician rated) (N, %)	No clear difference (significance not reported)
Premature termination due to inadequate efficacy (N, %)	No clear difference (significance not reported)
Adverse effects (N, %)	No clear difference (significance not reported)
Tolerability good or very good; fair; poor (physician rated) (N, %)	No clear difference (significance not reported)

^change: last 7 days of treatment minus baseline
*change: after 42 days minus baseline
**after a maximum of 8 weeks

Abbreviations: N: number; SD: standard deviation

2.2.26 Chronic periodontitis

One randomised controlled trial (Level II) was identified assessing the use of homeopathy in the treatment of chronic periodontitis (Mourão et al. 2013) (**Table 30**). The trial randomised 40 patients (aged 35 to 70) with chronic periodontitis to either conventional non-surgical periodontal therapy, or to homeopathy in addition to conventional therapy. The trial was judged to be at a moderate to high risk of bias overall. While the trial was described as *"randomized"* no details were provided

regarding sequence generation or allocation concealment methods, and thus the risk of selection bias was judged to be unclear. The trial was *"Single-Blind"* with outcome assessment performed by blinded examiners, but no blinding of participants; thus the risk of performance bias was judged to be high, and the risk of detection bias was judged to be low. There was no information on any losses to follow up or exclusions provided; thus the risk of attrition bias was unclear. Similarly, the risks of reporting bias and other sources of bias were judged to be unclear; the results reported in the manuscript tables did not appear to correspond with the results text, and for all outcomes, the statistical comparisons were made within groups (from baseline to 90 day follow up), not between groups. No information on baseline characteristics (apart from in relation to the clinical/serological parameters measured) were reported.

In Mourão et al. (2013) the main outcome was the clinical attachment level (CAL), assessed at baseline and at 90 fay follow-up. The results reported a statistically significant gain in mean CAL for the homeopathy group, but not for the control group. For the other clinical parameters: probing depth, probing index and bleeding on probing, significant reductions were observed from baseline to 90 days for both groups. Similarly, for serological parameters (total cholesterol, triglycerides, glucose, uric acid) significant decreases were observed for both groups; a significant decrease in low-density lipoprotein (LDL) cholesterol was observed only in the homeopathy group.

Table 30 Evidence summary table of Mourão et al. (2013) on the effectiveness of homeopathy for the treatment of chronic periodontitis

Study ID	Mourão 2013
Level of evidence	Level II
Risk of bias	Moderate to high risk of bias
N	40
Patient population	Patients of both genders aged 35 to 70 years, with chronic periodontitis.
Intervention	Conventional non-surgical periodontal therapy and homeopathy (Berberis 6CH (2 tablets, twice daily for 45 days); Mercurius solubilis/Belladonna/Hepar sulphur 6CH (2 tablets, 3 times a day for 15 days); Pyrogenium 200 CH (single weekly dose for 2 weeks).
Comparator	Conventional non-surgical periodontal therapy.
Outcomes	**Results**
CAL from baseline to day 90 (mean, SD)	Significant gain in homeopathy group, not control group
PD from baseline to day 90 (mean, SD)	Significant decrease in both groups
PI from baseline to day 90 (mean, SD)	Significant decrease in both groups
BOP from baseline to day 90 (mean, SD)	Significant decrease in both groups
Serological parameters from baseline to day 90 (LDL cholesterol; HDL cholesterol; total cholesterol; triglycerides; glucose; uric acid) (mean, SD)	Significant decrease in both groups for total, cholesterol, triglycerides, glucose and uric acid; no significant decrease in HDL cholesterol in both groups; significant reduction in LDL cholesterol in homeopathy group, not control group

Abbreviations: BOP: bleeding on probing; CAL: clinical attachment level; HDL: high-density lipoprotein; LDL: low-density lipoprotein; N: number; PI: plaque index; PD: probing depth: SD: standard deviation

2.2.27 Cat allergy

One randomised controlled trial (Level II) was identified that assessed the effects of a homeopathic complex on cat allergic adults (Naidoo and Pellow 2013) (**Table 31**). The trial randomised 30 adults with a positive skin prick test, who had been living with a cat for six months of more, and suffered from allergy-like symptoms when in the presence of a cat, to either a homeopathic complex (Cat Saliva 9cH and Histaminum 9cH) or placebo for four weeks. This trial was judged to be at a moderate to high risk of bias overall. While the trial was described as *"randomized"* the risk of selection bias was unclear, with unclear methods used to generate the random sequence and conceal allocation. The trial was blinded with the use of an identical placebo; thus the risks of performance bias and detection bias were judged to be low. There were no losses/exclusions from the study, and thus the risk of attrition bias was also low. The risk of reporting bias was judged to be high – for the results reported (in tables) to compare the homeopathy and control groups, it is unclear whether the results have been adjusted for baseline differences (and the results do not match those presented in other tables in the manuscript); adverse effects were mentioned (for the homeopathy group) in the Conclusion of the manuscript only; thus the risk of reporting bias was judged to be high. No baseline characteristics have been reported for the groups (expect for the baseline skin prick test results); thus the risk of other bias was considered unclear.

In Naidoo and Pellow (2013) the primary outcome was the mean wheal diameter score following the skin prick test at the end of the four week study period. The mean wheal diameter score (mm) was shown to be significantly lower in the homeopathy group. Similarly, the flare reaction scale (mm) and the level of itchiness were reported to be significantly lower (better) in the homeopathy group compared with the control group at the end of the study period. In the Conclusion it was reported that *"The remedies were well tolerated and no adverse effects were noted."*

Table 31 Evidence summary table of Naidoo and Pellow (2013) on the effectiveness of homeopathy for the treatment of cat allergy

Study ID	Naidoo 2013
Level of evidence	Level II
Risk of bias	Moderate to high risk of bias
N	30
Patient population	Participants with a positive SPT, who were living with a cat for a period of 6 months or more, who suffered from allergy-like symptoms when in the presence of a cat or when exposed to cat dander.
Intervention	Cat Saliva 9cH and Histaminum 9cH, two tablets under the tongue twice daily (morning and night) for 4 weeks
Comparator	Placebo tablets
Outcomes	**Results**
Wheal diameter score (mm) (mean, SD)	Significantly lower in the homeopathy group
Flare reaction scale (mm) (mean, SD)	Significantly lower in the homeopathy group
Level of itchiness (mean, SD)	Significantly lower in the homeopathy group

Abbreviations: mm: millimetres; N: number; SD: standard deviation; SPT: skin prick test

2.2.28 Diaper dermatitis

One randomised controlled trial (Level II) was identified assessing the use of homeopathy for diaper dermatitis (DD) (Pellow and Swanepoel 2013) (**Table 32**). The trial randomised 40 children with DD to either a homoeopathically medicated milking cream (containing Atropa belladonna 6cH 3%, Sulphuricum acidum 6cH 3% and Calendula officinalis D1 3%), or an un-medicated milking cream, applied to the affected area during the normal diaper changing routine, as well as after every bath for seven days. The trial was judged to be at a moderate to high risk of bias overall. While the trial was described as *"randomised"* the methods used to generate the random sequence and conceal allocation were not described in sufficient detail; thus the risk of selection bias was unclear. Performance bias was judged to be low, however blinding of outcome assessors was not clear (though the trial was described as *"double blind")* and thus the risk of detection bias was unclear. The risk of attrition bias was low, with one loss to follow up in the homeopathy group and two in the control group. The risk of reporting bias was judged to be high – for five of the 10 areas of skin, no results were presented as: "*The number of participants affected in the other five areas was too small for statistical analysis";* furthermore, adverse effects were mentioned only in the Discussion (none were reported to have occured).

Pellow and Swanepoel 2013 reported on the mean percentage area affected according to Modified Lund and Browder Chart, and mean rash severity according to the 4-Point Grading Scale for five areas: genital region, right and left inner thigh and right and left buttock, at baseline (day 1), day 2, 4 and 7. The authors reported that for the five areas, in both groups there were significant improvements (reductions) in mean percentage of area affected and mean rash severity by day 7 suggesting that *"both creams were effective in relieving the symptoms and signs of DD."* The results reported that no intergroup differences were observed for the genital region and right inner thigh, but that inter-group analysis revealed statistically significant differences between groups for left inner thigh, and right and left buttock areas *"indicating that the treatment cream outperformed the control cream."* It is unclear (considered unlikely) whether the results for between group comparisons that have been presented were adjusted for baseline differences between groups. In their Discussion, the authors reported that *"no adverse effects were noted by any participants', parents or guardians in either group."*

Table 32 Evidence summary table of Pellow and Swanepoel (2013) on the effectiveness of homeopathy for the treatment of diaper dermatitis

Study ID	Pellow 2013
Level of evidence	Level II
Risk of bias	Moderate to high risk of bias
N	40 randomised, 37 analysed
Patient population	Children with DD, between the ages of 3 months to 24 months, who were wearing disposable diapers on a daily basis.
Intervention	Homoeopathically medicated milking cream (containing Atropa belladonna 6cH 3%, Sulphuricum acidum 6cH 3% and Calendula officinalis D1 3%), applied to the affected area during the normal diaper changing routine, as well as after

	every bath for 7 days.
Comparator	Non-medicated milking cream
Outcomes	**Results**
Genital region mean percentage area affected* and mean rash severity^ at days 2, 4, 7	No significant differences
Right inner thigh mean percentage area affected* and mean rash severity^ at days 2, 4, 7	No significant differences
Left inner thigh mean percentage area affected* and mean rash severity^ at days 2, 4, 7	Significant differences in favour of homeopathy for percentage area and rash severity at days 4 and 7
Right buttock mean percentage area affected* and mean rash severity^ at days 2, 4, 7	Significant differences in favour of homeopathy for percentage area at days 4 and 7 and rash severity at days 2, 4 and 7
Left buttock mean percentage area affected* and mean rash severity^ at days 2, 4, 7	Significant differences in favour of homeopathy for percentage area at days 4 and 7 and rash severity at days 2, 4 and 7
Adverse effects	None in either group

*According to Modified Lund and Browder Chart
^According to the 4-Point Grading Scale

Abbreviations: N: number

2.2.29 Diabetic polyneuropathy

One prospective cohort study (Level III-2) was identified assessing the effects of homeopathic versus conventional therapies in patients with diabetic polyneuropathy (Pomposelli et al. 2009) (**Table 33**). The study included 77 patients who received either conventional therapy alone (e.g. diet, insulin or oral hypoglycaemic agent, physiotherapy), or conventional therapy with individualised homeopathy for a period of 12 months. The study was judged to be at a high risk of bias overall. The study included consecutive patients attending the same clinic, who were offered a choice of treatment (conventional therapy with/without individualised homeopathy), and thus the risk of selection bias was judged to be high. There was no blinding of study participants or personnel, and outcome assessment was therefore not blinded (conducted by patients themselves and the physicians); therefore the risks of performance and detection bias were also judged to be high. The rate of loss to follow up in an already small sample was notably higher in the homeopathy group (29% vs. 9%); the risk of attrition bias was therefore judged to be high. The risk of reporting bias was also high, as for a number of outcomes, general statements were made, with no data presented: *"No significant changes were observed… data not shown."* Due to the baseline differences between groups, and the comparatively high rate of loss to follow up in the homeopathy group, the study did not perform statistical comparisons between groups, and rather assessed within group changes over the course of the treatment.

In Pomposelli et al. (2009) the primary outcome was the change in mean diabetic neuropathy symptom score at six and 12 month follow up. A significantly lower (better) score was observed in the homeopathy group at 6 month follow up, and no significant change was observed for the conventional treatment group; no significant change at 12 month follow up was observed in either group. In electrophysiological conductivity studies of sensory nerves, no significant change for either

group was observed at follow up. Similarly, for fasting blood glucose, body weight and blood pressure, neither group experienced a significant change from baseline at six or 12 month follow up. In regards to quality of life measures, for the majority of domains, no changes were observed in either group at six or 12 month follow up, except for a significant improvement in physical function scores at 12 months (versus baseline) for the homeopathy group, and significant improvements in social function and role limitation scores at six months (versus baseline) for the homeopathy group. There were no adverse effects reported attributed to the homeopathy.

Table 33 Evidence summary table of Pomposelli et al. (2009) on the effectiveness of homeopathy for the treatment of diabetic polyneuropathy

Study ID	Pomposelli 2009
Level of evidence	Level III-2
Risk of bias	High risk of bias
N	77
Patient population	Patients with a diagnosis of diabetic polyneuropathy.
Intervention	Individualised homeopathic therapy – patients received homeopathic prescription from one of the four medical doctors.
Comparator	Conventional therapy alone (e.g. diet, insulin or oral hypoglycaemic agent, physiotherapy).
Outcomes	**Results**
DNS score baseline vs. 6 months (mean, SD)	Significantly lower (better) score in homeopathy group at 6 months; no significant change for conventional treatment group
DNS score baseline vs. 12 months (mean, SD)	No significant change for either group
Electrophysiological conductivity studies of sensory nerves baseline vs. 12 months: sural nerve and right ulnar nerve (mean, SD)	No significant change for either group
Fasting blood glucose baseline vs. 6 months and vs. 12 months (mean, SD)	No significant change for either group
Body weight and blood pressure over treatment duration (mean, SD)	No significant change for either group
Quality of life (physical function, role limitations, bodily pain, general health, vitality, social function, role limitations, mental health) (baseline vs. 6 months and vs. 12 months) (mean, SEM)	No significant changes for either group, except for: significant improvement in physical function score at 12 months vs. baseline for homeopathy group; significant improvement in social function and role limitation scores at 6 months vs. baseline for homeopathy group
Serious adverse effects attributed to homeopathy	None

Abbreviations: DNS: diabetic neuropathy symptom; N: number; SD: standard deviation; SEM: standard error of the mean

2.2.30 Post-tonsillectomy pain

One randomised controlled trial (Level II) was identified that investigated the effects of homeopathy for post-tonsillectomy analgesia (Robertson et al. 2007) (**Table 34**). The trial randomised 190 adults undergoing tonsillectomy to either Arnica montana 30C, two tablets six times in the first post-operative day and then two tablets twice a day for the next seven days, or to a placebo according to the same regimen. The trial was judged to be at a moderate risk of bias overall. Adequate methods were used for random sequence generation and allocation concealment and thus the trial was judged to be at a low risk of selection bias. Patients and study personnel were blinded with the use of an identical placebo, and thus the risks of performance and detection bias were also judged to be low. However, the risk of attrition bias was judged to be high – over 40% of participants were lost to follow up, and the reasons for the losses were not reported. The risk of reporting bias was unclear, as p values were only reported for outcomes with significant differences (and reported as *"p<0.05"* only); for some outcomes, measures of variance were not reported (i.e. median values presented only). The only baseline characteristic that was reported by groups was age.

In Robertson et al. (2007) the primary outcome was the change in pain (50 mm visual analogue scale (VAS)) recorded by the patient on a questionnaire over 14 days post-operatively. The homeopathy group was shown to have significantly lower mean pain scores than the placebo group on days 10, 11 and 14, but not on days 1-9, 12 or 13. From day 1 to day 14, the homeopathy group were shown to have greater mean drop in pain scores. No significant differences were shown for any of the secondary outcomes, including mean analgesia consumption on days 1-14 (cocodamol and diclofenac), visits to the general practitioner, antibiotic use, secondary haemorrhage, median day for returning to work and median day for swallowing to return to normal.

Table 34 Evidence summary table of Robertson et al. (2007) on the effectiveness of homeopathy for the treatment of post-tonsillectomy pain

Study ID	Robertson 2007
Level of evidence	Level II
Risk of bias	Moderate risk of bias
N	190 randomised, 111 analysed
Patient population	Patients over the age of 18 undergoing tonsillectomy.
Intervention	Arnica 30c, 2 tablets 6 times in the first post-operative day and then 2 tablets twice a day for the next 7 days
Comparator	Placebo
Outcomes	**Results**
Pain scores on day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 (VAS) (mean, SD)	No significant differences at days 1-9, 12, and 13; significantly lower for homeopathy group on days 10, 11 and 14
Drop in pain score from day 1 to 14 (VAS) (mean)	Significantly larger for homeopathy group versus placebo group
Analgesia consumption: cocodamol and diclofenac tablets on day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 (mean, SD)	No significant differences
Analgesia consumption: cocodamol and diclofenac tablets total from day 1 to 14 (mean)	No significant difference
Return to work (days) (median)	No significant difference
Return to normal swallowing (days) (median)	No significant difference

Visit to general practitioner (N, %)	No significant difference
Antibiotic use (required full course post-operatively) (N, %)	No significant difference
Secondary haemorrhage (N, %)	No significant difference

Abbreviations: N: number; SD: standard deviation; VAS: visual analogue scale

2.2.31 Essential hypertension

One randomised controlled trial (Level II) was identified investigating the use of homeopathy for the treatment of essential hypertension (Saha et al. 2013) (**Table 35**). The trial randomised 150 adults with a history of essential hypertension for at least six months to either the individualised homeopathy group or to a placebo group (where a placebo was prepared, and was identical in appearance to the homeopathic medicine). The trial was judged to be at a moderate to high risk of bias overall. The risk of selection bias was judged to be low, with a coin-toss used for sequence generation, and the allocation concealed, with code for 'heads' and 'tails' kept by the pharmacy who received the prescription for each participant sent by the treating physicians. The trial was also judged to be at a low risk of performance bias and detection bias, with participants, study physicians and outcome assessors all blind, through the use of a placebo. The risk of attrition bias was judged to be unclear; there were six (9%) drop-outs from the homeopathy group and 12 (15%) from the placebo group, who were all excluded from the analyses; the manuscript reports that *"Missing values were calculated by the maximum likelihood method of estimation of the lambda parameter of normal distribution,"* however it is not clear how much missing data there was in addition to the reported exclusions. The risk of reporting bias was judged to be high – a trial registration number was reported, and this online registration indicated that the trial was retrospectively registered, and that some secondary outcomes that had been pre-specified were not reported in the manuscript. The trial registration also detailed that "*the protocol needed amendments and the study was terminated prematurely"*, however in the trial manuscript it was not clear what the amendments were, and not indicated that the study was prematurely terminated.

In Saha et al. (2013) the primary outcome was the lowering of blood pressure following intervention. The trial reported that significantly more patients receiving individualised homeopathy had 'improved' blood pressure at six months (defined as lowering of systolic blood pressure by a minimum of 15 mm Hg, and diastolic blood pressure by a minimum of 6 mm Hg). Similarly, the trial reported that repeated measures ANOVA (performed comparing data obtained at baseline, three months and six months) showed a significant difference between groups for both systolic and diastolic blood pressure. The trial also reported that post hoc independent t tests, comparing three and six month values showed significant differences between groups at three and six months for both systolic and diastolic blood pressure. Considering serious adverse effects, one patient in the homeopathy group developed hepatitis and one in the placebo group had deterioration of condition; neither was attributed to the intervention. The results also reported that *"Mild-to-moderate homoeopathic aggravation, as per homoeopathic principles, was observed;"* with no further detail provided.

Table 35 Evidence summary table of Saha et al. (2013) on the effectiveness of homeopathy for the treatment of essential hypertension

Study ID	Saha 2013
Level of evidence	Level II

Risk of bias	Moderate to high risk of bias
N	150 randomised, 132 analysed
Patient population	Patients (males and females) with essential hypertension for at least 6 months, aged 18 to 65 years, with no obvious secondary cause.
Intervention	Individualised homeopathy.
Comparator	Placebo.
Outcomes	**Results**
BP improved at 6 months (defined as lowering of SBP by a minimum of 15 mm Hg and DBP by a minimum of 6 mm Hg) (N, %)	Significantly more patients in the homeopathy group
Change in SBP and DBP from baseline to 3 months and 6 months (mm Hg) (mean, SD)	Significantly improved in the homeopathy group
SBP at 3 months (mm Hg) (mean, SD)	Significantly lower in homeopathy group
SBP at 6 months (mm Hg) (mean, SD)	Significantly lower in homeopathy group
DBP at 3 months (mm Hg) (mean, SD)	Significantly lower in homeopathy group
DBP at 6 months (mm Hg) (mean, SD)	Significantly lower in homeopathy group
Serious adverse events	One case in homeopathy group (hepatitis); one case in control group (deterioration of condition); not attributed to treatment

Abbreviations: DBP: diastolic blood pressure; mm Hg: millimetres Mercury; N: number; SBP: systolic blood pressure; SD: standard deviation

2.2.32 End-stage renal failure

One randomised controlled trial (Level II) was identified that assessed the effects of homeopathy on intra-dialytic symptomatology in patients treated with chronic haemodialysis (Saruggia and Corghi 1992) (**Table 36**). The trial randomised 35 patients with end-stage renal failure on regular haemodialysis to either China ruba 9 CH (3 lactose granules on waking and in the evening) or placebo; after two weeks, the two groups were crossed-over. The trial was judged to be at a high risk of bias overall. While the trial was described as *"randomized"* no details were provided regarding methods for sequence generation or allocation concealment, and thus the risk of selection bias was judged to be unclear. The trial was considered to be at a low risk of performance and attrition bias, with the use of an *"indistinguishable"* placebo by the same regimen as the homeopathy (and the trial was described as *"double blind"*). The risk of attrition bias was unclear; losses were not described (in terms of numbers of participants lost/excluded), however 21 of the 840 questionnaires expected were *"not returned or were invalid;"* it was unclear which group(s) these questionnaires were excluded from. The trial was judged to be at a high risk of reporting bias, reporting only a numerical estimate for each outcome (symptoms), with no indication as to the scale/unit of measurement, and no measure of variation provided; furthermore, no outcome data were reported for one of the six symptoms pre-specified (muscle cramps). The trial was at a high risk of other bias, with no wash-out period described, and thus potential risk of a 'carry over' effect.

In Saruggia and Corghi (1992), symptoms were assessed by questionnaires (at the end of each dialysis session). For three of the symptoms (asthenia, lethargy and headache) the trial reported

statistically significant improvements on active treatment (China ruba) compared with placebo. No differences between groups were seen for the outcomes nausea or vomiting.

Table 36 Evidence summary table of Saruggia and Corghi (1992) on the effectiveness of homeopathy for the treatment of end-stage renal failure

Study ID	Saruggia 1992
Level of evidence	Level II
Risk of bias	High risk of bias
N	35 (crossover trial)
Patient population	Adult patients, aged 18 to 76 years, with end-stage renal failure on regular haemodialysis
Intervention	China ruba 9CH, 3 lactose granules on waking and in the evening for two weeks.
Comparator	Placebo
Outcomes	**Results**
Nausea (mean)	No significant difference
Vomiting (mean)	No significant difference
Headache (mean)	Significant improvement for homeopathy vs. placebo
Lethargy (mean)	Significant improvement for homeopathy vs. placebo
Asthenia (mean)	Significant improvement for homeopathy vs. placebo

Abbreviations: N: number

2.2.33 Subcutaneous mechanical injury

One randomised controlled trial (Level II) was identified assessing the use of homeopathy for subcutaneous mechanical injury (Schmidt 1996) (**Table 37**). The trial included 337 runners acknowledging muscle soreness (or anticipating soreness) attributable to a 3.5 mile running race, who were allocated to either Arnica 1X, Arnica 6C (both in petroleum jelly) or placebo (petroleum jelly), and were given a quarter of a teaspoon to be administered topically to the 'sorest' area of skin immediately after the race. The trial was judged to be at a high risk of bias overall. The risk of selection bias was unclear; a 'master researcher' who was reported to not be involved in any of the aspects of the project apart from coding the treatments, allocated different letters to the three treatments. The trial was described as *"double-blind"* for the participants and other study personnel, with the use of the petroleum jelly control according to an identical regimen; thus the risks of performance and detection bias were judged to be low. The risk of attrition bias was judged to be high, with only 42% of participants providing outcome data, and the reasons for losses not clearly reported by group. The risk of reporting bias was also judged to be high, with the only outcome reported being 'improvement', as rated by patients. The risk of other potential bias was also judged to be high, with no baseline characteristics reported (including as the author acknowledges, the participants usual level of physical activity).

In Schmidt et al. (1996), participants were asked *"How would you rate the condition of your injury after using the ointment?"* and were asked to answer on a scale of 0 to 10 (with 10 representing complete improvement in the condition of the muscle). Mean (and median and mode) scores were presented, and while no formal tests of significance were conducted the authors concluded that *"Both potencies of Arnica showed results clearly superior to that of the placebo under test conditions."*

Table 37 Evidence summary table of Schmidt (1996) on the effectiveness of homeopathy for the treatment of subcutaneous mechanical injuries

Study ID	Schmidt 1996
Level of evidence	Level II
Risk of bias	High risk of bias
N	337 randomised, 141 analysed
Patient population	People acknowledging muscle soreness (or anticipating muscle soreness) attributable to a 3.5 mile running race
Intervention	Arnica 1X ¼ teaspoon in petroleum jelly applied to the sorest area of skin immediately (not applied to broken skin)
Intervention	Arnica 6C as above
Comparator	Placebo (petroleum jelly) as above
Outcomes	**Results**
Condition of injury after treatment (0-10 scale; 10 = complete improvement) (mean, SD)	Higher scores for both arnica groups compared with placebo group (significance not reported)

Abbreviations: N: number; SD: standard deviation

2.2.34 Mucositis in stem cell therapy

One randomised controlled trial (Level II) was identified that investigating the use of homeopathy for the prevention and treatment of mucositis in young patients undergoing HSCT (Sencer et al. 2012) (**Table 38**). The trial randomised 195 patients aged three to 25 years to either Traumeel S or placebo, five times per day as a mouth rinse, started on the day prior to transplant and continued for a maximum of 22 days. The trial was judged to be at a moderate risk of bias overall. The trial was judged to be at a low risk of selection bias with adequate methods for sequence generation and allocation concealment. Similarly, the risks of performance and detection bias were judged to be low, with the use of an identical placebo. The risk of attrition bias was unclear, as there was a high level of missing data (only 56% of patients had full data for the primary outcome) (which was imputed using multiple imputation) and for some outcomes, denominators were not clearly reported; the risk of reporting bias was also judged to be unclear, with insufficient information to determine risk. The authors reported that there was considerable variation in the intervention delivery and data collection processes across study sites.

In Sencer et al. (2012) the primary outcome was the sum of Walsh scale scores for mucositis (assessed by the mean area under the curve (AUC)) from day -1 to day 20. The trial found no significant difference between the Traumeel and placebo groups for the primary outcome, when considering all patients, and also when considering subgroups of patients according to their degree of compliance with the intervention. Similarly, no significant differences between groups were seen for any of the secondary outcomes, including the World Health Organization mucositis score; doses of morphine; number of days of total parenteral nutrition; proportion of patients with nasogastric feeding; mortality proportion to 31 days after termination of protocol; venocclusive disease of the liver; graft-versus-host-disease; or for adverse effects. The authors concluded that *"We could not confirm that Traumeel is an effective treatment for mucositis in children undergoing HSCT."*

Table 38 Evidence summary table of Sencer et al. (2012) on the effectiveness of homeopathy for the treatment of mucositis in stem cell therapy

Study ID	Sencer 2012
Level of evidence	Level II
Risk of bias	Moderate risk of bias
N	195 randomised, 190 analysed
Patient population	Patients aged 3 to 25 years undergoing myeloablative HSCT.
Intervention	Traumeel S (started on day -1 as a 5 time daily mouth rinse), for a maximum of 22 days
Comparator	Placebo
Outcomes	**Results**
AUC of Walsh score (all patients) (mean, SE)	No significant difference
AUC of Walsh score (compliant < 30% days; 30-65% days; 65-99% days; 100% days) (mean, SE)	No significant difference
AUC of WHO oral mucositis score (mean, SE)	No significant difference
Total doses (in equivalent mg/kg) of morphine (mean, SE)	No significant difference
Number of days of total parenteral nutrition (mean, SE)	No significant difference
Patients with nasogastric feeding (N, %)	No significant difference
Mortality proportion to 31 days after termination of protocol therapy (N, %)	No significant difference
Venocclusive disease of the liver (N, %)	No significant difference
Acute GVHD (N, %)	No significant difference
Adverse events: gastrointestinal; cardiac; bleeding; infection; pain in lip, mouth, joint or back (N, %)	No significant differences

Abbreviations: AUC: area under the curve; GVHD: graft-versus-host-disease; HSCT: haematopoietic stem cell therapy; N: number; SE: standard error; WHO: World Health Organization

2.2.35 Post-rhinoplasty ecchymosis and oedema

One randomised controlled trial (Level II) was identified assessing arnica and corticosteroids in the management of post-rhinoplasty ecchymosis and oedema (Totonchi and Guyuron 2007) (**Table 39**). The trial randomised 48 primary rhinoplasty patients to either: arnica three times a day for four days, 10 mg dexamethasone intravenously intra-operatively followed by a six day oral tapering dose of methyl-prednisone, or to no treatment. The trial was judged to be at a moderate to high risk of bias overall. While it was noted that *"Patients were randomized into two groups",* no further detail was provided, and thus the risk of selection bias and allocation bias were judged to be unclear. Participants and study personnel were not blind and thus the risk of performance bias was judged to be high. Outcome assessment was performed by three blind panellists who assessed photographs on

post-operative days 2 and 8; thus the risk of detection bias was judged to be low. Insufficient information was provided to determine risk of attrition bias. The risk of reporting bias, was however, judged to be high, with the numbers of participants randomised to each group not stated, and only mean values (no standard deviations / measures of variance) reported for the outcomes. No baseline characteristics were reported.

Totonchi and Guyuron (2007) assessed extent and intensity of ecchymosis and severity of oedema on post-operative days 2 and 8. On post-operative day 2, there were no differences across groups in the mean scores for extent or intensity of ecchymosis; the mean oedema score however was shown to be significantly higher in the control group compared with the homeopathy and corticosteroid groups. On post-operative day 8, the mean scores for extent and intensity of ecchymosis were shown to be significantly higher in the corticosteroid group, compared with the homeopathy and control groups; no difference between groups was shown for mean oedema score. Considering the differences in mean extent and intensity of ecchymosis scores from day 2 to day 8 post-operatively, the homeopathy and control groups, compared with the corticosteroid group, had significantly higher scores (demonstrating more resolution/improvement). In regards to change in oedema, the control group demonstrated significantly greater change compared with the homeopathy and corticosteroid groups. The authors noted that *"The results of the present study demonstrated no differences between the patients receiving arnica and the control patients with respect to the extent an intensity of ecchymosis... However, patients who received arnica had significantly less edema compared with controls during the early postoperative period."*

Table 39 Evidence summary table of Totonchi and Guyuron (2007) on the effectiveness of homeopathy for the treatment of post-rhinoplasty ecchymosis and oedema

Study ID	Totonchi 2007
Level of evidence	Level II
Risk of bias	Moderate to high risk of bias
N	48
Patient population	Patients, aged 15 to 65 years, who had undergone a primary rhinoplasty with osteotomy
Intervention	**Homeopathy:** Arnica 3 times a day for 4 days. **Corticosteroids:** 10 mg intravenous dexamethasone intra-operatively followed by a 6 day oral tapering dose of methyl-prednisone.
Comparator	No treatment
Outcomes	**Results**
Extent of ecchymosis post-operative day 2 (mean)	No significant difference
Intensity of ecchymosis post-operative day 2 (mean)	No significant difference
Severity of oedema post-operative day 2 (mean)	Significantly more oedema in control group compared with homeopathy and corticosteroid groups
Extent of ecchymosis post-operative day 8 (mean)	Significantly larger extent of ecchymosis in corticosteroid group compared with homeopathy and control groups
Intensity of ecchymosis post-operative day 8 (mean)	Significantly greater intensity of ecchymosis in corticosteroid group compared with homeopathy and control groups
Severity of oedema post-operative day 8 (mean)	No significant difference
Difference in extent of ecchymosis	Significantly more resolution in homeopathy and control

from post-operative day 2 to day 8 (mean)	groups compared with corticosteroid group
Difference in intensity of ecchymosis from post-operative day 2 to day 8 (mean)	Significantly more improvement in homeopathy and control groups compared with corticosteroid group
Difference in severity of oedema from post-operative day 2 to day 8 (mean)	Significantly greater change control group compared with homeopathy and corticosteroid groups

Abbreviations: N: number

2.2.36 Malnourishment

One randomised controlled trial (Level II) was identified assessing the use of homeopathy for malnourished children (Villanueva et al. 2012) (**Table 40**). The trial randomised 99 children aged between 1 and 19 years old with a weight-height ratio below the third percentile, to either a homeopathic complex (Calcarea fluorica 30 cH, Calcarea carbonica 30 cH, Calcarea phosphorica 30 cH) or no treatment; all children were prescribed a diet adjusted to their age and gender, and a poly-vitamin. The trial was judged to be at a high risk of bias overall. While the randomisation sequence was computer generated, no method for concealing allocation was detailed; thus the risk of selection bias was unclear. With no placebo used (and thus no blinding), the risks of performance and detection bias were judged to be high. It was not clearly stated whether there were any losses to follow up or exclusions (though the 'exit criteria' from the study were stated); thus the risk of attrition bias was unclear. The only outcome reported was 'recovery to normal weight', and the risk of reporting bias was judged as unclear. Age was the only baseline characteristic reported by group, and though it appeared that there were potential differences (i.e. age 10-14:18% homeopathy group; 37% control group) the authors reported *"no significant differences between both groups (data not shown)."*

In Villanueva et al. (2012), significantly more children in the homeopathy group returned to normal weight (defined as 10^{th} to 90^{th} percentile) compared with the control group (84% versus 30%). The difference between groups was statistically significant for the 1-4 years, 5-9 years and 10-14 years age groups; however no significant difference was shown for the 15-19 years group.

Table 40 Evidence summary table of Villanueva et al. (2012) on the effectiveness of homeopathy for the treatment of malnourishment

Study ID	Villanueva 2012
Level of evidence	Level II
Risk of bias	High risk of bias
N	99
Patient population	Malnourished children aged between 1 and 19 years old with a weight-height ratio below the 3^{rd} percentile.
Intervention	Homeopathic complex (Calcarea fluorica 30 cH, Calcarea carbonica 30 cH, Calcarea phosphorica 30 cH).
Comparator	Prescribed a diet adjusted to their age and gender and a poly-vitamin.
Outcomes	**Results**
Recovery to normal weight (N, %)	Significantly more children in the homeopathy group
Recovery to normal weight (age 1-4	Significantly more children in the homeopathy group

years) (N, %)	
Recovery to normal weight (age 5-9 years) (N, %)	Significantly more children in the homeopathy group
Recovery to normal weight (age 10-14 years) (N, %)	Significantly more children in the homeopathy group
Recovery to normal weight (age 15-19 years) (N, %)	No significant difference

Abbreviations: N: number

3 References

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

NHMRC (2009). NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. National Health and Medical Research Council, Canberra ACT. Available at: https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf

Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [accessed 2014]. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm

Appendix A List of excluded submitted literature

Title	Level of evidence	Reason for exclusion
Journal articles		
Aabel S. No beneficial effect of isopathic prophylactic treatment for birch pollen allergy during a low-pollen season: a double-blind, placebo-controlled clinical trial of homeopathic Betula 30c. British Homeopathic Journal 2000, 89(4): 169-173.	Level II	Study included within a systematic review in the *Overview Report*.
Banerjee A, Chakrabarty SB, Karmakar SR, Chakrabarty A, Biswas SJ, Haque S, et al. Can homeopathy bring additional benefits to thalassemic patients on hydroxyureatherapy encouraging results of a preliminary study. Evidence-Based Complementary and Alternative Medicine 2010, 7(1):129-136.	Level III-2	Full text review. Excluded. Wrong outcomes (very few clinical outcomes relating to effectiveness; not reported in a way that allows treatment effects to be determined).
Bell IR, Howerter A, Jackson N, Aickin M, Bootzin RR, Brooks AJ. Nonlinear dynamical systems effects of homeopathic remedies on multiscale entropy and correlation dimension of slow wave sleep EEG in young adults with histories of coffee-induced insomnia. Homeopathy 2012, 101(3):182-192.	Level III-2	Full text review. Excluded. Wrong outcomes.
Bernstein JA, Davis BP, Picard JK, Cooper JP, Zheng S, Levin LS. A randomized, double-blind, parallel trial comparing capsaicin nasal spray with placebo in subjects with a significant component of nonallergic rhinitis. Annals of Allergy, Asthma and Immunology 2011, 107(2):171-178.	Level II	Full text review. Excluded. Out of scope - homeopathy used in conjunction with other therapies where the design of the study confounds the results (i.e. where the specific effect of homeopathy cannot be determined).
Bononi M. [*Echinacea compositum forte S nella profilassi delle infezioni post-operatorie. Studio comparative* versus *ceftazidime e ceftriaxone]*. [Article in Italian] Echinacea comp. Forte S in the prophylaxis of post-operative infections. A comparative study versus ceftazidime and ceftriaxone. La Medicina Biologica 2001, 1:17-32.	Level III-1 or III-2 – unclear from abstract	Excluded. Out of scope - homeopathy for prophylactic use.
Bornhöft G, Wolf U, von Ammon K, Righetti M, Maxion-Bergemann S, Baumgartner S et al. Effectiveness, safety and cost-effectiveness of homeopathy in general practice - summarized health technology assessment. Forschende Komplementärmedizin 2006; 13(Suppl 2):19-29.	Unable to assign level of evidence – summarised health technology assessment	Full text review. Excluded. Wrong research type or publication type.

Title	Level of evidence	Reason for exclusion
Bracho G, Varela E, Fernandez R, Ordaz B, Marzoa N, Menendez J et al. Large-scale application of highly-diluted bacteria for Leptospirosis epidemic control. Homeopathy 2010, 99(3):156-166.	Level III-2	Excluded. Out of scope - homeopathy for prophylactic use.
Brydak LB, Denys A. The evaluation of humoral response and the clinical evaluation of a risk-group patients' state of health after administration of the preparation Gripp-Heel during the influenza epidemic season 1993/94. International Review of Allergology and Clinical Immunology 1999, 5(4):223-227.	Level II or Level III-1– unclear	Excluded. Out of scope - homeopathy for prophylactic use.
Campistranous- Lavout JL, Riveron-Garrote M, Fernandez-Arguelles R, Rodriguez FM, Guajardo G. [Estudio controlado y aleatorizado del manejo de la hypertension arterial con homeopatia] Hypertension Trial. Boletin Mexicano, 1999, 32(2):42-47.	Level II	English title: Hypertension Trial' available at first screening, however, no abstract available. Full text obtained however not published in English. Excluded.
Chapman EH, Weintraub RJ, Milburn MA, Pirozzo TO, Woo E. Homeopathic treatment of mild traumatic brain injury: A randomized, double-blind, placebo-controlled clinical trial. Journal of Head Trauma and Rehabilitation 1999, 14(6):521-542.	Level II	Study included within a systematic review in the *Overview Report*.
Charlton BG. The uses and abuses of meta-analysis. Family Practice 1996, 13(4):397-401.	Unable to assign a level of evidence – commentary	Excluded. Wrong research type or publication type.
Chatterjee A, Biswas J, Chatterjee A, Bhattacharya S, Mukhopadhay B, Mandal S. Psorinum therapy in treating stomach, gall bladder, pancreatic, and liver cancers: a prospective clinical study. Evidence-Based Complementary and Alternative Medicine 2011, 2011:724743.	Level IV	Excluded. Wrong research type or publication type. No comparison group.
Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. New England Journal of Medicine 2000, 342:1887-1892	Unable to assign a level of evidence - narrative review	Excluded. Wrong research type or publication type.
Demicheli V, Jefferson T, Al-Ansary LA, Ferroni E, Rivetti A, Di Pietrantonj C. Vaccines for preventing influenza in healthy adults. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD001269. DOI: 10.1002/14651858.CD001269.pub5	Level I	Excluded. Wrong intervention.
Downing NS, Cheng T, Krumholz HM, Shah ND, Ross JS. Descriptions and	Unable to assign a	Excluded. Wrong research type or publication

Title	Level of evidence	Reason for exclusion
interpretations of the ACCORD-lipid trial in the news and biomedical literature: a cross-sectional analysis. JAMA Internal Medicine 2014, 174(7):1176-1182.	level of evidence – special communication	type.
Ernst E. Homeopathic Galphimia glauca for hay fever: A systematic review of randomised clinical trials and a critique of a published meta-analysis. Focus on Alternative and Complementary Therapies 2011, 16(3):200-203.	Level I	Systematic review included in the *Overview Report*.
Ferrara P, Marrone G, Emmanuele V, Nicoletti A, Mastrangelo A, Tiberi E, et al. Homotoxicological remedies versus desmopressin versus placebo in the treatment of enuresis: a randomised, double-blind, controlled trial. Pediatric Nephrology 2008, 23(2):269–274.	Level II	Full text review. Excluded. Wrong intervention. Homotoxicology.
Frei H, Thurneysen A. Treatment for hyperactive children: homeopathy and methylphenidate compared in a family setting. British Homoeopathic Journal 2001, 90(4): 183-188.	Level IV	Excluded. Wrong research type or publication type. No comparison group.
Frei H, Thurneysen A. Homeopathy in acute otitis media in children: treatment effect or spontaneous resolution? British Homoeopathic Journal 2001, 90(4):180-182.	Level IV	Full text review. Excluded. Wrong research type or publication type. No comparison group.
Frenkel M, Mishra BM, Sen S, Yang P, Pawlus A, Vence L, et al. Cytotoxic effects of ultra-diluted remedies on breast cancer cells. International Journal of Oncology 2010, 36(2):395-403.	Unable to assign a level of evidence – in vitro study	Excluded. Wrong research type or publication type. In vitro study.
Friese KH, Kruse S, Ludtke R, Moeller H. The homoeopathic treatment of otitis media in children - comparisons with conventional therapy. International Journal of Clinical Pharmacology and Therapeutics 1997, 35(7):296-301.	Level II	Study included within a systematic review in the *Overview Report*.
Furuta SE, Weckx LLM, Figueiredo CR. Tratamento Homeopático da amigdalite recorrente em crianças: um estudo randomizado controlado [Homeopathic treatment of recurrent tonsillitis in children: a randomized controlled trial]. Revista de Homeopatia 2007, 70:21-26.	Level II	Excluded. Study not published in the English language.
Golden I, Bracho G. A Reevaluation of the Effectiveness of Homoeoprophylaxis Against Leptospirosis in Cuba in 2007 and 2008. Journal of evidence-based complementary & alternative medicine 2014; 19:155-160.	Level III-2	Excluded. Out of scope. Homeopathy for prophylactic use.
Gmünder R, Kissling R. [The Efficacy of homeopathy in the treatment of chronic	Level II	Excluded. Study not published in the English

Title	Level of evidence	Reason for exclusion
low back pain compared to standardized physiotherapy]. [Article in German] Zeitschrift fur Orthopadie und ihre Grenzgebiete 2002, 140:503-508.		language.
Heirs M, Dean ME. Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD005648. DOI: 10.1002/14651858.CD005648.pub2.	Level I	Systematic review included in the *Overview Report*.
Hutsol L, Hutsol M, Tsymbal I. Homeopathy in cardiac arrhythmia [Homoopathie bei Herzrhythmusstorugen]. Allegemeine Homoopathische Zeitung 2005, 205-224.	Level IV	Excluded. Wrong research type or publication type. No comparison group.
Ivanovas G. Critique of pure evidence. Homeopathy and evidence-based medicine Part 1. Homeopathic Links 2012, 25(1):13-17.	Unable to assign a level of evidence – commentary	Excluded. Wrong research type or publication type.
Ivanovas G. Individualisation and the practitioner's paradox. Homeopathy and evidence-based medicine Part 2. Homeopathic Links 2012, 25(2):122-125.	Unable to assign a level of evidence – commentary	Excluded. Wrong research type or publication type.
Jacobs J, Jimminez LM, Glyods SS, Casares FE, Gaitan MP, Crothers D. Homoeopathic treatment of acute childhood diarrhoea: a randomized clinical trial in Nicaragua. British Homeopathic Journal 1993, 82:83-86.	Level II	Study included within a systematic review in the *Overview Report*.
Jacobs J, Jimenez LM, Gloyd SS, Gale JL, Crothers D. Treatment of acute childhood diarrhea with homeopathic medicine: a randomized clinical trial in Nicaragua. Pediatrics 1994, 93(5):719-725.	Level II	Study included within a systematic review in the *Overview Report*.
Jacobs J, Jimenez LM, Malthouse S, Chapman E, Crothers D, Masuk M, et al. Homeopathic treatment of acute childhood diarrhea: results from a clinical trial in Nepal. Journal of Alternative and Complementary Medicine 2000, 6(2):131-139.	Level II	Study included within a systematic review in the *Overview Report*.
Jacobs J, Springer DA, Crothers D. Homeopathic treatment of acute otitis media in children: a preliminary randomized placebo-controlled trial. The Pediatric Infectious Disease Journal 2001, 20(2):177-183.	Level II	Study included within a systematic review in the *Overview Report*.
Jacobs J, Jonas WB, Jimenez-Perez M, Crothers D. Homeopathy for childhood diarrhea: combined results and metaanalysis from three randomized, controlled clinical trials, The Pediatric Infectious Disease Journal 2003,	Level II	Study included within a systematic review in the *Overview Report*.

Title	Level of evidence	Reason for exclusion
22(3):229-34.		
Jacobs J, Guthrie BL, Montes GA, Jacobs LE, Mickey-Colman N, Wilson AR et al. Homeopathic combination remedy in the treatment of acute childhood diarrhea in Honduras. Journal of Alternative and Complementary Medicine 2006, 12(8):723-732.	Level II	Study included within a systematic review in the *Overview Report*.
Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, Spencer EA, Onakpoya I, Mahtani KR, Nunan D, Howick J, Heneghan CJ. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD008965. DOI: 10.1002/14651858.CD008965.pub4	Level I	Excluded. Wrong intervention.
Khuda-Bukhsh AR, Roy-Karmakar S, Banerjee A, Banerjee P, Pathak S, Biswas SJ, et al. A follow-up study on the efficacy of the homeopathic remedy Arsenicum Album in volunteers living in high risk arsenic contaminated areas. Evidence-Based Complementary and Alternative Medicine 2011, 2011:129214	Level III-2	Full text review. Excluded. Wrong research type or publication type. No relevant comparison group.
Kneis KC, Gandjour A. Economic evaluation of Sinfrontal in the treatment of acute maxillary sinusitis in adults. Applied Health Economics and Health Policy 2009, 7(3):181-191.	Unable to assign a level of evidence - economic study	Excluded. Wrong outcomes.
Kuzeff RM. Homeopathy, sensation of well-being and CD4 levels: A placebo-controlled, randomized trial. Complementary Therapies in Medicine 1998, 6(1):4-9.	Level II	Full text review. Excluded. Wrong outcomes. Trial assessed CD4 levels and overall wellbeing, with a wide range of diagnoses.
Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. Lancet 1997; 350(9081): 834-843.	Level I	Systematic review included in the *Overview Report*.
Marino R. Homeopathy and Collective Health: The Case of Dengue Epidemics. International Journal of High Dilution Research 2008, 7(25):179-185.	Level III-2	Excluded. Out of scope. Homeopathy for prophylactic use.
Mazzocchi A, Montanaro F. Observational study of the use of Symphytum 5CH in the management of pain and swelling after dental implant surgery. Homeopathy 2012, 101(4):211-216.	Level III-2	Full text review. Wrong research type or publication type. Retrospective cohort study.
Oberai P, Gopinadhan S, Varanasi R, Mishra A, Singh V, Nayak C. Homoeopathic management of attention deficit hyperactivity disorder: A randomised placebo-	Level II	Full text review. Excluded. Out of scope - homeopathy used in conjunction with other

Title	Level of evidence	Reason for exclusion
controlled pilot trial. Indian Journal of Research in Homeopathy 2013, 7(4):158-162.		therapies where the design of the study confounds the results (i.e. where the specific effect of homeopathy cannot be determined).
Oberbaum M, Galoyan N, Lerner-Geva L, Singer SR, Grisaru S, Shashar D, et al. The effect of the homeopathic remedies Arnica montana and Bellis perennis on mild postpartum bleeding--a randomized, double-blind, placebo-controlled study--preliminary results. Complementary Therapies in Medicine 2005, 13(2):87-90.	Level II	Full text review. Excluded. Out of scope - homeopathy for prophylactic use.
Pathak S, Multani AS, Banerji P, Banerji P. Ruta 6 selectively induces cell death in brain cancer cells but proliferation in normal peripheral blood lymphocytes: A novel treatment for human brain cancer. International Journal of Oncology 2003, 23(4):975-82.	Level IV	Excluded. Wrong research type or publication type. No comparison group.
Pirotta MV. Opposing view: Is it ethical for medical practitioners to prescribe alternative and complementary treatments that may lack an evidence base? – Yes. Medical Journal of Australia 2011, 192(2):78.	Unable to assign a level of evidence – commentary	Excluded. Wrong research type or publication type.
Reilly DT, Mcsharry C, Taylor MA, Aitchison T. Is homoeopathy a placebo response? Controlled trial of homoeopathic potency, with pollen in hay fever as model. Lancet 1986, 328(8512):881-886.	Level II	Study included within a systematic review in the *Overview Report*.
Rossignol M, Begaud B, Engel P, Avouac B, Lert F, Rouillon F, et al. Impact of physician preferences for homeopathic or conventional medicines on patients with musculoskeletal disorders: results from the EPI3-MSD cohort. Pharmacoepidemiology and Drug Safety 2012, 21(10):1093-1101.	Level III-2	Full text review. Wrong intervention. Examines the effects of physician preference for homeopathy.
Sackett DL, Rosenberg WMC, Muir Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. British Medical Journal 1996, 312(7023):72-72.	Unable to assign a level of evidence – commentary	Excluded. Wrong research type or publication type.
Sackett D. Evidence based medicine. Seminars in Perinatology 1997, 21(1):3-5.	Unable to assign a level of evidence – commentary	Excluded. Wrong research type or publication type.
Sainte-Laudy J, Belon P. Inhibition of basophil activation by histamine: a sensitive and reproducible model for the study of the biological activity of high dilutions. Homeopathy: The Journal of the Faculty of Homeopathy 2009,	Unable to assign a level of evidence - animal and	Excluded. Wrong research type or publication type. Non-human study and in vitro study.

Title	Level of evidence	Reason for exclusion
98:186-197.	laboratory study	
Schneider B, Klein P, Weiser M. Treatment of vertigo with a homeopathic complex remedy compared with usual treatments - a meta-analysis of clinical trials, Arzneimittelforschung 2005, 55(1):23-29.	Level I/II	Full text review. Meta-analysis of primary studies already included in the *Overview Report* or the *Review of Submitted Literature*.
Shang A, Huwiler-Muntener K, Nartey L, Juni P, Dorig S, Sterna JA, et al. Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. Lancet 2005, 366(9487):726-732.	Level I	Full text review. Excluded. Wrong outcomes.
Sharma S, Sharma N, Sharma R. Accelerating the healing of bone fracture using homeopathy: a prospective, randomized double-blind controlled study. BMC Complementary and Alternative Medicine 2012, 12(Suppl 1):O61.	Level II	Excluded. Wrong research type or publication type. Published as abstract only.
Sharma S, Sharma N. Long term evaluation of homeopathy on post treatment impairment of pulmonary tuberculosis. BMC Complementary and Alternative Medicine 2012, 12(Suppl 1):P223.	Level II	Excluded. Wrong research type or publication type. Published as abstract only.
Sinha MN, Siddiquiu VA, Nayak C, Singh V, Dixit R, Dewan D, et al. Randomised controlled pilot study to compare Homeopathy and conventional therapy in Acute Otitis Media. Homeopathy 2012, 101(1):5-12.	Level II	Study included in the *Review of Submitted Literature*.
Stamatakis E, Weiler R, Ioannidis JP. Undue industry influences that distort healthcare research, strategy, expenditure and practice: a review. European Journal of Clinical Investigation 2013, 43:469-475.	Unable to assign a level of evidence – narrative review/commentary	Excluded. Wrong research type or publication type.
Strauss LC. The efficacy of a homeopathic preparation in the management of attention deficit hyperactivity disorder. Biomedical Therapy 2000, 18(2):197-201.	Level II	Study included within a systematic review in the *Overview Report*.
Teixeira MZ. Effectiveness of individualized homeopathic treatment in perennial allergic rhinitis (PAR). International Journal of High Dilution Research 2009, 8(28):141-143.	Level II	Excluded. Study not published in the English language.
Trichard M, Chaufferin G, Dubreuil C, Nicoloyannis N, Duru G. Effectiveness, quality of life, and cost of caring for children in France with recurrent acute rhinopharyngitis managed by homeopathic or non-homeopathic general	Level III-2	Full text review. Excluded. Out of scope - homeopathy used in conjunction with other therapies where the design of the study

Title	Level of evidence	Reason for exclusion
practitioners: A pragmatic, prospective observational study. Disease Management and Health Outcomes 2004, 12(6):419-427.		confounds the results (i.e. where the specific effect of homeopathy cannot be determined).
Tveiten D, Bruset S. Effect of Arnica D30 in marathon runners. Pooled results from two double-blind placebo controlled studies. Homeopathy 2003, 92(4):187-189.	Level I/II	Full text review. Meta-analysis of primary studies already included in the *Overview Report* or the *Review of Submitted Literature*.
Vincent S, Demonceaux A, Deswarte D, Scimeca D, Bordet MF. Management of influenza-like illness by homeopathic and allopathic general practitioners in France during the 2009-2010 influenza Sseason. Journal of Alternative and Complementary Medicine 2013, 19(2):146-152.	Level III-2	Full text review. Wrong intervention (management by homeopathic vs. allopathic practitioner; some participants in both groups received homeopathy).
Walach H, Möllinger H, Sherr J, Schneider R. Homeopathic pathogenetic trials produce more specific than non-specific symptoms: results from two double-blind placebo controlled trials. Journal of Psychopharmacology 2008, 22(5):543-552.	Level II	Excluded. Wrong research type or publication type. Healthy volunteers included.
Wiesenauer M, Lüdtke R. [A meta-analysis of the homeopathic treatment of pollinosis with Galphimia glauca]. Forschende Komplementärmedizin 1996; 3(5):230-234.	Level I/II – unclear due to language	Excluded. Study not published in the English language.
Weiser M, Clasen BPE. Controlled double blind study of a homoeopathic sinusitis medication. Biological Therapy 1995, 13(1):4-11.	Level II	Primary study already included in the *Overview Report*.
Williamson AV, Mackie WL, Crawford WJ, Rennie B. A trial of sepia 200. British Homeopathic Journal 1995, 84(1):14-20.	Unable to assign a level of evidence – animal study	Excluded. Wrong research type or publication type. Non-human study.
Witt CM, Ludtke R, Mengler N, Willich SN. How healthy are chronically ill patients after eight years of homeopathic treatment? – Results from a long term observational study. BMC Public Health 2008, 8:413.	Level III-2	Excluded. Wrong research type or publication type. Prospective cohort study, however all participants received homeopathy.
Wollumbin J. Homoeopathy, humanitarian aid and homoeoprophylaxis: Part 2. Journal of the Australian Traditional-Medicine Society 2014, 20(1):20-23.	Unable to assign a level of evidence – unclear	Excluded. Out of scope. Homeopathy for prophylactic use.
Books		
Bornhöft G, Matthiessen P, editors. Homeopathy in healthcare – Effectiveness, appropriateness, safety, costs. Berlin: Springer, 2012.	Unable to assign a level of evidence –	Excluded. Wrong research type or publication type.

Title	Level of evidence	Reason for exclusion
	book	
Angell M. The truth about the drug companies: how they deceive us and what to do about it. New York; Random House: 2004.	Unable to assign a level of evidence – book	Excluded. Wrong research type or publication type.
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration; 2011. Available from: www.cochrane-handbook.org	Unable to assign a level of evidence - book	Excluded. Wrong research type or publication type.
Goldacre B. Bad Pharma: How Drug Companies Mislead Doctors and Harm Patients Fourth Estate, London: 2012.	Unable to assign a level of evidence – book	Excluded. Wrong research type or publication type.
News media		
Bob Grant. Australia Officially Debunks Homeopathy. The Scientist 14 April 2014 http://www.the-scientist.com/?articles.view/articleNo/39703/title/Australia-Officially-Debunks-Homeopathy/	Unable to assign a level of evidence – news item	Excluded. Wrong research type or publication type.
David Mark. Homeopathy: National Health and Medical Research Council says Australians 'wasting money' with the alternative therapy. ABC website; 9 April 2014. Available at: http://www.abc.net.au/news/2014-04-09/australians-wasting-time-with-homeopathy3a-peak-research-counc/5377886	Unable to assign a level of evidence – news item	Excluded. Wrong research type or publication type.
Paul Smith. GP Bulk-bills for homeopathy. Australian Doctor 8 March 2010. Available at: http://www.australiandoctor.com.au/news/latest-news/gp-bulk-bills-for-homeopathy	Unable to assign a level of evidence – news item	Excluded. Wrong research type or publication type.
Paul Smith. NHMRC declares: homeopathy 'not efficacious'. Australian Doctor 20 April 2011. http://www.australiandoctor.com.au/news/latest-news/nhmrc-declares--homeopathy---8216;not-efficacious-	Unable to assign a level of evidence – news item	Excluded. Wrong research type or publication type.
Websites and webpages		
http://www.australiannaturaltherapistsassociation.com.au/therapies/naturopathy.php	Unable to assign a level of evidence - website	Excluded. Wrong research type or publication type.
http://www.australiannaturaltherapistsassociation.com.au/courses/recognised	Unable to assign a	Excluded. Wrong research type or publication

Title	Level of evidence	Reason for exclusion
_homoeopathy.php	level of evidence - website	type.
http://www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Homeopathy	Unable to assign a level of evidence - website	Excluded. Wrong research type or publication type.
https://www.brauer.com.au/discover-more/how-homeopathy-works	Unable to assign a level of evidence - website	Excluded. Wrong research type or publication type.
www.britishhomoeopathic.org	Unable to assign a level of evidence - website	Excluded. Wrong research type or publication type.
www.homoeopathyapanacea.com	Unable to assign a level of evidence - website	Excluded. Wrong research type or publication type.
https://www.facebook.com/homeopathyapanacea?ref=hl	Unable to assign a level of evidence - website	Excluded. Wrong research type or publication type.
Heel (Germany) reports at www.heel.com controlled trials for their complexes	Unable to assign a level of evidence - website	Excluded. Wrong research type or publication type.
http://homeopathswithoutborders-na.org/?p=1275	Unable to assign a level of evidence - website	Excluded. Wrong research type or publication type.
http://www.morethanphysio.com.au/services/homeopathy	Unable to assign a level of evidence - website	Excluded. Wrong research type or publication type.
The Institute of Classical Homoeopathy – Montreal. (www.michmontreal.com)	Unable to assign a level of evidence - website	Excluded. Wrong research type or publication type.
http://www.nicm.edu.au/images/stories/policy/docs/Complementary_Medicin	Unable to assign a	Excluded. Wrong research type or publication

Title	Level of evidence	Reason for exclusion
e_3_Vital_Investment_Priorities.pdf	level of evidence - website	type.
http://www.optum.com/about.html	Unable to assign a level of evidence – website	Excluded. Wrong research type or publication type.
http://www.debbierayfield.com/	Unable to assign a level of evidence – website	Excluded. Wrong research type or publication type.
http://www.homeopathy-soh.org/	Unable to assign a level of evidence – website	Excluded. Wrong research type or publication type.
http://hpathy.com/clinical-cases/a-case-of-prostate-cancer-with-bilateral-grade-i-medical-renal-disease/	Level IV (case report)	Excluded. Wrong research type or publication type.
http://hpathy.com/clinical-cases/a-case-of-vocal-cord-cancer/	Level IV (case report)	Excluded. Wrong research type or publication type.
http://statistics.about.com/od/Inferential-Statistics/a/The-Difference-Between-The-Null-Hypothesis-And-Alternative-Hypothesis.htm	Unable to assign a level of evidence – website	Excluded. Wrong research type or publication type.
http://en.wikipedia.org/wiki/Pharmaceutical_industry	Unable to assign a level of evidence – website	Excluded. Wrong research type or publication type.
http://www.lotusdental.com.au/homeopathy-dentistry	Unable to assign a level of evidence - website	Excluded. Wrong research type or publication type.
https://www.google.com.au/search?q=Carol+Boyce+Homeopathy+around+the+wor...	Unable to assign a level of evidence - website incomplete	Excluded. Wrong research type or publication type.
http://joettecalabrese.com/uncategorized/great-women-homeopathy-youre-on...	Unable to assign a level of evidence - website incomplete	Excluded. Wrong research type or publication type.

Title	Level of evidence	Reason for exclusion
http://crofsblogs.typepad.com/h5n1/2014/03/thailand-ministry-to-try-home...	Unable to assign a level of evidence - website incomplete	Excluded. Wrong research type or publication type.
Reports		
House of Commons Science and Technology Committee. Evidence check 2: Homeopathy. London: The Stationery Office; 2010.	Unable to assign a level of evidence – report	Excluded. Wrong research type or publication type.
'The Baxter report' (may refer to: TFG International Pty Ltd. Structural barriers to reform of the Australian health and hospital public system. Australian Centre for Health Research; South Melbourne: January 2010. Available at: http://www.achr.com.au/pdfs/kenbaxter.pdf)	Unable to assign a level of evidence – report	Excluded. Wrong research type or publication type.
Government documents		
Australian Government Department of Health. The Review of the Australian Government Rebate on Private Health Insurance for Natural Therapies [web page]. https://www.health.gov.au/internet/main/publishing.nsf/Content/phi-natural-therapies	Unable to assign a level of evidence – Government report	Excluded. Wrong research type or publication type.
Australian Government Department of Health. Therapeutic Goods Administration. Schedule 1 certificates [Web page] 8 April 2011 http://www.tga.gov.au/industry/advertising-schedule1-certificates.htm#.U0mwfVeLX3A	Unable to assign a level of evidence – Government website	Excluded. Wrong research type or publication type.
Australian Government Department of Health. Therapeutic Goods Administration. [web page] [search results for 'homeopathy'] http://agencysearch.australia.gov.au/s/search.html?query=homeopathic&collection=agencies&profile=tga	Unable to assign a level of evidence – Government website	Excluded. Wrong research type or publication type.
Miscellaneous		
Clinical Evidence. What conclusions has Clinical Evidence drawn about what works, what doesn't based on randomised controlled trial evidence? http://clinicalevidence.bmj.com/x/set/static/cms/efficacy-categorisations.html	Unable to assign level of evidence	Excluded. Wrong research type or publication type.

Title	Level of evidence	Reason for exclusion
Dwyer J, MacLennan A, Morrison R, Costa M, Marron L, Ieraci S, Benhamu J; on behalf of Friends of Science in Medicine. [Letter] 8 April 2014 http://www.scienceinmedicine.org.au/images/pdf/nhmrcfsmopenletr.pdf	Unable to assign a level of evidence – letter	Excluded. Wrong research type or publication type.
The Australian Register of Homoeopathy (AROH)'s submission of evidence (Table 1, page 21 of their submission to NHMRC.)	Unable to assign a level of evidence – submission	Excluded. Wrong research type or publication type.
A submission from the homoeopathy profession to the Natural Therapy Review Advisory Committee in Feb-April 2013	Unable to assign a level of evidence – submission	Excluded. Wrong research type or publication type.
Submissions by the Australian Homoeopathic Association (AHA)	Unable to assign a level of evidence – submission	Excluded. Wrong research type or publication type.
Letter to Cathy Connor of NHMRC from the Australian Homoeopathic Association dated 18 August 2011	Unable to assign a level of evidence – letter	Excluded. Wrong research type or publication type.
Submissions by the Australian Medical Fellowship of Homoeopathy (AMFoH)	Unable to assign a level of evidence – submission	Excluded. Wrong research type or publication type.
Complementary Health Care Council of Australia	Unable to assign a level of evidence	Excluded. Wrong research type or publication type.

Appendix B List of included studies

Bell IR, Howerter A, Jackson N, Aickin M, Baldwin CM, Bootzin RR. Effects of homeopathic medicines on polysomnographic sleep of young adults with histories of coffee-related insomnia. Sleep Medicine 2011, 12(5):505-511.

Belon P, Banerjee A, Karmakar SR, Biswas SJ, Choudhury SC, Banerjee P, et al. Homeopathic remedy for arsenic toxicity? Evidence-based findings from a randomized placebo-controlled double blind human trial. Science of the Total Environment 2007, 384(1-3):141-150.

Bignamini M, Saruggia M, Sansonetti G.Homeopathic treatment of anal fissures using nitricum acidum. Berlin Journal of Research in Homeopathy 1991, 1(4/5): 286-287.

Brien S, Lachance L, Prescott P, McDermott C, Lewith G. Homeopathy has clinical benefits in rheumatoid arthritis patients that are attributable to the consultation process but not the homeopathic remedy: a randomized controlled clinical trial. Rheumatology 2011, 50(6):1070-1082.

Chakraborty PS, Varanasi R, Majumdar AK, Banoth K, Prasad S, Ghosh MS, et al. Effect of homoeopathic LM potencies in acute attacks of haemorrhoidal disease: A multicentric randomized single-blind placebo-controlled trial. Indian Journal of Research in Homoeopathy 2013, 7:72-80.

Chakraborty PS, Lamba CD, Nayak D, John MD, Sarkar DB, Poddar A et al. Effect of individualized homoeopathic treatment in influenza like illness: A multicentre, single blind, randomized placebo controlled study. Indian Journal of Research in Homoeopathy 2013, 7(1):22-30.

Chand KS, Manchanda RK, Mittal R, Batra S, Banavaliker JN, De I. Homeopathic treatment in addition to standard care in multi drug resistant pulmonary tuberculosis: a randomized, double blind, placebo controlled clinical trial. Homeopathy 2014, 103:97-107.

Clark J, Percivall A. A preliminary investigation into the effectiveness of the homeopathic remedy, Ruta graveolens, in the treatment of pain in plantar fasciitis. British Journal of Podiatry 2000, 3(3):81-85.

Colau JC, Vincent S, Marijnen P, Allaert FA. Efficacy of a non-hormonal treatment, BRN-01, on menopausal hot flashes: A multicenter, randomized, double-blind, placebo-controlled trial. Drugs in R and D 2012, 12(3):107-119.

Dean ME, Karsandas R, Bland JM, Gooch D, MacPherson H. Homeopathy for mental fatigue: lessons from a randomized, triple blind, placebo-controlled cross-over clinical trial. BMC Complementary and Alternative Medicine 2012;12:167.

Derasse M, Klein P, Weiser M. The effects of a complex homeopathic medicine compared with acetaminophen in the symptomatic treatment of acute febrile infections in children: an observational study. Explore: The Journal of Science and Healing 2005, 1(1):33-39.

Ernst E, Saradeth T, Resch KL. Complementary treatment of varicose veins. Phebology 1990, 5:157-163.

Friese KH, Zabalotnyi DI. Homoopathie bei akuter rhinosinusitis: Eine doppelblinde, placebokontrollierte studie belegt die wirksamkeit und vertraglichkeit eines homoopathischen

kombinationsarzneimittels [Homeopathy in acute rhinosinusitis: a double-blind, placebo controlled study shows the efficiency and tolerability of a homeopathic combination remedy]. HNO 2007, 55(4):271-277.

González de Vega C, Speed C, Wolfarth B, González J. Traumeel vs. diclofenac for reducing pain and improving ankle mobility after acute ankle sprain: A multicentre, randomised, blinded, controlled and non-inferiority trial. International Journal of Clinical Practice 2013, 67:979-989.

Haila S, Koskinen A, Tenovuo J. Effects of homeopathic treatment on salivary flow rate and subjective symptoms in patients with oral dryness: a randomized trial. Homeopathy 2005, 94(3):175-181.

Harrison CC, Solomon EM, Pellow J . The effect of a homeopathic complex on psychophysiological onset insomnia in males: a randomized pilot study. Alternative Therapies in Health and Medicine 2013, 19:38-43.

Hellhammer J, Schubert M. Effects of a homeopathic combination remedy on the acute stress response, well-being, and sleep: a double-blind, randomized clinical trial. Journal of Alternative and Complementary Medicine 2013, 19:161-169.

Issing W, Klein P, Weiser M. The homeopathic preparation Vertigoheel versus Ginkgo biloba in the treatment of vertigo in an elderly population: a double-blinded, randomized, controlled clinical trial. Journal of Alternative and Complementary Medicine 2005, 11(1):155-160.

Khuda-Bukhsh AR, Banerjee A, Biswas SJ, Karmakar SR, Banerjee P, Pathak S, et al. An initial report on the efficacy of a millesimal potency Arsenicum Album LM 0/3 in ameliorating arsenic toxicity in humans living in a high-risk arsenic village. Zhong Xi Yi Jie He XueBao: Journal of Chinese Integrative Medicine 2011, 9(6):596-604.

Kulkarni A, Nagarkar BM, Burde GS. Radiation protection by use of homoeopathic medicines. Hahnemannian Homoeopathic Sandesh 1988, 12:20-23.

Manchanda RK, Mehan N, Bahl R, Atey R. Double blind placebo controlled clinical trials of homoeopathic medicines in warts and molluscum contagiosum. CCRH Quarterly Bulletin 1997, 19:25-29.

Maronna U, Weiser M, Klein P. [Orale Behandlung der Gonarthrose mit Zeel comp. - Ergebnisse einer doppelblinden Äquivalenzstudie versus Diclofenac. Orthopädische Praxis. 2000, 36(5)] International Journal for Biomedical Research and Therapy 2000, 29(3):157–158.
As reported in:

- Porcher-Spark A. Comparison of the efficacy and tolerance of Zeel® comp. and diclofenac for the oral treatment of gonarthrosis: results of a double blind equivalence study [Summary of trial published in German]; and
- Strosser W, Weiser M. Osteoarthritis patients regain mobility. A double-blind study of a homeopathic medication International Journal of Biomedical Research (2000) 29(6): 295-299.

Mourão LC, Moutinho H, Canabarro A. Additional benefits of homeopathy in the treatment of chronic periodontitis: A randomized clinical trial. Complement Therapies in Clinical Practice 2013, 19:246-250.

Naidoo P, Pellow J. A randomized placebo-controlled pilot study of Cat saliva 9cH and Histaminum 9cH in cat allergic adults. Homeopathy 2013, 102:123–129.

Pach D, Brinkhaus B, Roll S, Wegscheider K, Icke K, Willich SN, et al. Efficacy of injections with Disci/Rhus toxicodendron compositum for chronic low back pain – A randomized placebo-controlled trial. PLoS One 2011, 6:e26166.

Pellow J, Swanepoel M. A randomised pilot study on the efficacy of milking cream and a homeopathic complex topical cream on diaper dermatitis. Health SA Gesondheid 2013,18(1):680.

Pomposelli R, Piasere V, Andreoni C, Costini G, Tonini E, Spalluzzi A, et al. Observational study of homeopathic and conventional therapies in patients with diabetic polyneuropathy. Homeopathy 2009, 98(1):17-25.

Relton C, O'Cathain A, Nicholl J. A pilot 'cohort multiple randomised controlled trial' of treatment by a homeopath for women with menopausal hot flushes. Contemporary Clinical Trials 2012, 33:853-859.

Robertson A, Suryanarayanan R, Banerjee A. Homeopathic Arnica montana for post-tonsillectomy analgesia: a randomised placebo control trial. Homeopathy 2007, 96(1):17-21.

Saha S, Koley M, Hossain SI, Mundle M, Ghosh S, Nag G, et al. Individualized homoeopathy versus placebo in essential hypertension: A double-blind randomized controlled trial. Indian Journal of Research in Homoeopathy 2013, 7:62-71.

Saruggia M, Corghi E. Effects of homoeopathic dilutions of China rubra on intradialytic symptomatology in patients treated with chronic haemodialysis. British Homoeopathic Journal 1992, 81(2):86-88.

Schmidt C A. Double blind, placebo-controlled trial: arnica montana applied topically to subcutaneous mechanical injuries. Journal of the American Institute of Homeopathy 1996, 89(4):186-193.

Sencer SF, Zhou T, Freedman LS, Ives JA, Chen Z, Wall D, et al. Traumeel S in preventing and treating mucositis in young patients undergoing SCT: a report of the Children's Oncology Group. Bone Marrow Transplant 2012, 47:1409-1414.

Steinsbekk A, Fønnebø V, Lewith G, Bentzen N. Homeopathic care for the prevention of upper respiratory tract infections in children: a pragmatic, randomized, controlled trial comparing randomized homeopathic care and waiting-list controls. Complementary Therapies in Medicine 2005, 13:231-238.

Taylor JA, Jacobs J. Homeopathic ear drops as an adjunct to standard therapy in children with acute otitis media. Homeopathy 2011, 100:109-115.

Totonchi A, Guyuron B. A randomized, controlled comparison between arnica and steroids in the management of postrhinoplasty ecchymosis and edema. Plastic and Reconstructive Surgery 2007, 120(1):271-274.

Villanueva DFD, Rodríguez AP, García LRG, Osés CAM. Use of homeopathic formula in malnourished children. International Journal of High Dilution Research 2012, 11(38):25-32.

Weiser M, Strosser W, Klein P. Homeopathic vs conventional treatment of vertigo: a randomized double-blind controlled clinical study. Archives of Otolaryngology--Head and Neck Surgery 1998, 124(8):879-885.

Wolschner U, Strösser W, Weiser M, Klein P. Treating vertigo - homeopathic combination remedy therapeutically equivalent to dimenhydrinate. Biologische Medezin 2001, 30(4):184-190.

Zanasi A, Mazzolini M, Tursi F, Morselli-Labate AM, Paccapelo A, Lecchi M. Homeopathic medicine for acute cough in upper respiratory tractinfections and acute bronchitis: A randomized, double-blind, placebo-controlled trial. Pulmonary Pharmacology and Therapeutics 2014, 27(1);102-108.

Appendix C Data extraction and quality assessment forms

Homeopathy data extraction form: Bell et al. 2011

Reference: Bell IR, Howerter A, Jackson N, Aickin M, Baldwin CM, Bootzin RR. Effects of homeopathic medicines on polysomnographic sleep of young adults with histories of coffee-related insomnia. Sleep Medicine 2011, 12(5):505-511.				
Study design: Non-randomised prospective study (within subjects comparison)				
Source of funds: National Center for Complementary and Alternative Medicine Grants. **Conflicts of interest:** Dr Bell is a consultant to Standard Homeopathic Co/Hylands Inc (none of the company's products were used in this study).				
Participants and setting **Setting:** University of Arizona, USA (participants undertook sleep recordings in their own homes). **Inclusion criteria:** Young adults (male and female college psychology students) aged 18 to 31 with above average scores on standardised personality scales for either cynical hostility or anxiety sensitivity (but not both) and a history of coffee-induced insomnia, with a global health score of 3 or more out of 5 [high anxiety sensitivity subgroup: ASI ≥ 16.8 for males and ≥ 19.1 for females and < 11.0 on the CMHO; and high hostility subgroup: < 16.8 for males and < 19.1 on the ASI and ≥ 11.0 on the CMHO]. Participants had to be willing to eliminate drinking coffee for the full duration of the study (4 weeks). **Exclusion criteria:** pregnancy or planning to become pregnant, major psychiatric or serious chronic medical conditions, chronic use of medications other than contraceptive drugs, and/or a history of anaphylactic shock.				
NOTE: 54 participants in the analyses for the study, who all received the control (placebo) on night 8, and the intervention (homeopathy) on night 22				
Intervention **Homeopathy:** either Nux Vomica pellets (n=28) or Coffea Cruda pellets on night 22 (n=26)				
Comparison **Control:** Placebo pellets on night 8 (n=54)				
All participants PSGs were performed on pairs of consecutive nights over 4 weeks (nights 1-2, 8-9, 15-16 and 22-23); week 1: baseline; week 2: placebo pellets on night 8; week 3: repeat baseline; week 4: homeopathy pellets on night 22.				
Outcomes: Polysomnographic and actigraphic recordings (total sleep time, stage 2, NREM, SWS, stage changes, awakenings, arousal index, type 2 arousals); self-reported POMS-fatigue and weekly PSQI global score.				
Very brief summary of study authors' main findings/conclusions: verum remedies increased sleep time, NREM, and awakenings, but changes in actigraphic and self-rated scale effects were not significant.				
Risk of bias assessment: unclear (to high)				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☒	☐	"Within-subjects" design with no randomisation for allocation to homeopathy or placebo first/second (i.e. no crossover of treatments, with all patients receiving the placebo first and the homeopathic remedy second).
Allocation concealment *(selection bias)*	☐	☒	☐	As above; no randomisation to timing of placebo and homeopathy. On night 22, half of the patients received Coffea Cruda and half received Nux

				Vomica; they were *"dynamically assigned";* using their CMHO and ASI scores, age and sex as balancing factors.
Blinding of participants and personnel *(performance bias)*	☐	☐	☒	Participants blinded with the use of an identical placebo *("single-blind placebo"*). Study personnel not blinded – i.e. were aware that placebo was given on night 8 and homeopathy given on night 22. Study personnel were however blind to the homeopathic remedy allocated on night 22 (*"double-blind remedies"*). Unclear if and how lack of blinding of study personnel would have impacted on findings.
Blinding of outcome assessment *(detection bias)*	☐	☐	☒	Not stated; see above.
Incomplete outcome data *(attrition bias)*	☐	☒	☐	70 participants were enrolled; 5 were withdrawn for protocol violations (beginning medication on the exclusion list, an undisclosed health problem on the exclusion list); 3 left the study (schedule conflicts, flu) and 3 were not within the targeted age range for the study. 59 participants received treatment and completed the study – 5 of the 59 did not meet the criterion for the minimum 4 hour sleep per night and/or did not have enough data on their baseline recordings for analysis; for various reasons (e.g. unavailability on some nights, dislodgement of equipment during sleep) there was partial data loss – data were available for 2.96 [SD 1.00] out of 4 baseline nights; 1.39 [SD 0.74] and 1.33 [SD 0.67] out of 2 placebo and remedy nights respectively. Missing data were imputed by linear interpolation or last value carried forward.
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	Primary outcome not specified; not enough detail available to further assess selective reporting; exit interviews mentioned in discussion but results from these interviews were not reported; outcomes largely address feasibility rather than insomnia.

Other bias	☐	☐	☒	Insufficient information to determine other risk of bias.
Notes:	Complex analysis; raw results not reported or discussed.			

Regression for within-subject analyses on means for combined remedy nights (nights 22/23) versus means for combined placebo nights (nights 8/9) – controlling for gender, personality scores, total time in bed, and means for combined baseline nights (nights 1/2/15/16)

	Both remedies (n=54) vs. placebo (n=54)		**Nux Vomica (n=28) vs. placebo (n=54)**		**Coffea Cruda (n=26) vs. placebo (n=54)**	
	β (R^2)	**95% CI (p value)**	**β (R^2)**	**95% CI (p value)**	**β (R^2)**	**95% CI (p value)**
Total sleep time	69.5 (0.52)	39.4 to 99.7 (< 0.001)	52.8 (0.60)	14.9 to 90.8 (< 0.01)	92.7 (0.51)	38.3 to 147.1 (< 0.01)
Stage 2 (min)	36.6 (0.51)	19.6 to 53.6 (< 0.001)	29.3 (0.60)	8.3 to 50.3 (< 0.01)	45.9 (0.46)	14.9 to 76.8 (< 0.01)
NREM	54.8 (0.50)	32.0 to 77.6 (< 0.001)	45.9 (0.60)	19.4 to 72.3 (< 0.01)	67.3 (0.44)	24.8 to 109.8 (< 0.01)
SWS	13.3 (0.46)	5.3 to 21.4 (< 0.01)	12.4 (0.47)	1.8 to 23.0 (< 0.05)	15.2 (0.48)	1.5 to 28.8 (< 0.05)
Stage changes	22.9 (0.47)	12.1 to 33.7 (< 0.001)	20.9 (0.49)	5.9 to 35.8 (< 0.01)	25.0 (0.44)	7.3 to 42.8 (< 0.01)
Awakenings	4.1 (0.49)	2.0 to 6.2 (< 0.001)	4.1 (0.45)	1.0 to 7.2 (< 0.05)	4.1 (0.61)	0.9 to 7.2 (< 0.05)
Arousal index	0.8 (0.63)	-0.6 to 1.6 pns (< 0.10)	1.3 (0.77)	0.5 to 2.1 (< 0.01)	0.2 (0.61)	-1.4 to 1.8 pns
Type 2 arousals	3.1 (0.51)	0.99 to 5.2 (< 0.01)	3.0 (0.49)	0.2 to 5.8 (< 0.05)	3.2 (0.55)	-0.3 to 6.7 (< 0.10)
POMS-fatigue	-1.1 (0.45)	-2.0 to -0.2 (< 0.05)	-1.0 (0.52)	-2.3 to -0.1 pns	-1.3 (0.34)	-2.6 to 0.04 pns
Weekly PSQI global score*	-0.2 (0.30)	-0.9 to 0.5 pns	-0.2 (0.24)	-1.3 to 1.0 pns	-0.3 (0.43)	-1.2 to 0.6 pns

Adjusted for gender, personality scores, total time in bed, and means for combined baseline nights (1/2/15/16)

*Higher scores mean poorer subjective sleep; trend to poorer subjective sleep for Nux Vomica compared with placebo, controlling for personality and sex (OR 0.29 95% CI 0.08 to 1.11; p = 0.07)

Abbreviations: ASI: anxiety sensitivity index (16 items); CI: confidence interval; CMHO: Cook-Medley Cynical Hostility Scale (27 items); min: minutes; n: number; NREM: non rapid eye movement sleep; pns: p value not significant (> 0.05); POMS; profile of mood states scale; PSG: polysomnography; PSQI: Pittsburgh sleep quality index; SWS: slow wave sleep (stages 3 and 4 mins)

Homeopathy data extraction form: Belon et al. 2007

Reference: Belon P, Banerjee A, Karmakar SR, Biswas SJ, Choudhury SC, Banerjee P, et al. Homeopathic remedy for arsenic toxicity? Evidence-based findings from a randomized placebo-controlled double blind human trial. Science of the Total Environment 2007, 384(1-3):141-150.
Study design: Randomised controlled trial.
Source of funds: Boiron Laboratories, Lyon, France.

Conflicts of interest: not reported.

Participants and setting

Setting: Dasdiya village, West Bengal, India (this village is arsenic contaminated (arsenic content of wells between 55 and 95 ppb).

Inclusion criteria: individuals showing initial signs/symptoms of arsenic poisoning (weakness, anaemia, skin symptoms, liver or alimentary system disorders, pains and burning sensation in muscles and joints).

Exclusion criteria: none reported.

Intervention

Homeopathy: Arsenicum Album-30**.**

Total number randomised: n=22 randomised, n=20 analysed

Comparison

Control: sugar globules soaked with alcohol 30 (placebo).

Total number randomised: n=17 randomised, n=5 analysed

All participants: asked to take 8 medicine-soaked sugar globules twice daily for 14-15 days and then none for the next 10-12 days; repeated until blood and urine collection at 2 months.

Outcomes: Arsenic content in blood and urine; packed cell volume; haemoglobin; erythrocyte sedimentation rate; triglycerides; creatinine; neutrophil; eosinophil; GSH; AST; ALT; LPO; G-6-PD; GGT.

Very brief summary of study authors' main findings/conclusions: decreased biomarker concentrations, better appetite and improved general health.

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☐	☒	Not reported, probably not done.
Allocation concealment *(selection bias)*	☐	☒	☐	50 similar bottles were prepared (25 of verum and 25 placebo) "*marked with numerical codes (not disclosed to the researchers"* and kept on a tray. *"The subjects were asked to pick up a vial as per their choice."*
Blinding of participants and personnel *(performance bias)*	☐	☐	☒	Probably done (see above); but differential losses indicate that blinding may not have been successful.
Blinding of outcome assessment *(detection bias)*	☐	☐	☒	Not reported.
Incomplete outcome data *(attrition bias)*	☐	☒	☐	Of the 39 participants who picked a vial, 25 returned after 2 months (36% loss to follow-up), with a differential loss (2/22 (9%) for verum and 12/17 (71%) for placebo).
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	Exact results not reported (generally only p values); health outcomes only reported narratively; primary and secondary outcomes not specified
Other bias	☐	☐	☒	22 participants in the verum group and 17 in the placebo group suggests possible randomisation imbalance
Notes	Comparisons between Dasdiya participants and an arsenic-free village were not considered here, as these were not part of the trial assessing			

	homeopathic treatment.

	Outcome measures (continuous)	Total number of participants in study = 25						
		Intervention group Total no. in group = 20			**Control group** Total no. in group = 5			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Packed cell volume (%)	NR	NR	NR	NR	NR	NR	0.000
	Haemoglobin (g/dL)	NR	NR	NR	NR	NR	NR	0.361
	Erythrocyte sedimentation rate (mm/hour)	NR	NR	NR	NR	NR	NR	0.091
	Triglycerides (no units reported)	NR	NR	NR	NR	NR	NR	0.354
	Creatinine (units only reported as *"amount")*	NR	NR	NR	NR	NR	NR	0.167
	Neutrophil (%)	NR	NR	NR	NR	NR	NR	0.004
	Eosinophil (%)	NR	NR	NR	NR	NR	NR	0.000
	GSH (nM/mL)	NR	NR	NR	NR	NR	NR	0.66
	AST (nM/100 mg protein/min)	NR	NR	NR	NR	NR	NR	0.131
	ALT (nM/100 mg protein/min)	NR	NR	NR	NR	NR	NR	0.000
	LPO (nM/MDA/mL)	NR	NR	NR	NR	NR	NR	0.000
	G-6-PD (IU/L)	NR	NR	NR	NR	NR	NR	0.216
	GGT (IU/L)	NR	NR	NR	NR	NR	NR	0.000
	Arsenic concentration in urine (ppb)	NR	NR	NR	NR	NR	NR	0.364
	Arsenic concentration in blood (ppb)	NR	NR	NR	NR	NR	NR	0.002

Abbreviations: ALT: alanine aminotransaminase; AST: aspartate aminotransferase; dL: decilitres; g: grams; G-6-PD: glucose-6-phosphate-dehydrogenase; GGT: gamma-gluamyl transferase; GSH: reduced glutathione; IU: international unit; L: litre; LPO: lipid peroxidation; MDA: malondialdehyde; mg: milligrams; mL: millilitres; mm: millimetres; n: number; nM: nanometre; NR: not reported; ppb: parts per billion; U: units

Homeopathy data extraction form: Bignamini et al. 1991

Reference: Bignamini M, Saruggia M, Sansonetti G.Homeopathic treatment of anal fissures using nitricum acidum. Berlin Journal of Research in Homeopathy 1991, 1(4/5): 286-287.
Study design: Randomised controlled trial.
Source of funds: Not stated. **Conflicts of interest:** Not stated.
Participants and setting **Setting:** Milano, Italy. **Inclusion criteria:** patients with anal fissure symptomatology (males and females; mean age: 37 years; symptomatology dating back on average, 11 months). **Exclusion criteria:** none stated.
Intervention **Homeopathy:** Nitricum acidum 9 CH (5 granules dissolved sublingually) each morning for 15 days. **Total number randomised: n=16** No local treatment was employed.
Comparison **Control:** Placebo.

Total number randomised: n=15				
Outcomes: Proctodynia (pain during and after defecation); proctorrhagia (bleeding from the anus); itching; burning; the appearance of the lesion; the subject's judgement with respect to efficacy of the treatment.				
Very brief summary of <u>study authors'</u> main findings/conclusions: *"In general, the active treatment appeared to be satisfactory, but was statistically significant only in two of the six parameters considered: burning sensation and the subjective opinion of the patient regarding efficacy of the treatment."*				
Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☐	☒	Quote: *"The subjects were randomly divided into two groups."* No further details provided.
Allocation concealment *(selection bias)*	☐	☐	☒	As above.
Blinding of participants and personnel *(performance bias)*	☐	☐	☒	Placebo was used, although no details provided regarding characteristics of placebo; blinding of study personnel not stated.
Blinding of outcome assessment *(detection bias)*	☐	☐	☒	No detail re: blinding of outcome assessors.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	Insufficient information to determine risk of attrition bias.
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	For four of the six outcomes, p = n.s. reported (not the actual p value).
Other bias	☐	☐	☒	Groups similar at baseline: *"The two groups were similar in mean age, sexual combination and the period in which symptoms began. The two groups were also symptomatically homogenous…and had a similar distribution of scoring when the symptoms were evaluated ona scale of 1 to 10."* Insufficient information to determine other risk of bias.
Notes	Very little methodological detail provided (short report).			

	Outcome measures (dichotomous)	Total number of participants in study = 31				
		<u>Intervention group</u> Total no. in group = 16		**<u>Control group</u>** Total no. in group = 15		
		Events	**Total**	**Events**	**Total**	**P value**
	Proctodynia	2	16	3	15	*"n.s."*
	Proctorrhagia	2	16	5	15	*"n.s."*
	Itching	1	16	5	15	*"n.s."*
	Burning sensation	0	16	6	15	< 0.005
	Lesions	3	16	5	15	*"n.s."*
	Subjective opinion					
	Unchanged	2	16	5	15	<0.05
	Improved	2	16	2	15	
	Healed	12	16	6	15	

	Exacerbated	0	16	2	15	

Abbreviations: n: number; *"n.s."*: non-significant

Homeopathy data extraction form: Brien et al. 2011

Reference: Brien S, Lachance L, Prescott P, McDermott C, Lewith G. Homeopathy has clinical benefits in rheumatoid arthritis patients that are attributable to the consultation process but not the homeopathic remedy: a randomized controlled clinical trial. Rheumatology 2011, 50(6):1070-1082.		
Study design: Randomised controlled trial.		
Affiliation/source of funds: NIHR; Samueli Institute, USA; Southampton Complementary Medicine Research Trust; The Rufford Maurice Laing Foundation; Dreluso Pharmazeutika GmBH; National Health Service Fund for Science. **Conflicts of interest:** Authors declared no conflict of interest.		
Participants and setting **Setting:** Three rheumatology outpatient departments in the United Kingdom (recruited from January 2006 to July 2008). **Inclusion criteria:** Patients aged > 18 years; diagnosis of RA for > 2 years [1987 ACR guidelines]; current disease activity minimum DAS-28 score > 2.6; patient GA score ≥ 30 mm; stable medication for > 3 months. **Exclusion criteria:** Severe RA (functional status class IV); taking biological DMARDS e.g. anti-TNF; severe comorbidities that would affect their RA; used homeopathy for < 3 months; pregnant or breastfeeding; participated in an investigational trial within 45 days before enrolment.		
Patients were randomised to either **homeopathic consultation** or **non-homeopathic consultation**. The consultation groups were further randomized to individualized treatment (**Group 1, n = 17**), a homeopathic complex for RA (**Group 2, n = 15**) or placebo (**Group 3, n = 17**). Non-consultation participants were allocated complex (**Group 4, n = 18**) or placebo (**Group 5, n = 16**). The trial period was 40 weeks; patients attended for seven further clinic visits on a 4 weekly basis during treatment (visits 2-8); follow-up was week 40 (visit 9). **Intervention** **Individualized homeopathy (Group 1, n = 17):** tablets twice daily (posted to participants after visits 2-7 by an offsite homoeopathic pharmacist; the homoeopaths *"prescribed from the entire homoeopathic repertoire"; "post-analysis review confirmed that all individualized homeopathy was prescribed at ultra-molecular doses (all fifty millesimal potency scale potencies)".* **Standardized commercial homeopathic complex (Groups 2 (n = 15) and 4 (n = 18)):** previously reported as efficacious for RA; Rheumaselect (liquid taken 20 drops/dose twice daily (containing Rhus Toxicodendron D4, Bryonia cretica D4, Strychnos nux-vomica D4, Berberis vulgaris D4 and Ledum palustre D4 in 20 mL.		
Comparison **Control groups (Groups 3 (n = 17) and 5 (n = 16)):** two placebos identical in appearance, taste and small to tablets and liquid complex.		
Outcomes: Primary outcomes: ACR 20% improvement (ACR20) criteria; 35% change in patient monthly global assessment (GA) (100-mm VAS); Secondary outcomes: 28-joint DAS (DAS-28 (includes objective measures – ESR, CRP, swollen joint counts) and subjective measure (tender joint counts; patient GA score)); individual measures within the ACR20; 15% improvement in the MYMOP; changes in mood (PANAS); changes in weekly pain and patient GA: adverse events.		
Very brief summary of study authors' main findings/conclusions: *"Homeopathic consultations but not homeopathic remedies are associated with clinically relevant benefits for patients with active but relatively stable RA."*		
Risk of bias assessment		
Domain	**Risk of bias**	***Support for judgement***

	Low	High	Unclear	
Random sequence generation *(selection bias)*	☒	☐	☐	Computer generated sequence – separate randomisation codes for each study site; blocks of five.
Allocation concealment *(selection bias)*	☒	☐	☐	Allocation concealment: two-stage process using *"sequentially ordered sealed envelopes";* the first envelope was opened *"once the patient passed baseline screening to identify allocation to consultation or no consultation… When the patient returned for treatment visits, the enclosed sealed second envelope was opened by staff unrelated to the study trial to identify the patient's treatment allocation; this was faxed to the independent off site pharmacist to allocate the correct medication."*
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	Blinding of homeopathy vs. placebo. All patients received one bottle of tablets (individualised remedy or placebo) and a bottle of liquid (homeopathic complex or placebo), with a standardised dosing frequency to ensure blinding. Blinding was confirmed as secure. Consultation/no consultation not blinded *"patients and study staff were aware of consultation allocation but were all blinded to treatment allocation."*
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	As above.
Incomplete outcome data *(attrition bias)*	☒	☐	☐	83 randomised; 6 (7%) dropped out after randomisation but before receiving treatment: ITT population: 77/83; PP population: 52/83. **Group 1:** 17 allocated; 1 withdrew (non-compliance); 4 discontinued treatment; 12 completed follow-up: 16 analysed ITT; 12 PP. **Group 2:** 15 allocated; 1 withdrew (did not wish to continue); 4 discontinued treatment; 10 completed follow-up; 14 analysed ITT; 10 PP. **Group 3:** 17 allocated; 1 withdrew (breached inclusion criteria); 3 discontinued; 11 completed follow-up; 16 analysed ITT; 11 PP. **Group 4:** 18 allocated; 3 withdrew (1

				non-compliance; 2 did not wish to continue); 5 discontinued treatment; 9 completed follow-up; 15 analysed ITT, 9 PP. **Group 5:** 16 allocated; 0 withdrew; 5 discontinued treatment; 10 completed follow-up; 16 analysed ITT; 10 PP.
Selective outcome reporting? *(reporting bias)*	☒	☐	☐	The study protocol is not available but the published report includes many expected outcomes, including those that were pre-specified as primary/secondary in the online trial registration.
Other bias	☒	☐	☐	No significant differences seen in baseline characteristics. No other obvious sources of bias identified.
Notes	The study was underpowered for dichotomous outcomes due to under recruitment, and a slightly higher rate of attrition than anticipated (27% vs. 20%). It was adequate powered for continuous variables.			

	Outcome measures (dichotomous)	Total number of participants in study = 83										
		Group 1 Total no. in group = 17 (16 analysed)		**Group 2** Total no. in group = 15 (14 analysed)		**Group 3** Total no. in group = 17 (16 analysed)		**Group 4** Total no. in group = 18 (15 analysed)		**Group 5** Total no. in group = 16 (16 analysed)		
		Events	**Total**	**Events**	**Total**	**Events**	**Total**	**Events**	**Total**	**Events**	**Total**	**P value**
	Primary											
	Achieved ACR20	5	16	2	14	5	16	2	15	2	16	*
	Achieved 35% patient GA	6	16	6	14	6	16	4	15	6	16	**
	Secondary											
	Adverse events	72	16	55	14	58	16	60	15	37	16	***
	Serious adverse events	1 (fractured femur)	16	2 (stomach pains and admission to hospital; fractured metacarpal)	14	0	16	1 (mild heart attack)	15	0	16	***
	Non-serious adverse events	71	16	53	14	58	16	59	15	37	16	***
	Patient attribution of adverse event	16	16	22	14	15	16	19	15	18	16	***

	to study medication											

* Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.216; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.324; Individual (Group 1) vs. complex (Group 2): 0.177; Individual (Group 1) vs. placebo (Group 3): 0.778

** Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.582; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.816; Individual (Group 1) vs. complex (Group 2): 0.927; Individual (Group 1) vs. placebo (Group 3): 0.953

****"No significant differences were identified between treatment groups."*

	Outcome measures (continuous)	Total number of participants in study = 83
	Secondary (mean, SD)****	**Contrast p values after 24 weeks of treatment**
	Rheumatological measures	
	DAS-28	Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.005; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.579; Individual (Group 1) vs. complex (Group 2): 0.787; Individual (Group 1) vs. placebo (Group 3): 0.547
	Swollen joint count	Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.003; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.279; Individual (Group 1) vs. complex (Group 2): 0.479; Individual (Group 1) vs. placebo (Group 3): 0.964
	Tender joint count	Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.229; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.776; Individual (Group 1) vs. complex (Group 2): 0.353; Individual (Group 1) vs. placebo (Group 3): 0.316
	Current pain (VAS)	Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.038; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.521; Individual (Group 1) vs. complex (Group 2): 0.169; Individual (Group 1) vs. placebo (Group 3): 0.611
	CRP (mg/L)	Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.948; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.770; Individual (Group 1) vs. complex (Group 2): 0.584; Individual (Group 1) vs. placebo (Group 3): 0.819
	ESR (mm/hour)	Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.347; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.333; Individual (Group 1) vs. complex (Group 2): 0.707; Individual (Group 1) vs. placebo (Group 3): 0.382
	HAQ	Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.218; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.810; Individual (Group 1) vs. complex (Group 2): 0.844; Individual (Group 1) vs. placebo (Group 3): 0.903
	Patient GA	Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.074; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.906; Individual (Group 1) vs. complex (Group 2): 0.182; Individual (Group 1) vs. placebo (Group 3): 0.912
	Physician GA	Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.159; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.776; Individual (Group 1) vs. complex (Group 2): 0.239; Individual (Group 1) vs. placebo (Group 3): 0.597
	Other measures	

	Positive mood	Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.098; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.631; Individual (Group 1) vs. complex (Group 2): 0.308; Individual (Group 1) vs. placebo (Group 3): 0.186
	Negative mood	Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.015; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.074; Individual (Group 1) vs. complex (Group 2): 0.563; Individual (Group 1) vs. placebo (Group 3): 0.302
	MYMOP	Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.424; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.407; Individual (Group 1) vs. complex (Group 2): 0.668; Individual (Group 1) vs. placebo (Group 3): 0.207
	Weekly pain scores (VAS)	Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.045; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.615; Individual (Group 1) vs. complex (Group 2): 0.203; Individual (Group 1) vs. placebo (Group 3): 0.254
	Weekly GA	Consultation (Groups 2,3) vs. no consultation (Groups 4,5): 0.036; Complex (Groups 2, 4) vs. placebo (Groups 3,5): 0.205; Individual (Group 1) vs. complex (Group 2): 0.114; Individual (Group 1) vs. placebo (Group 3): 0.008 (patients receiving placebo compared with IH reported significant improved GA)

********Means and standard deviations per group are presented in the manuscript.

Abbreviations: ACR: American College of Rheumatology; ACR20: American College of Rheumatology 20% improvement criteria; CRP: c-reactive protein; DAS-28: Disease Activity Score 28; DMARDS: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; GA: global assessment; HAQ: Health Assessment Questionnaire; mL: millilitres; MYMOP: Measure Yourself Medical Outcome Profile; PANAS: Positive and Negative Affect Schedule; PP: per protocol; RA: rheumatoid arthritis; SD: standard deviation; TNF: tumour necrosis factor; VAS: visual analogue scale

Homeopathy data extraction form: Chakraborty et al. 2013a

Reference: Chakraborty PS, Varanasi R, Majumdar AK, Banoth K, Prasad S, Ghosh MS, et al. Effect of homoeopathic LM potencies in acute attacks of haemorrhoidal disease: A multicentric randomized single-blind placebo-controlled trial. Indian Journal of Research in Homoeopathy 2013, 7:72-80.
Study design: Randomised controlled trial (registered in the Clinical Trials Registry – India: CTRI/2012/04/002541
Source of funds: not reported **Conflicts of interest:** not reported
Participants and setting **Setting:** six centres in India (Central Council for Research in Homoeopathy) **Inclusion criteria:** males and females between 25 and 60 years with internal haemorrhoids presenting with any of the symptoms (bleeding, pain (including discomfort and tenemus during defaecation or any other time), heaviness, pruritus and mucus discharge with or without anitis. Individuals with controlled diabetes (HbA1C < 8%) and controlled hypertension and thyroid disorders were also eligible, as were those using topical agents for haemorrhoids after a wash-out period of one week and subject to persistence and signs of haemorrhoids. **Exclusion criteria:** anal fissure, fistula in ano, inflammatory bowel disease, chronic alcoholism, recreational drug abuse, coagulation disorders, external haemorrhoids, previous history of surgery for haemorrhoids, hypertrophic anal papillae, haemoglobin < 7 g/dL, malignancies of the rectum, history of leukemia, obstruction

of the portal circulation, lactating mothers, psychiatric disorders, inability to comply with the study protocol.

Intervention

Homeopathy: individualised homeopathic medicine for 90 days: starting with 0/1 potency, followed by the next higher potency, serially, as needed. One globule (poppy seed size) of the desired potency was dissolved in 120 mL of distilled water containing 2.4 mL of (2% v/v) of dispensing alcohol, with 10 uniformly forceful downward strokes give against the bottom of the phial. The medicine was given six hourly in mild cases, four hourly in moderate cases, two hourly in severe cases and less than two hourly for very intense conditions. Each participant was advised to give 10 uniformly forceful downward strokes to the bottle and to take 15 mL (3 doses) and mix with 40 mL of water after stirring. If any change was triggered after administration (improvement/deterioration), change of remedy "followed homoeopathic principles".
19 medicines used: Phosphorus (30); Sulphur (25); Nux Vomica (22); Nitric acid (17); Lycopodium, clavatum (9); Arsenicum album (7); Pulsatilla pratensis (6); Ignatia (5); Aesculus hippocastanum (4); Carbo vegetabilis (2); Calcarea carbonica (2); Chamomilla (2); Fluoric acid (2); Natrum mriaticum (2); Aloes socotrina (1); Graphites (1); Kalium carbonicum (1); Lachesis (1); Mercurius solubilis (1).
Total number randomised: n=140, 140 analysed

Comparison

Control: placebo for 90 days, mode of dispensing was similar the intervention arm. If a participant worsened after 14 days of taking placebo, the investigator was instructed to give these participants *"rescue homoeopathic medicine due to ethical reasons."*
Total number randomised: n=139, 138 analysed

Outcomes: Primary: changes in haemorrhoidal symptoms – bleeding followed by pain, heaviness, discharge, itching. (Bleeding assessed on a scale of 0-3; 3 = severe [occurred > 5 times a week]; 2 = moderate [< 3-5 times a week; 1=mild [1 to < 3 times a week]; 0 = no bleeding at all. Pain, heaviness and discharge were measured on a VAS 0-10 where 0 = no symptoms and 10 corresponded to the worst possible symptoms.)
Anoscopic examination was done by consultant surgeons at baseline, 7^{th}, 14^{th}, 28^{th}, 60^{th} and 90^{th} day on a scale from 0-2: 0 = no signs of inflammation, 1 = a rather active grade, haemorrhoids without overt inflammatory findings (mild anitis), 2 = actively or easily bleeding haemorrhoids with overt signs of inflammation and oedema (anitis).
Secondary: changes in quality of life (WHOQOL-BREF) – 26 items divided into four domains (physical, psychological, social relationships and environmental (has been validated in the Indian population); assessed at baseline and at end of study (90 days).
Symptomatic assessments were done at baseline, day 0 (before treatment), 3^{rd}, 7^{th}, 14^{th}, 28^{th}, 60^{th} and 90^{th} day by the study investigator and the consultant surgeons at the respective centres.
Haemoglobin, packed cell volume, mean cell haemoglobin, mean cell haemoglobin concentration were done at baseline and every month.

Very brief summary of study authors' main findings/conclusions: homeopathy relieved acute haemorrhoidal symptoms early compared with placebo.

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	Computer-generated sequence of random numbers (23 sets of two unique numbers per set were generated using block design and the same set of random numbers was used in each centre).
Allocation concealment *(selection bias)*	☐	☐	☒	Not reported.
Blinding of participants and personnel	☐	☐	☒	Homeopathic medicine and placebo were identical, participants were

(performance bias)				blinded but investigators were not, due to the need to individualise the homeopathic treatment.
Blinding of outcome assessment *(detection bias)*	☐	☐	☒	Not reported.
Incomplete outcome data *(attrition bias)*	☒	☐	☐	Losses to follow-up were counted in the group to which they were originally allocated; Homeopathy group: 32/140 (23%) dropped out but were included in the analysis. Placebo group: 17/139 participants were given rescue treatment at day 14. *"if a patient entered early escape [for rescue] at day 14, the baseline values were carried forward to impute missing values"*; leaving 122, of whom 35 (29%) dropped out: 138/139 were analysed on an intention-to-treat basis; with 1 excluded due to a protocol variation (external haemorrhoids).
Selective outcome reporting? *(reporting bias)*	☒	☐	☐	Most expected outcomes reported. No other obvious risk of reporting bias.
Other bias	☒	☐	☐	No baseline imbalance apart from lower discharge score in the placebo group.
Notes				

	Outcome measures (dichotomous)	Total number of participants in study = 279 randomised, 278 analysed				
		<u>Intervention group</u> Total no. in group = 140		**<u>Control group</u>** Total no. in group = 138		
		Events	**Total**	**Events**	**Total**	**P value**
	Secondary					
	Bleeding clearance at 90 days (%)	136	140	53	138	NR *"much higher"*
	Pain clearance at 90 days (%)	105	140	19	138	NR
	Bleeding improvement at day 90	132	140	60	138	<0.0001
	Pain improvement at day 90	130	140	70	138	<0.0001
	Heaviness improvement at day 90	125	140	59	138	<0.0001
	Discharge improvement at day 90	70	140	35	138	<0.0001
	Itching improvement at day 90	115	140	66	138	<0.0001

		Total number of participants in study = 279 randomised, 278 analysed

	Outcome measures	Intervention group Total no. in group = 140			Control group Total no. in group = 138			
	Primary	**Median**	**95% CI**	**Total**	**Median**	**95% CI**	**Total**	**P value**
	Bleeding (AUC)	18.0	(15.4 to 26.0)	140	90.0	(56.5 to 146.9)	138	0.0001
	Pain (AUC)	105.0	(82.2 to 121.0)	140	342.7	(304.5 to 423.8)	138	0.0001
	Heaviness (AUC)	82.5	(69.0 to 103.0)	140	292.0	(272.0 to 343.4)	138	0.001
	Itching (AUC)	57.5	(41.9 to 69.0)	140	270.0	(216.0 to 332.9)	138	0.0001
	Discharge (AUC)	21.0	(10.4 to 37.1)	140	30.7	(10.4 to 37.1)	138	0.1386
	Secondary							
	Anitis (AUC)	21.0	(10.5 to 25.5)	140	90.0	(75.0 to 90.0)	138	0.0001
	WHOQOL-BREF							
	Physical domain	63.0	(63.0 to 69.0)	140	56.0	(56.0 to 56.0)	138	0.0001
	Psychological domain	56.0	(56.0 to 63.0)	140	50.0	(44.0 to 56.0)	138	0.0001
	Social domain	53.0	(50.0 to 56.0)	140	50.0	(44.0 to 55.9)	138	0.0803
	Environment domain	50.0	(50.0 to 56.0)	140	44.0	(38.0 to 50.0)	138	0.0005
	Bleeding clearance time (days)	14	*"IQR 53"*	140	90	*"IQR 76"*	138	0.0001
	Pain clearance time (days)	60	*"IQR 62"*	140	90	*"IQR 0"*	138	0.0001

Abbreviations: AUC: area under the curve; CI: confidence interval; dL: decilitres; mL: millilitres; n: number; NR: not reported; VAS: visual analogue scale; WHOQOL-BREF: World Health Organization Quality of Life-BREF

Homeopathy data extraction form: Chakraborty et al. 2013b

Reference: Chakraborty PS, Lamba CD, Nayak D, John MD, Sarkar DB, Poddar A et al. Effect of individualized homoeopathic treatment in influenza like illness: A multicentre, single blind, randomized placebo controlled study. Indian Journal of Research in Homoeopathy 2013, 7(1):22-30.

Study design: Randomised controlled trial.

Affiliation/source of funds: Central Council for Research in Homoeopathy.
Conflicts of interest: None declared.

Participants and setting

Setting: Nine Institutes and Units of Central Council for Research in Homoeopathy (CCRH) from June 2009 to December 2010.

Inclusion criteria: Patients of either sex, 12 to 60 years, presenting within 36 hours of onset of ILI characterized by abrupt onset of fever (≥100.4°F or 38°C body temperature) with at least one respiratory symptom (cough, sore throat, or nasal symptom) and at least one constitutional symptom (headache, malaise, myalgia, sweats, chills, or fatigue).

Exclusion criteria: Patients who had received any other medication (particularly anti‑viral) within the previous 36 hours of his/her presentation, immunization against influenza or ILI for that season, patients suffering from psychiatric, cardiac, pulmonary, renal diseases, hemoglobinopathies, immune compromised or any other clinically active illness, pregnant women, lactating mothers, patients with history of drug or alcohol abuse.

Intervention

Individualised homeopathy

The investigator had an in-depth interview with the patient/parent, and framed the totality of symptoms and made a symptom repertory manually/using software. Final selection of medicine was done in consultation with Materia Medica.

Intervention I: LM potency

Patients had treatment initiated with 0/1 potency, followed by next higher potency as per need. One globule (poppy seed size, comprising milk sugar lactose and the homeopathic medicine) of the desired potency was dissolved in 120 mL distilled water containing 2.4 mL alcohol pre-mixed, followed by 10 uniformly forceful downward strokes against the bottom of the phial (patients were told to repeat this before each taking each dose). 3 teaspoonsful (15 mL) of the solution were mixed with 8 teaspoonsful (40 mL) of water in a glass, and one teaspoonful (5 mL) constituted one dose (with remaining liquid discarded).

Intervention II: Centesimal potency

Patients had treatment initiated in 30C potency. Each dose of the indicated medicine in the Centesimal potency consisted of four homoeopathic globules (size no. 20) in a case of adults and two globules (size no. 20) in the case of children.

Repetition of doses for both LM and Centesimal scales

The indicated medicines were repeated every few minutes to hours depending upon the requirement of the patient. *"The most commonly indicated medicines were Arsenic album (n = 75), followed by Bryonia (n = 33) and Rhus toxicodendron (n = 32)".* 22 different medicines were indicated.

Daily follow-up and assessment was carried out for 9 days; subsequent follow-ups were done on 17th, 24th and 30th day of illness for any complications related to ILI.

Total number randomised: LM potency: n=152, Centesimal potency: n=147

Comparison

Control: Patients were given a placebo (globules impregnated with non‑succussed dispensing alcohol).

Total number randomised: n=148

Outcomes: Symptoms of ILI (assessed daily for 9 days): fever, headache, myalgia, malaise, sore throat, fatigue, nasal complaints, chill, sweat, cough (severity on VAS; 0 = no complaint; 10 = worse possible complaint); oral temperature; cough (cough score scale by Hsu et al. Eur Respir J 1994;7: 1246-53); complication/sequel related to ILI on follow up.

Very brief summary of study authors' main findings/conclusions: *"The study revealed the significant effect of individualized homoeopathic treatment in the patients suffering from ILI with no significant difference between LM and Centesimal groups. The complication/sequel rate was also significantly less in the intervention groups."*

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	A *"computer generated randomization chart"* was used.
Allocation concealment *(selection bias)*	☐	☐	☒	Not described.
Blinding of participants and personnel *(performance bias)*	☐	☐	☒	Placebo blinded, though described as *"single blind"* in the title (blinding of participants only); considered unclear as to whether blinding was successful as study personnel were aware of allocation.
Blinding of outcome assessment *(detection bias)*	☐	☒	☐	As above; no blinding of study personnel.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	Drop-outs or referrals because of persistent high fever:

				• LM group: 14/152 (9%) • Centesimal group: 10/147 (7%) • Placebo group: 24/148 (16%) Some indication of more referrals in the placebo group. Missing data of patients withdrawn due to non-reporting, referral and protocol deviations were replaced using the last-observation-carried-forward principle.
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	The day of significant improvement for each symptom was not reported for the placebo group in Table 3 or in Results text; and rather, was reported in the Discussion. Similarly the mean/IQR VAS scores for each symptom on the day of significant improvement were not reported for the placebo group. P values were not reported for the LM versus Centesimal comparisons; quote *"there was no statistically significant difference of treatment outcome between LM and Centesimal treatment groups."* For nasal complaints the data (day of significant improvement, and p value) do not seem to be correct (i.e. greater difference in Cestesimal vs. placebo comparison, though p value not significant). Day of significant improvement for placebo group for temperature/fever was not reported.
Other bias	☐	☐	☒	Groups were similar with respect to age, duration of illness, and symptom scores. Insufficient information to determine other risk of bias.
Notes	**Adjunct therapy:** In the homeopathy groups, paracetamol was given if the temperature of the patients continued to exceed 102°F after having been treated with the study medication; *"in a similar way as in the placebo group, where Paracetamol was given as and when required."* The authors note that past medical history was not clearly documented and that complications could have been exacerbations of past history or ILI.			

	Outcome measures (dichotomous)	Total number of participants in study = 447			
		<u>LM potency group</u> Total no. in group = 152	**<u>Centesimal potency group</u>** Total no. in group = 147	**<u>Control group</u>** Total no. in group = 148	

		Events	Total	Events	Total	Events	Total	P value
	Requirement for paracetamol	33	152	30	147	89	148	*"the medicinal group… required lesser number of Paracetamol tablets";* p value NR
	Complications (bronchitis, sinusitis, bronchial asthma, tracheobronchitis)	1	152	6	147	16	148	*"significantly less in the treatment group"*; p value NR

	Outcome measures (continuous)	Total number of participants in study = 447		
		LM potency group Total no. in group = 152	**Centesimal potency group** Total no. in group = 147	**Control group** Total no. in group = 148
		LM vs. placebo (day of significant improvement, p value)	Cestesimal vs. placebo – (day of significant improvement, p value)	
	Fever	2 vs. NR*, 0.023	2 vs. NR*, 0.020	
	Headache	1 vs. 6, 0.064	1 vs. 6, 0.002	
	Myalgia	1 vs. 5, 0.089	1 vs. 5, 0.047	
	Malaise	2 vs. 6, 0.006	2 vs. 6, 0.002	
	Sore throat	1 vs. 5, 0.008	2 vs. 5, 0.011	
	Fatigue	2 vs. 7, 0.049	3 vs. 7, 0.022	
	Nasal complaints	2 vs. 5, 0.047	1 vs. 5, 0.133	
	Chill	3 vs. 4, 0.029	1 vs. 4, 0.034	
	Sweat	1 vs. 3, 0.040	1 vs. 3, 0.015	
	Cough	3 vs. 5, 0.058	3 vs. 5, 0.063	

**"Temperature showed a significant difference from 2nd day onward in LM and Centesimal groups and temperature became normal by 5th day of treatment while it became normal on 7th day in the placebo group."*

Abbreviations: ILI: influenza-like illness; IQR: interquartile range; mL: millilitres; n: number; NR: not reported; VAS: visual analogue scale

Homeopathy data extraction form: Chand et al. 2014

Reference: Chand KS, Manchanda RK, Mittal R, Batra S, Banavaliker JN, De I. Homeopathic treatment in addition to standard care in multi drug resistant pulmonary tuberculosis: a randomized, double blind, placebo controlled clinical trial. Homeopathy 2014, 103:97-107.
Study design: Randomised controlled trial.
Source of funds: Not reported. **Conflicts of interest:** Authors reported that they had no conflicts of interest.
Participants and setting **Setting:** DOTS plus site at Gulabi Bagh Chest Clinic, New Delhi, India. **Inclusion criteria:** Patients of all age groups, diagnosed with chronic tuberculosis (MDR-TB on the basis of DST); culture positive (new) (n = 81) and culture negative (being treated with the standard regimen but still symptomatic) (n = 39) patients referred by the TB specialist to the homeopathic centre. Further assessment of eligibility was conducted by the homeopathic doctors.

Exclusion criteria: pregnant women and patients with concomitant disease such as HIV and malignancy

Intervention

Homeopathy: Homeopathy and SR

Preparation of homeopathy: identical batches from the 15 predefined homeopathic medicines in different potencies namely *Arsenicum album (Ars) 30 c*; *Bryonia alba (Bry) 30 c 200c*; *Calcarea carbonica (Calc) 30 c*; *Ipecacuanha (Ip) 30 c*; *Lycopodium clavatum (Lyc) 30 c*; *Natrum muriaticum (Nat-m) 30 c*; *Nux vomica (Nux-v) 30 c*;

Phosphorus (Phos) 30 c, 200 c; *Pulsatilla (Puls) 30 c*; *Sepia (Sep) 30 c, 200 c*; *Sulphur (Sulph) 30 c*; *Tuberculinum bovinum (Tub) 200 c*; were prepared in 30 size globules. Each batch consisted of 15 2 drachm (approx. 7 g) glass vials), each labelled with the name of the medicine. 30 drops of the respective medicine was added in each vial and all globules were fully saturated.

Selection of homeopathic medicine: every patient was examined by two experienced homeopathic doctors and further discussed with a senior consultant with 15 years homeopathic experience. Medicine was prescribed in one or two doses weekly, interspersed with un-medicated pills to be taken three times a day.

Medicine/potency was changed when no improvement was observed and it was dispensed from the same batch of medicines, assigned to the patient at the time of enrolment into the study, which was maintained throughout the study period. Duration of homeopathic medicine was 24 months and patients were followed up to 6-36 months after treatment.

Total number randomised: n=60

Comparison

Control: SR and placebo

Batches similar to the homeopathy vials were prepared with placebo (ethyl alcohol) and labelled.

Total number randomised: n=60

Standard regimen = six drugs (kanamycin, levofloxacin, ethionamide, pyrazinamide, ethambutol, cycloserine during 6-9 months of the intensive phase and four drugs – levofloxacin, ethionamide, ethambitol and cyclosterine during 18 months of the continuation phase.

Outcomes: sputum culture conversion, changes in chest X-ray, haemoglobin, erythrocyte sedimentation rate, weight gain, clinical improvement.

Patients were followed up every 15 days for clinical assessment in terms of absence (0) or presence (1) of eight common symptoms (cough, pain in chest, haemoptysis, expectoration, lassitude, anorexia, dyspnoea and fever) to calculate a symptom score.

Sputum smear and culture were assessed every three months; Hb and ESR were measured at baseline and at the end. Chest x-rays were evaluated at 6 month intervals and each was graded by a team of chest specialists and a senior clinical radiologist. A radiological assessment tool (RAT) was developed and validated by this team using a 3 point Likert scale +1 to -1) based on the change in infiltration, size of lesions, number and size of cavities, fibrosis, and compensatory emphysema. The total score ranged from +5 to -5.

RNTCP assessment criteria:

Cure – completed treatment, consistently culture negative (with at least 5 consecutive negative results in the last 12-15 months). If one follow-up culture positive is reported during the last three quarters, the patient will be considered cured provided it is followed by three consecutive negative cultures, taken at least 30 days apart, provided there is clinical evidence of improvement.

Treatment failure – if two or more of the five cultures recorded in the final 12-15 months are positive or if any of the three final are culture positive.

Defaulter – a patient whose treatment was interrupted for two or more consecutive months for any reasons. In this study patients who did not complete treatment for 24 months were considered as defaulters.

Time to culture conversion - duration from initiation of treatment to the date of the first two consecutive negative cultures, taken at least one month apart, irrespective of the subsequent results.

Culture negative patients were assessed for change in clinical symptoms and for recurrence rate (culture conversion from negative to positive).

Very brief summary of study authors' main findings/conclusions:

Add on homeopathy in addition to standard therapy appears to improve outcome in MDR-TB.				
Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	*"simple random tables."*
Allocation concealment *(selection bias)*	☐	☐	☒	*"batches of medicine/placebo were randomized and coded by the Project Director"; "at the time of enrollment each patient was assigned a batch number and the medicine was dispensed from the same batch by the pharmacist as per the prescription."* Not clear how the individualised homeopathic treatment was allocated in a concealed manner.
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	*"The treating physicians, pharmacist and the patient remained blinded throughout the study."*
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	As above.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	Homeopathy: 11/60 (18.3%) missing data (no two culture report (n = 6); not two x-rays (n = 5)); placebo: 11/60 (18.3%) missing data (no two culture report (n = 7); not two x-rays (n = 4)). Thus PP analysis had 49 in each group ITT: used LOCF method.
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	Primary and secondary outcomes not pre-specified.
Other bias	☒	☐	☐	There was some baseline imbalance between groups for culture status: homeopathy: 44/60 (73%) culture positive; placebo: 37/60 (62%) culture positive.
Notes				

	Outcome measures (dichotomous)	Total number of participants in study = 120				
		Intervention group Total no. in group =60		**Control group** Total no. in group = 60		
		Events	**Total**	**Events**	**Total**	**P value**
	Sputum conversion					
	Positive to negative (ITT)	27	60	28	60	0.862
	Positive to negative (PP)	25	49	26	49	0.826
	Culture conversion					
	Positive to negative (ITT)	29	60	23	60	0.269
	Positive to negative (PP)	27	49	21	49	0.225
	Chest x-ray improvement	37	60	20	60	0.002
	Chest x-ray deterioration	2	60	18	60	0.0001

	Compliance	38	60	37	60	NR
	Relapse after treatment completed	0	60	0	60	NA
	Culture positive subgroup of patients					
	Cure	23 (52.3)	44	18 (48.7)	37	0.737
	Treatment failure	3 (6.8)	44	6 (16.2)	37	0.187
	Default	18 (40.9)	44	13 (35.1)	37	0.603
	Smear					
	Improvement (positive to negative)	25 (56.8)	44	24 (64.9)	37	0.451
	Radiological changes					
	Chest x-ray improvement	31 (70.4)	44	15 (40.5)	37	0.006
	Chest x-ray static	12 (27.3)	44	10 (27.1)	37	0.972
	Chest x-ray deterioration	1 (2.3)	44	12 (32.4)	37	0.0001

	Outcome measures (continuous)	Total number of participants in study = 120						
		Intervention group Total no. in group = 60			**Control group** Total no. in group = 60			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Weight gain, kg (ITT)	2.4	4.9	60	0.8	4.4	60	0.071
	ESR reduction, mm (ITT)	-8.7	13.2	60	-3.9	15.4	60	0.068
	Haemoglobin increase, g% (ITT)	0.6	1.7	60	0.3	2.3	60	0.440
	Symptom score (ITT)	2.0	2.2	60	1.9	2.0	60	0.900
	Culture positive subgroup of patients							
	Weight gain, kg (ITT)	-3.2	5.0	44	-0.92	4.7	37	0.037
	ESR reduction, mm (ITT)	10.2	14.1	44	2.58	16.0	37	0.028
	Haemoglobin increase, g% (ITT)	0.9	1.8	44	-0.06	1.5	37	0.008
	Symptom score (ITT)	1.9	2.1	44	2.22	1.9	37	0.511

Abbreviations: DOTS: Directly Observed Treatment Strategy; DST: Drug Sensitivity Test; ESR: erythrocyte sedimentation rate; g: grams; Hb: haemoglobin; ITT: intention-to-treat; kg: kilograms; LOCF: Last-observation-carried-forward; mm: millimetres; MDR-TB: Multi-drug-resistant tuberculosis; n: number; NA: not applicable; NR: not reported PP: per protocol; RNTCP: Revised National Tuberculosis Control Programme; SR: standard regimen

Homeopathy data extraction form: Clark and Percivall 2000

Reference: Clark J, Percivall A. A preliminary investigation into the effectiveness of the homeopathic remedy, Ruta graveolens, in the treatment of pain in plantar fasciitis. British Journal of Podiatry 2000, 3(3):81-85.
Study design: Randomised controlled trial.
Source of funds: The Royal London Homeopathic Hospital NHS Trust provided the bottles of homeopathic remedy and placebo. **Conflicts of interest:** Not detailed.
Participants and setting **Setting:** Mainly the Northampton School of Podiatry Clinic. **Inclusion criteria:** Patients with plantar fasciitis aged 16 to 70 years. **Exclusion criteria:** Patients with biomechanical dysfunction, disease or medication that would mask the effects of the treatment; pregnant women; patients whose normal show heel height was greater than 2.5 cm were excluded.

Intervention

Homeopathy: Patients received a bottle containing 100 sugar tablets with two drops of 30C strength Ruta graveolens preparation, and were instructed to take 2 tablets, 3 times a day.

Total number randomised: n=9 (assumed, not stated) n=7 analysed

For all participants in both groups, a simple heel raise cut from 8.0 mm high-density EVA (for durability and effectiveness over a wide range of patient weights) and covered with 1.5 mm poron (for cushioning and shock absorption) was made for both feet, to prevent limb length discrepancy problems. They were made and fitted by a single investigator.

Comparison

Control: Patients received a bottle containing 100 sugar tablets (placebo).

Total number randomised: n=9 (assumed, not stated) n=7 analysed

Outcomes: Pain (as measured daily by patients for 124 days using a VAS (100 mm horizontal scale; with 0 = 'no pain')).

Very brief summary of study authors' main findings/conclusions: *"The rate of resolution of plantar fasciitis appeared to be faster and more complete by the end of the study in the active remedy group than in the placebo group."*

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☐	☒	Not detailed.
Allocation concealment *(selection bias)*	☐	☐	☒	Randomly numbered bottles were used; *"One bottle was given, in a random manner, to each patients as they presented for treatment."*
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	Trial described as *"double blind"* with an identical placebo used.
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	Participants, who were blinded with the use of a placebo, assessed pain on a VAS.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	Did not specify the numbers randomised to each group. 4/18 patients (22%) were excluded from the analysis: 1 was non-compliant (did not wear heel raises after day 2); 1 did not return to the clinic; 1 undertook occupational activities ('scooting on postal bicycle) that prevented the heel raise from acting; 1 was discovered to have ankle joint osteoarthritis.
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	Mean VAS for each of the 14 days was the only outcome reported (i.e. no information reported on adverse effects or other efficacy measures, although in the Discussion mention *"negligible side-effects"*).
Other bias	☐	☒	☐	Though baseline characteristics were recorded *"similar relevant data were*

				collected about each patient…" only BMI was reported, and individually (not by group) for the 14 patients analysed). In the Discussion, the authors note the inter-patient activity variation, before onset of the plantar fasciitis, and the variation in the amount of activity/rest during the study.
Notes				

	Outcome measures (continuous)	Total number of participants in study = 18 (14 analysed)						
		Intervention group Total no. in group = 7			**Control group** Total no. in group = 7			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Pain at day 1 (VAS value (mm))	46.42	11.05	7	63.31	12.14	7	NR
	Pain at day 2 (VAS value (mm))	48.92	17.61	7	53.06	18.77	7	NR
	Pain at day 3 (VAS value (mm))	31.33	18.36	7	50.50	24.18	7	NR
	Pain at day 4 (VAS value (mm))	26.42	18.52	7	48.94	24.45	7	*"The results show a significant ($p<0.05$) difference in the means by day 4"*; p value NR
	Pain at day 5 (VAS value (mm))	30.83	28.66	7	51.13	24.78	7	NR
	Pain at day 6 (VAS value (mm))	25.83	16.59	7	51.45	18.78	7	NR
	Pain at day 7 (VAS value (mm))	32.83	29.90	7	46.38	17.69	7	NR
	Pain at day 8 (VAS value (mm))	31.67	28.42	7	53.50	12.81	7	NR
	Pain at day 9 (VAS value (mm))	22.75	28.26	7	55.94	21.05	7	NR
	Pain at day 10 (VAS value (mm))	25.25	30.14	7	48.88	22.24	7	NR
	Pain at day 11 (VAS value (mm))	16.33	17.39	7	42.94	18.77	7	NR
	Pain at day 12 (VAS value (mm))	19.17	29.69	7	41.31	18.78	7	NR
	Pain at day 13 (VAS value (mm))	12.25	15.90	7	48.31	21.51	7	NR
	Pain at day 14 (VAS value (mm))	13.75	23.37	7	45.75	23.42	7	NR
	"linear regression analysis of the daily mean VAS values gives a gradient of -2.2999 (SE 0.3488) for the active remedy with 95% confidence intervals (CI) of -3.05997 to -1.53981 compared with a gradient of -0.8701 with 95% CI of -1.49849 to -0.24174 for the placebo. Thus the gradient for the active remedy is greater than that of the placebo (significant at the 95% Confidence Level) indicating a faster resolution of pain level over the same time period."							

Abbreviations: BMI: body mass index; CI: confidence interval; cm: centimetres; EVA: ethylene vinyl acetate; mm: millimetres; n: number; NR: not reported; SD: standard deviation; SE: standard error; VAS: Visual Analogue Scale

Homeopathy data extraction form: Colau et al. 2012

Reference: Colau JC, Vincent S, Marijnen P, Allaert FA. Efficacy of a non-hormonal treatment, BRN-01, on menopausal hot flashes: A multicenter, randomized, double-blind, placebo-controlled trial. Drugs in R and D 2012, 12(3):107-119.
Study design: Randomised controlled trial.
Affiliation/source of funds: *"Laboratoires Boiron provided BRN-01, its matching placebo, and financial support for the study… The authors thank Newmed Publishing Services for medical writing assistance, funded by Laboratoires Boiron."* **Conflicts of interest:** *"Stephane Vincent, PharmD, and Philippe Marijnen, MD, are employees of Laboratoires Boiron."*
Participants and setting **Setting:** 35 centres in France (private gynaecology practices) from June 2010 to July 2011. **Inclusion criteria:** Menopausal women ≥ 50 years of age, amenorrhoea > 12 months, menopause < 24 months, spontaneously complained of hot flashes starting < 2 years previously, ≥ 5 hot flashes a day causing significant negative life effect – socially or professionally, ≥ 40 mm on a visual analogue scale (VAS) ranging from 0 to 100 mm; able to understand, speak and write French, affiliated with a social security plan and gave informed written consent. **Exclusion criteria:** Receiving or had ever received HRT; if they were receiving or had received (within 2 weeks prior to enrolment) b-alanine (Abufene), food supplements (phytoestrogens, etc.), vitamin E, or courses of acupuncture aimed at relieving hot flashes; or if they were receiving or had received (within 1 week prior to enrolment) other homeopathic treatments aimed at relieving hot flashes; menopause induced artificially by surgery, chemotherapy, or radiotherapy; hot flashes that could be iatrogenic in origin or could be caused by an associated pathology; receiving treatments that could reduce the frequency of hot flashes, such as antihypertensive treatment with clonidine, antidepressant treatment with SNRIs (venlafaxine), SSRIs (citalopram, paroxetine), mirtazapine (a noradrenergic and specific serotonergic antidepressant), or antiepileptic treatment with gabapentin; and a risk of not complying with the protocol.
Intervention **Homeopathy:** BRN-01 tablets (registered homeopathic medicine): Actaea racemosa (4 centesimal dilutions [4CH]), Arnica montana (4CH), Glonoinum (4CH), Lachesis mutus (5CH), and Sanguinaria canadensis (4CH); (Actheane). Oral treatment (2 to 4 tablets per day) was started on day 3 after study enrolment and was continued for 12 weeks. Women were able to take up to 4 tablets a day if required (for severity of vasomotor symptoms). **Total number randomised: n=54, n=50 analysed**
Comparison **Control:** Identical placebo tablets (containing saccharose, lactose, magnesium stearate and purified water). **Total number randomised: n=54, n=51 analysed**
Outcomes: Main outcome measure: hot flash score (HFS) (1 = mild; 4 = very strong). Secondary outcomes: quality of life (Hot Flash Related Daily Interference Scale (HFRDIS)); severity of symptoms (Menopause Rating Scale); effect of hot flashes on professional and personal life (VAS 0-100 mm); evolution of mean dosage; compliance (Morisky-Green score: 0=high attendance; 3-4= low adherence or non-adherence); adverse effects.
Very brief summary of study authors' main findings/conclusions: *"BRN-01 seemed to have a significant effect on the HFS, compared with placebo. According to the results of this clinical trial, BRN-01 may be considered a new therapeutic option with a safe profile for hot flashes in menopausal women who do not want or are not able to take hormone replacement therapy or other recognized treatments for this indication."*

Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	Computer generated randomisation lists were provided to each hospital.
Allocation concealment *(selection bias)*	☒	☐	☐	Central randomisation.
Blinding of participants and personnel *(performance bias)*	☐	☐	☒	Placebo controlled trial; however it is unclear whether blinding was successful, with lower compliance in the placebo group.
Blinding of outcome assessment *(detection bias)*	☐	☐	☒	As above (subjective outcomes assessed by participants).
Incomplete outcome data *(attrition bias)*	☒	☐	☐	Intention-to-treat analysis included all patients who took at least one dose of the study treatment and had a least one post-enrolment evaluation: 108 (54/54) randomised; 4 excluded from BRN-01 group due to not starting treatment; 3 excluded from placebo due to not starting treatment. Last-observation-carried-forward method used for missing data.
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	For two outcomes (reduction in distress in patients' professional and/or personal life; number of night sweats between week 1 and 12) it was reported that *"A similar reduction was also found (data not shown)."*
Other bias	☒	☐	☐	No difference in baseline demographic characteristics or in baseline vasomotor symptoms. No other obvious sources of bias identified.
Notes				

	Outcome measures (dichotomous)	Total number of participants in study = 108				
		Intervention group Total no. in group = 54		**Control group** Total no. in group = 54		
		Events	**Total**	**Events**	**Total**	**P value**
	Secondary					
	Morisky-Green scores for compliance	*	50	*	51	0.0113
	Adverse events (including severe adverse events**): BRN-01 group: diverticular intestinal abscess**; sensation of thirst at night; removal of cyst under left foot**; pruritus; migraine Placebo group: gastritis; headaches;	5	50	4	51	0.7409

	wrist fracture**; recurrence of hot flashes					

*Compliance (very satisfactory, not very satisfactory, not satisfactory, poor) reported as percentage of women in each group in Figure 6 in manuscript

**Denotes serious adverse effects

	Outcome measures (continuous)	Total number of participants in study = 108						
		Intervention group Total no. in group = 54			**Control group** Total no. in group = 54			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Primary							
	Global HFS over 12 weeks of treatment (using AUC)	82.3	49.4	50	113.0	88.2	51	0.0338
	Adjusted global HFS over 12 weeks of treatment (using AUC)	88.2	6.5	50	107.2	6.4	51	0.0411
	Clinically relevant decrease of 3 points in HFS (weeks)	3.2	1.5	50	3.6	2.5	51	0.3632
	Secondary							
	HFRDIS score for QoL at 12 weeks	2.3	1.9	50	2.8	2.4	51	0.2430
	Reduction in HFRDIS score for QoL at week 12	2.3	2.3	50	2.0	2.7	51	0.5121
	Reduction in MRS score at week 12	5.1	5.9	50	7.8	9.5	51	0.1774
	Reduction in distress in patients' professional and/or personal life	*"A similar reduction was also found (data not shown)."*						
	Number of night sweats between week 1 and 12 (using a VAS)	*"A similar reduction was also found (data not shown)."*						
	Number of unused tablets returned by patients	167.0	98.2	50	185.5	98.4	51	0.3733

Abbreviations: AUC: area under the curve; HFRDIS: Hot Flash Related Daily Interference Scale; HFS: hot flash score; mm: millimetres; MRS: Menopause Rating Scale; n: number; QoL: quality of life; SD: standard deviation; SNRIs: serotonin–norepinephrine reuptake inhibitors; SSRIs: selective serotonin re-uptake inhibitors; VAS: visual analogue scale

Homeopathy data extraction form: Dean et al. 2012

Reference: Dean ME, Karsandas R, Bland JM, Gooch D, MacPherson H. Homeopathy for mental fatigue: lessons from a randomized, triple blind, placebo-controlled cross-over clinical trial. BMC Complementary and Alternative Medicine 2012;12:167.
Study design: Randomised controlled trial.
Source of funds: Kali Phos 6x and placebo were supplied by Helios Pharmacy; M. Dean was funded by a post-doctoral award from the National Institute for Health Research. **Conflicts of interest:** authors declared no competing interests.
Participants and setting **Setting:** students and staff from University of York, York, UK. **Inclusion criteria:** healthy adults self-reporting difficulties in sustaining attention or experiencing mental fatigue; able to communicate in English and consent to avoiding the use of self-prescribed stimulants, such as caffeine and energy drinks, on the day of each test.

Exclusion criteria: current use of a homeopathic preparation for any condition, current use of prescribed stimulant medication such as those used for attention deficit/hyperactivity disorder and people diagnosed with chronic fatigue syndrome or myalgic encephalomyelitis.

Intervention

Homeopathy: Kali phos 6x (Kalium phosphoricum), homeopathic potassium phosphate (dilution equivalent to one part in 1,000,000, potentised by serial agitation) in 90% ethanol/water solution**.**

Total number randomised: n=86 (crossover)

Comparison

Control: placebo (single dose of 0.6 g lactose powder treated with unmedicated 90% ethanol/water solution).

Total number randomised: n=86 (crossover)

All participants

In both periods the participants completed the 4-question mental fatigue sub-scale of the Chalder Fatigue questionnaire, giving an integer score between 0 and 4. They subsequently took a single dose of one of the randomly allocated preparations. They then performed the test, 10 minutes after taking either the homeopathic preparation or the placebo and each participant repeated this at the same time of day, seven days later (wash-out period), those who received Khali phos in period 1 receiving the placebo and vice versa.

Outcomes: Primary: Stroop Colour-Word test (conflict resolution test task) – maximum accuracy score of 108 Mental fatigue scores (Chalder).

Very brief summary of study authors' main findings/conclusions:

Kali phos 6x was not found to be effective in reducing mental fatigue.

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	Clinstat software used to allocate 86 participants into equal groups in block of random sizes 4, 6, 8 or 10.
Allocation concealment *(selection bias)*	☒	☐	☐	Pharmacy coded batches of A and B *"so nobody at the trial centre was aware which powder was placebo and which Kali phos."*
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	Quote: *"no noticeable difference in taste or appearance"* between the homeopathic and placebo preparations; identity of powders was not revealed by the pharmacy until after completion of the analysis; described as *"triple-blinded."*
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	As above.
Incomplete outcome data *(attrition bias)*	☒	☐	☐	Two participants in group B (Kali phos first and placebo second).
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	Only two outcomes were reported.
Other bias	☒	☐	☐	No apparent baseline differences.
Notes	The Stroop Colour-Word test and limitations in how it was able to be administered mean that the test was not sufficiently challenging and therefore not sufficiently sensitive, giving a 'ceiling effect'.			

		Total number of participants in study = 86

	Outcome measures (continuous)	Intervention group Total no. in group = 86 (crossover)	Control group Total no. in group = 86 (crossover)	P value
	Primary			
	Stroop Colour-Word test (conflict resolution test task) (treatment effect, 95% CI)	Khali phos minus placebo -1.1, -3.0 to 0.9		0.3
	Mental fatigue score (Chalder) (treatment effect, 95% CI)	Khali phos minus placebo -1.2, -3.1 to 0.8		0.2

Abbreviations: CI: confidence interval; n: number

Homeopathy data extraction form: Derasse et al. 2005

Reference: Derasse M, Klein P, Weiser M. The effects of a complex homeopathic medicine compared with acetaminophen in the symptomatic treatment of acute febrile infections in children: an observational study. Explore: The Journal of Science and Healing 2005, 1(1):33-39.
Study design: Non-randomised prospective cohort study (using propensity score adjustment; and specifying a 10% noninferiority margin).
Source of funds: Biologische Heilmittel Heel GmbH. **Conflicts of interest:** Third author employed by Biologische Heilmittel Heel GmbH.
Participants and setting **Setting:** 38 Belgian centres practising homeopathy and conventional medicine. **Inclusion criteria:** children < 12 years with acute infections accompanied by fevers. **Exclusion criteria:** children older than 12 years, without symptoms at the time of treatment.
Intervention **Homeopathy:** viburcol (drops) for 2 weeks maximum (1 vial; 3 x 5 drops) daily for children under 1; 1 to 2 vials daily for children up to 5 years; 2 vials daily for older children. Choice of treatment for each individual patient was left to the practitioner's discretion: Per vial: Camomilla (chamomile) D4 (25.0 mg); Belladonna (deadly nightshade) D6 (11.0 mg); Dulcamara (woody nightshade D6 (25.0 mg); Plantago major (rat-tail plantain D4 (25.0 mg); Pulsatilla pratensis (pasque flower) D6 (50.0 mg); calcium carbonate D8 (75.0 mg). **Total number: n=107**
Comparison **Control:** acetaminophen (pills, capsules, or liquid form) for 2 weeks maximum. **Total number: n=91**
Both groups: additional drugs were allowed in both groups and were given to 52.3% of viburcol patients and 65.9% of acetaminophen patients (e.g. Euphorbium, menthol, cough syrups, Oteel, penicillin).
Outcomes: fever, cramps, distress, disturbed sleep, crying and difficulties with eating or drinking; Symptom scale (0-3): 0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms Severity of infection: 5 point scale (0-4) Body temperature (baseline and final visit) Heath status, subjective (as rated by carers): 1 = well; 2 = moderately well; 3 = unwell; 4 = very unwell Time to first improvement of symptoms Global evaluation of treatment effect (carer and practitioner together): excellent (= complete regression of symptoms); good; moderate; none; worsening of symptoms Tolerability: 4 point scale: excellent (= complete regression of symptoms); good; moderate; poor Compliance (rated as carer's compliance) was evaluated on a similar 4-point scale Adverse events

Very brief summary of <u>study authors'</u> main findings/conclusions: Viburcol was an effective alternative to acetaminophen treatment and significantly better tolerated.				
Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☒	☐	No randomisation. The choice of treatment was left to the practitioner's discretion.
Allocation concealment *(selection bias)*	☐	☒	☐	As above.
Blinding of participants and personnel *(performance bias)*	☐	☒	☐	No blinding of participants or study personnel.
Blinding of outcome assessment *(detection bias)*	☐	☒	☐	No blinding of outcomes assessment.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	26 (24.3% of Viburcol patients and 17 (18.7%) acetaminophen patients discontinued treatment before the end of the study *"for reasons of symptom disappearance."*
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	Some results only reported as graphs, not actual data; actual p values not always reported.
Other bias	☐	☐	☒	Unbalanced group numbers.
Notes (Newcastle-Ottawa Scale considerations)	Selection: treatment (exposed) and control (non-exposed) groups enrolled from the same community/population (however treatment selected by the treating practitioner). Comparability: some differences in baseline characteristics (i.e. adjunctive treatment; degree of fever); the authors applied a propensity score adjustment to reduce the risk of bias associated with these potential confounders. Outcome: Non-blinding outcome assessment; proportion of subjects lost to follow up likely to introduce bias.			

	Outcome measures (dichotomous)	Total number of participants in study = 198				
		<u>Intervention group</u> Total no. in group =107		**<u>Control group</u>** Total no. in group =91		
		Events	**Total**	**Events**	**Total**	**P value**
	Treatment rated as excellent	74 (69.2%)	107	52 (57.1%)	91	0.008
	Global evaluation of moderate or lower	3 (2.8%)	107	11 (12.1%)	91	NR
	Tolerability rated as excellent (all patients in both groups rated tolerability as excellent or good)	100 (93.3%)	107	73 (80.4%)	91	0.004
	Compliance rated as excellent	72 (67.3%)	107	55 (60.4%)	91	NR
	Time to symptomatic improvement (24 hours)	42 (39.2%)	107	35 (38.5%)	91	0.55
	Time to symptomatic improvement (48	86 (80.3%)	107	69 (75.9%)	91	

	hours)					
	Time to symptomatic improvement (72 hours)	101 (94.3%)	107	84 (92.4%)	91	
	Adverse events	None reported				

	Outcome measures (continuous)	Total number of participants in study = 198						
		Intervention group Total no. in group = 107			**Control group** Total no. in group = 91			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Temperature (°C) (change from baseline)	-1.7	0.7	107	-1.9	0.9	91	NR
	Fever score (final)	0.1	0.2	107	0.2	0.5	91	NR
	Severity of infection (final)	0.0	0.2	107	0.2	0.6	91	NR
	Fever, cramps, distress, crying, temperature, disturbed sleep, total score eating/drinking difficulties, overall severity of infection	NR (for the non-inferiority analysis: *"The confidence intervals for all scores were well within the predefined boundary"*)						

Abbreviations: mg: milligrams; n: number; NR: not reported; ns: not significant; SD: standard deviation

Homeopathy data extraction form: Ernst et al. 1990

Reference: Ernst E, Saradeth T, Resch KL. Complementary treatment of varicose veins. Phebology 1990, 5:157-163.
Study design: Randomised controlled trial.
Source of funds: not reported. **Conflicts of interest:** none reported.
Participants and setting **Setting:** rehabilitation clinic, Vienna, Austria. **Inclusion criteria:** clinical diagnosis of primary varicose veins by the same investigator using established clinical tests, other physical signs, present symptoms and past history. Light reflection rheography was used to confirm the clinical diagnosis. **Exclusion criteria:** post-traumatic or post-thrombotic chronic venous insufficiency, lymphoedema hereditary vascular abnormalities, venous compression syndromes, congestive heart disease, liver and kidney disorders, malignancy, inflammatory disease, haematological abnormalities and peripheral arterial occlusive disease.
Intervention **Homeopathy:** Poikiven 20 drops t.i.d (100 mL contains Meliotus office D1 20 mL; Aesculus D1 20 mL, Hamamelis D1 20 mL, Carduus marianus D1 10 mL, Arnica ϕ 5 mL; Lycopodium D4 10 mL, Lachesis D4 10mL; Rutin D1 5 mL) for 24 days. **Total number randomised: n=31 (62 legs)**
Comparison **Control:** placebo (no further description reported). **Total number randomised: n=30 (60 legs)**
All patients: no compression stockings were prescribed during the trial; patients already wearing such stockings continued to do so.
Outcomes: assessed before first dose, after 12 days, on day 24**.** Venous filling time (by light reflex rheography);

leg volumes; haematocrit, plasma viscosity at 37C, blood viscosity; subjective improvement (patient-reported complaints on a scale between 1-82 (calf cramps, itching in legs, heaviness of legs, pain during prolonged standing, need to rest legs in elevated position) at baseline and day 24.
Very brief summary of <u>study authors'</u> main findings/conclusions: Oral treatment of primary varicose veins using Poikiven is feasible and effective.
Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☐	☒	Not reported.
Allocation concealment *(selection bias)*	☐	☐	☒	Not reported.
Blinding of participants and personnel *(performance bias)*	☐	☐	☒	Not reported.
Blinding of outcome assessment *(detection bias)*	☐	☐	☒	Not reported.
Incomplete outcome data *(attrition bias)*	☒	☐	☐	No losses to follow-up reported.
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	Primary and secondary outcomes not pre-specified; outcomes and p values not fully reported.
Other bias	☐	☒	☐	Baseline venous filling time was significantly longer in the placebo group compared with the Poikiven group. Poikiven patients were less likely than placebo patients to have hypertension and to be obese; more Poikiven patients than placebo patients had concomitant ginkgo biloba and fibrates, and fewer nitrates. No indication that results were adjusted for lack of independence (analysed by legs not by individual).
Notes				

	Outcome measures (dichotomous)	Total number of participants in study = 61				
		<u>Intervention group</u> Total no. in group = 31		**<u>Control group</u>** Total no. in group = 30		
		Events	**Total**	**Events**	**Total**	**P value**
Subjective symptoms (patient-reported)						
	Amelioration of cramps	22	31	13	30	< 0.05
	Itching	21	31	13	30	0.02
	Leg heaviness	26	31	20	30	0.003
	Pain on prolonged standing	26	31	20	30	0.003
	Reduced need for leg elevation	25	31	15	30	0.02

		Total number of participants in study = 61

	Outcome measures (continuous)	Intervention group Total no. in group = 62 legs			Control group Total no. in group = 60 legs			
		Mean	**SEM**	**Total**	**Mean**	**SEM**	**Total**	**P value** (intergroup diffs)
	Venous filling time (day 12), seconds	29.2	2.5	62	28.7	2.5	60	*"n.s."*
	Venous filling time (day 24), seconds	34.4	3.0	62	26.1	2.2	60	< 0.05
	Leg volume (day 12), mL	3085	44.0	62	3104	48.7	60	*"n.s."*
	Leg volume (day 24), mL	3113.2	48.0	62	3104.1	47.6	60	*"n.s."*
	Calf circumference (day 12), cm	36.5	0.3	62	36.9	0.4	60	*"n.s."*
	Calf circumference (day 24), cm	36.6	0.3	62	36.6	0.4	60	*"n.s."*
	Haematocrit	*"There were no intra-group changes or inter-group differences in haematocrit."*						NR
	Plasma viscosity	*"There are no inter-group differences in this variable at any point"*						NR
	Blood viscosity at 45% haematocrit	*"The same applies for blood viscosity"* (as above)						NR

Abbreviations: cm: centimetres; mL: millilitres; n: number; NR: not reported; *"n.s."*: not significant; SEM: standard error of the mean; t.i.d: three times daily

Homeopathy data extraction form: Friese and Zabalotnyi 2007

Reference: Friese KH, Zabalotnyi DI. Homoopathie bei akuter rhinosinusitis: Eine doppelblinde, placebokontrollierte studie belegt die wirksamkeit und vertraglichkeit eines homoopathischen kombinationsarzneimittels [Homeopathy in acute rhinosinusitis: a double-blind, placebo controlled study shows the efficiency and tolerability of a homeopathic combination remedy]. HNO 2007, 55(4):271-277.

Study design: Randomised controlled trial.

Affiliation/source of funds: Not stated in the translation.
Conflicts of interest: None declared.

Participants and setting

Setting: Kiev, Ukraine (10 centres); April 2001 to May 2002.
Inclusion criteria: Patients aged 18 to 65 with chronic sinusitis (confirmed with a PA x-ray – thickening of upper lateral rim of the maxillary sinous mucous membrane of at least 5 mm, or shading of the sinus, or presence of a fluid level); all patients underwent rhinoscopy; sum of scores for 5 sinusitis symptoms (0 [no symptoms] to 4 [severe symptoms]) had to be between 8 and 20 points.
Exclusion criteria: Patients with high grade septal deviations, polyps, dental aetiology, prior sinus surgery or more than 2 sinusitis episodes in the 12 months before the start of the study, other use of antibiotics, homoeopathic or herbal medications during the four weeks before the study, severe somatic disease, medication or alcohol abuse.

Intervention

Homeopathy: Homoeopathic complex (Cinnabaris (red mercury sulphide) Pentarkan H: Cinnabaris 3X, Echinacea 1X, Hydrastis 3X (Canadian golden root), Kali bichromicum 3X. Medication was taken hourly until improvement began, up to 12 tablets a day; followed by 2 tablets 3 times a day as maintenance. Patients were examined after 7, 14 and 21 days.
Supportive treatment: saltwater nasal rinsing 3 times daily, and if temperature was >38.5°C during the first week, 500 mg paracetamol was allowed.
Total number randomised: n=72

<u>Comparison</u> **Control:** Placebo – not further described in the translation. **Total number randomised: n=72**				
Outcomes: Main end-point: reduction of total symptom score after 7 days of treatment. Secondary outcomes: change in single symptoms (headache, pressure pain in maxillary sinus, obstruction to breathing through the nose, anterior and posterior nasal secretion); assessment by doctors and patients ranging from 'symptom free' to 'worsening'; time until improvement began; frequency of application of supportive measures; assessment of compliance and satisfaction with treatment; side effects; complications; inflammatory markers.				
Very brief summary of <u>study authors'</u> main findings/conclusions: *"a homeopathic combination medicine is an effective and risk-free treatment for acute rhinosinusitis."*				
Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☐	☒	Trial described as 'randomised' – no further described in the translation.
Allocation concealment *(selection bias)*	☐	☐	☒	As above.
Blinding of participants and personnel *(performance bias)*	☐	☐	☒	Quote: *"double-blind placebo-controlled"* – not further described in the translation (and see below re: high rate of drop out in placebo group).
Blinding of outcome assessment *(detection bias)*	☐	☐	☒	As above. No further detail provided on blind outcome assessment.
Incomplete outcome data *(attrition bias)*	☐	☒	☐	1/72 lost to follow-up in homeopathy group; 63/72 in the placebo group dropped out (54 after 7 days and a further 9 after 14 days). Data from patients who finished the study early were handled using the last-observation-carried-forward method.
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	Insufficient information to determine risk of reporting bias. Results of tests of significance not reported for most outcomes. Data on inflammatory markers not clearly reported.
Other bias	☐	☐	☒	Baseline characteristics described as similar in the translation (*"no significant differences").* Insufficient methodological detail to determine risk of other bias.
Notes	Information translated from German by Dr R Lorenz			

	Outcome measures (dichotomous)	Total number of participants in study = 144				
		<u>Intervention group</u> Total no. in group = 72		**<u>Control group</u>** Total no. in group = 72		
		Events	**Total**	**Events**	**Total**	**P value**
	Secondary					
	Headache improvement at 7 days	71	72	24	72	NR

	Maxillary sinus pressure pain improvement at 7 days	66	72	15	72	NR
	Nasal obstruction improvement at 7 days	60	72	15	72	NR
	Nasal secretion improvement at 7 days	50	72	11	72	NR
	'Post nasal' secretion improvement at 7 days	67	72	10	72	NR
	Improvement within first 7 days	59	72	6	72	NR
	Complete recovery at 7 days	65	72	2	72	NR
	No improvement at 7 days	1	72	51	72	NR
	Worsening of symptoms	0	72	13	72	NR
	Compliance	*"According to the medical records, compliance during study participation in both groups was over 95%"*				
	Use of supportive measures up to day 7	51	72	55	72	NR
	Use of paracetamol	33	72	34	72	NR
	Tolerability (very good or good)	72	72	51	72	NR
	Side effects (coughing for two weeks)	0	72	1	72	NR
	Satisfaction (very satisfied or satisfied)	67	72	8	72	NR

	Outcome measures (continuous)	Total number of participants in study = 144						
		Intervention group Total no. in group = 72			**Control group** Total no. in group = 72			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Primary							
	Sum of symptom scores after 7 days	5.9	2.0	72	11.0	2.9	72	<0.0001
	Sum of symptom scores after 21 days*	0.3	1.4	72	10.6	4.1	72	NR
	Secondary							
	Average duration of participation in study	19.5	3.5	72	8.5	5.1	72	NR
	Inflammatory markers: ESR at 7 days (mm/h)	*"Elevation of the ESR over the 7 days occurred in 2 of the Hg patients as compared with 7 patients of the Pg."*						
	Inflammatory markers: leukocyte counts (/nL)	Not clearly reported						

*Result not considered valid due to use of last-observational-carried-forward method

Abbreviations: ESR: erythrocyte sedimentation rate; h: hour; Hg: homeopathy group; PA: posterior to anterior; Pg: placebo group; mg: milligrams; mm: millimetres; n: number; nL: nanolitre; NR: not reported

González de Vega et al. 2013

Reference: González de Vega C, Speed C, Wolfarth B, González J. Traumeel vs. diclofenac for reducing pain and improving ankle mobility after acute ankle sprain: A multicentre, randomised, blinded, controlled and non-inferiority trial. International Journal of Clinical Practice 2013, 67:979-989.
Study design: Randomised controlled trial.
Affiliation/source of funds: Biologische Hellmittel Heel GmbH, from August 2009 to September 2011.

Conflicts of interest: Three authors are board members for Traumeel for Biologische Hellmittel Heel GmbH, authors have received consultancy fees from Biologische Hellmittel Heel GmbH and Johnson and Johnson; authors have received speaker's fees and other funding from Biologische Hellmittel Heel GmbH, Astra Zeneca, Berlin Chemie, Bristol-Myers Squibb.

Participants and setting

Setting: 15 outpatient centres in Spain.

Inclusion criteria: Physically active adults, aged 18 to 40 years, with acute unilateral ankle sprain of the lateral ligaments in the past 24 hours; with moderate (100 point VAS score 30-60 mm) to severe (> 60 mm) pain on weight bearing and be unable to perform their usual training/sports activities. Grade of ankle sprain was evaluated at baseline by physician's assessment and x-ray to eliminate fracture and on day 7 by using a stress test (pronation stress of the ankle with predefined power).

Exclusion criteria: Sustained a similar injury of the same joint within the last 6 months, bilateral ankle injury, complete rupture of the ankle ligaments in need of surgical intervention (i.e. grade 3 ankle sprain), confirmed fracture or injury concurrent with knee injury, or required bed rest, hospitalisation, casting or surgery. Also excluded if clinically important laboratory text abnormalities or debilitating acute/chronic illness, or had used corticosteroids in previous 8 weeks**;** long-acting NSAIDS, COX-inhibitors or tramadol in the previous 24 h; any other analgesics in the previous 6 hours; or were abusing medical substances or alcohol.

Intervention

Homeopathy: 2 g Traumeel ointment (T-O) or gel (T-G) for ankle sprain (Traumeel is a fixed homeopathic combination of plant and mineral extracts) administered topically to the ankle three times a day for 14 days, with 6-weeks follow up.

Total number randomised: n=302 (152 ointment; 150 gel)

Comparison

Control: 2 g diclofenac gel (D-G) (NSAID) administered topically to the ankle three times a day for 14 days, with 6-weeks follow up.

Total number randomised: n=147

Outcomes: Primary outcomes: percentage change from baseline to day 7 for participants' assessment of ankle pain (100 mm VAS, 0 = no pain; 100 = worst imaginable pain); change from baseline to day 7 of the Foot and Ankle Ability Measure (FAAM) Activity of Daily Living subscale (ADL) (0 = worst level of physical function; 100 = highest level of physical function). Secondary outcomes (days 4, 7, 14, 42): percentage change from baseline of ankle pain (100 mm VAS); change from baseline of the FAAM sports subscale; swelling; normal function/activity (5-point scale, 0 = normal; 4 = severely restricted because of pain); time to normal function; global assessment of treatment efficacy (5-point scale; 1 = very good; 5 = worsening of symptoms) on day 14; rescue medication use; adverse events.

Very brief summary of study authors' main findings/conclusions: *"T-O and T-G decreased pain and improved joint function to the same extent as D-G in acute ankle sprain, and were well tolerated."*

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	Computerised randomisation achieved centrally, with randomisation schedule degenerated by *"IDV Data Analysis & Study Planning"* (kits supplied to investigators to be used on the basis of the order of the kit receipt).
Allocation concealment *(selection bias)*	☒	☐	☐	Central allocation.
Blinding of participants and personnel	☐	☐	☒	Blinded for Traumeel gel and diclofenac gel, but not for Traumeel

(performance bias)				ointment.
Blinding of outcome assessment *(detection bias)*	☐	☐	☒	As above.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	T-O: ITT 143/152; PP 126/152; completed 121/152. T-G: ITT 140/148; PP 127/148; completed 124/148. D-G: ITT 137/147; PP 132/147; completed 127/147. Reasons reported in flow diagram; missing data handled by last-observation-carried-forward method. Some suggestion of higher rate of exclusion in T-O group from PP population, particularly due to non-compliance.
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	For primary outcomes, and FAAM ADL subscale scores and pain (VAS) scores over time, p-values are presented; for secondary outcomes, results of test of significance not reported (and figures not presented in results). Group medians/means are reported for secondary outcomes, with no measures of variance (i.e. interquartile ranges, or standard deviations).
Other bias	☐	☐	☒	No evident baseline differences apart from more smokers in the Traumeel ointment group.
Notes	Reported pre-specified non-inferiority margins (e.g. 0.4 for pain VAS); two stage trial (stage 2 commenced after knowledge of results of stage 1; results not reported separately per stage). The authors note that the *"study did not include a placebo-control arm, which may have had some relevance to the assessment of an injury that usually resolved without treatment."*			

	Outcome measures (dichotomous)	Total number of participants in study = 449						
		T-O Group Total no. in group = 152		**T-G Group** Total no. in group = 150		**D-G Group** Total no. in group = 147		
		Events	**Total**			**Events**	**Total**	**P value**
	Secondary							
	Compliance below 80% (non-compliance)	12	143	5	140	5	137	0.1139
	Concomitant medications (analgesics, antipyretics for headache, infection, pain) for participants with adverse effects	3	9	5	14	3	8	*"No significant difference"*; p value NR
	Total pain relief at day 7	12	143	7	140	8	137	*"T-O and T-*

								G were non-inferior to D-G on all secondary outcome variables"; p value NR
	Normal function/activity (patients reporting scores of 0 or 1) at day 14	128	143	133	140	131	137	As above.
	Global assessment of treatment efficacy on day 14 (reporting 'very good' or 'good')	131	143	128	140	127	137	As above.
	Rescue medication (paracetamol) in treatment and follow-up period	28	143	29	140	20	137	*"No significant difference"*; p value NR
	Adverse events	9	152	14	148	8	147	0.3310
	Adverse events 'possibly' or 'probably' related to treatment	5 pain, joint injury, joint sprain, hypoaesthesia, erythema, pruritus)	152	3 (joint sprain, dry skin, pruritus)	148	3 (swelling, pruritus)	147	As above.

	Outcome measures (continuous)	Total number of participants in study = 449						
		T-O Group Total no. in group = 152		**T-G Group** Total no. in group = 150		**D-G Group** Total no. in group = 147		
		Median	**Total**	**Median**	**Total**	**Median**	**Total**	**P value**
	Primary							
	Median percentage reductions in pain VAS scores (100 mm) on day 7 (%)	60.6	143	71.1	140	68.9	137	T-O vs. D-G: 0.8205 T-G vs. D-G: 0.3422
		"At all visits in the main treatment period, the confidence intervals were above the predefined lower equivalence margin (0.40), demonstrating non-inferiority of T-O and T-G vs. D-G for the treatment of pain and for the improvement of ankle function."						
	Median improvement in FAAM ADL subscale score on day 7 (points)	26.2	143	26.2	140	25.0	137	T-O vs. D-G: 0.3155 T-G vs. D-G: 0.1584
	Secondary							
	Ankle pain (VAS) score change from baseline on day 14 (%)	-94.3	143	-93.4	140	-94.8	137	T-O vs. D-G: 0.7312 T-G vs. D-G: 0. 7640

	Ankle pain (VAS) score change from baseline on day 42 (%)	100.0	143	100.0	140	100.0	137	T-O vs. D-G: 0.9267 T-G vs. D-G: 0.8314
	FAAM ADL subscale score change from baseline on day 14 (points)	41.7	143	40.5	140	41.7	137	T-O vs. D-G: 0.4963 T-G vs. D-G: 0.6665
	FAAM ADL subscale score change from baseline on day 42 (points)	48.3	143	44.0	140	48.8	137	T-O vs. D-G: 0.4030 T-G vs. D-G: 0.7588
	FAAM Sports subscale score change from baseline on day 14 (points)	50.0	143	50.0	140	50.0	137	*"T-O and T-G were non-inferior to D-G on all secondary outcome variables";* p value NR
	Ankle swelling, figure of eight change from baseline on day 14 (cm)	-0.67	143	-0.67	140	-0.57	137	As above.
	Global assessment of treatment efficacy on day 14 (mean)	1.6	143	1.6	140	1.5	137	As above.
	Rescue medication (paracetamol) tablets per participant (mean)	1.5	143	1.6	140	1.0	137	*"No significant difference";* p value NR

Abbreviations: ADL: Activity of Daily Living; FAAM: cm: centimetres; Foot and Ankle Disability Measure; D-G: diclofenac gel; g: grams; ITT; intention-to-treat; mm: millimetres; n: number; NR: not reported; NSAID: non-steroidal anti-inflammatory drug; PP: per protocol; T-O: Traumeel ointment; T-G: Traumeel gel; VAS: visual analogue scale

Homeopathy data extraction form: Haila et al. 2005

Reference: Haila S, Koskinen A, Tenovuo J. Effects of homeopathic treatment on salivary flow rate and subjective symptoms in patients with oral dryness: a randomized trial. Homeopathy 2005, 94(3):175-181.
Study design: Randomised controlled trial.
Affiliation/source of funds: Turku University Central Hospital and the Finnish Dental Society. **Conflicts of interest:** Not reported.
Participants and setting **Setting:** Private general dental practice, Pori, Finland, in 2002. **Inclusion criteria:** Patients with symptoms of dry mouth (15 with Sjogren's syndrome and 10 with rheumatoid arthritis). **Exclusion criteria:** Over 60 years; history of irradiation to head or neck area.

Intervention

Individualised homeopathy: Individualised homeopathic treatments (3 granules daily of the D12 (12x) potency or 4 granules twice a week of the D30 (30x) or 5 granules of D200 (200x) once a week. Treatment lasted for 6 weeks. Homeopathic medicines needed according to patients' symptoms in this study were Arsenicum album, Acidum phosphoricum, Calcium carbonicum, Ignatia amara, Iodum, Kalium Carbonicum, Lycopodium clavatum, Magnesium carbonicum, Mercurius solubilis, Natrium muriaticum, Nux vomica, Phosphorus, Pulsatilla, Sepia, Silicea, Spongia tosta, Staphisagria, Sulphur and Thuja occidentalis. Prescriptions included 1–4 different homeopathic medicines.

Total number randomised: n=15

Comparison

Control: Placebo (sugar granules) (*"looked and tasted identical"*) for 6 weeks.

Total number randomised: n=14

Outcomes: Unstimulated and stimulated salivary flow rates; VAS scores for dryness while eating, need to sip liquid to aid swallowing, need to drink during the night, amount of salivation; salivary IgA and IgG.

Very brief summary of study authors' main findings/conclusions: *"Our results suggest individually prescribed homeopathic medicine could be a valuable adjunct to the treatment of oral discomfort and xerostomic symptoms."*

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	Coin-toss.
Allocation concealment *(selection bias)*	☐	☐	☒	Not described.
Blinding of participants and personnel *(performance bias)*	☐	☐	☒	Trial described as *"single blind"* – it is unclear as to whether blinding of participants would have been successfully achieved given that the study personnel had knowledge of the intervention. *"In this single blinded study the patients did not know whether they received homeopathic or placebo treatment and during the entire 6-week experimental period no contact was allowed between the subjects and the dentist (SH), who prescribed the homeopathic medication. The patients were not allowed to change the homeopathic medicines or meet any of the authors."*
Blinding of outcome assessment *(detection bias)*	☐	☒	☐	Investigators were not blind (*"the dentist knew the patients' group at the time of saliva collection").*
Incomplete outcome data *(attrition bias)*	☒	☐	☐	29 randomised (15 homeopathy group, 14 placebo group): 1/14 in placebo group excluded due to vomiting; no other losses.
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	Insufficient information to permit judgement of 'High' or 'Low' risk of

				bias. For salivary IgA and IgG concentrations it was reported that *"no significant longitudinal changes were found (data not shown)."*
Other bias	☒	☐	☐	No apparent baseline differences between groups. No other obvious sources of bias identified.
Notes	Patients were un-blinded at 6 weeks and all participants in placebo group were then given verum, and followed up for a further 12 weeks (data from this period have not been included in this report).			

	Outcome measures (dichotomous)	Total number of participants in study = 29				
		Intervention group Total no. in group = 15		**Control group** Total no. in group = 14		
		Events	**Total**	**Events**	**Total**	**P value**
	Unstimulated flow rate increased during 6 week period	9	13	10	13	NR
	Stimulated flow rate increased during 6 week period	9	13	9	13	NR

	Outcome measures (continuous)	Total number of participants in study = 29						
		Intervention group Total no. in group = 15			**Control group** Total no. in group = 14			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Primary							
	Dryness while eating (VAS* score) at 6 weeks	**		15	**		13	0.02
	Need to sip liquid to aid swallowing (VAS* score) at 6 weeks	**		15	**		13	0.03
	Need to drink during the night (VAS* score) at 6 weeks	**		15	**		13	0.03
	Amount of salivation (VAS* score) at 6 weeks	**		15	**		13	0.01

*VAS questions were: (a) severe mouth dryness while eating a meal – 0; no mouth dryness while eating a meal - 10, (b) I need a lot of liquids to aid swallowing – 0; I do not need liquids to aid swallowing - 10, (c) I often need to sip water at night – 0; I do not need water at night - 10 (d) Salivation feels scanty – 0; salivation feels normal – 10.
**Results presented in Figures 2 and 3 of the manuscript.

Abbreviations: IgA: immunoglobulin A; IgG: immunoglobulin G; n: number; NR: not reported; SH: Sirkka Haila (author); VAS: visual analogue scale

Homeopathy data extraction form: Harrison et al. 2013

Reference: Harrison CC, Solomon EM, Pellow J. The effect of a homeopathic complex on psychophysiological onset insomnia in males: a randomized pilot study. Alternative Therapies in Health and Medicine 2013, 19:38-43.
Study design: Randomised controlled trial.

Affiliation/source of funds: The study was funded by the University of Johannesburg.
Conflicts of interest: Not described.

Participants and setting

Setting: The Homeopathy Health Clinic at the University of Johannesburg in Johannesburg, South Africa from February to September 2010.

Inclusion criteria: Males between 18 and 40 years with chronic primary insomnia, who had insomnia at least 3 days per week for a minimum of 1 month, and for not more than 10 years. The Pre-sleep Arousal Scale (PSAS) was used to establish the presence of primary insomnia.

Exclusion criteria: Patients using any medication (inducing sleep-inducing drugs) or recreational drugs, ingesting more than 20 units of alcohol per week, with mental or psychiatric disorders, with sleep disorders such as restless leg syndrome, narcolepsy, or obstructive sleep apnoea, or with medical disorders where discomfort of pain resulted in the development of insomnia or where sleeplessness was concomitant to their illness. Females were excluded (due to variability of hormones during menstruation).

Intervention

Homeopathy: Homeopathic complex, made in 20% alcohol; participants used 5 drops of the medication under their tongue in the evening before supper, and again before going to bed. The remedies chosen for the complex were selected and combined based on their indications for common symptoms of PI: Abmra grisea 6cH, Arsenicum album 6cH, Coffea cruda 6cH, Delphinium staphisagria 6cH, Ignatia amara 6cH, Lycopodium clavatum 6cH, Passiflora incarnate 6cH, Valeriana officinalis 6cH. The medication was dispensed in 30 mL amber-glass dropper bottles. Participants were advised not to take the medication within 15 minutes of eating, drinking or brushing their teeth. Follow up for 28 days.

Total number randomised: n=18 randomised, n=14 analysed

Comparison

Control: Placebo formula, consisting of the un-medicated vehicle only (no discernible differences existed in taste or appearance).

Total number randomised: n=16 randomised, n=14 analysed

Outcomes: Pre-Sleep Arousal Scale (PSAS*) (16 questions organised into 2 subscales for cognitive and somatic arousal) (1 = not at all; 5 = extremely) completed every night; Sleep Diary: used to estimate length of time taken to fall asleep each night (sleep onset and latency) completed every morning.

Very brief summary of study authors' main findings/conclusions: *"Findings suggest that daily use of the homeopathic complex does have an effect over a 4-week period on physiological and cognitive arousal at bedtime as well as on sleep onset latency in PI sufferers. Further research on the use of this complex for PI is warranted before any definitive conclusions can be drawn."*

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	Participants placed into matched pairs according to their duration of insomnia. The medication was manufactured and randomised by an accredited homeopathic laboratory and placed in boxes labelled A and B. One participant of the pairs randomly selected a bottle from one of the boxes; the matched person received medication from the other box.
Allocation concealment *(selection bias)*	☒	☐	☐	As above.
Blinding of participants and personnel	☒	☐	☐	Placebo-blinding of participants and study personnel.

(performance bias)				
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	As above (outcomes assessed by participants).
Incomplete outcome data *(attrition bias)*	☐	☒	☐	Drop outs were due to different reasons and were relatively high (in homeopathy group) in an already small sample. Homeopathy group: 4/18 (22%) (shift work, scheduling difficulties, non-compliance) Placebo group: 2/16 (12.5%) (intake of insomnia medications).
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	Only subjectively measured outcomes were reported (arousal (PSAS) and sleep onset latency (sleep diary); for these outcomes results were presented in Figures, with only mean/median values presented in text, and no measures of variance were reported. Adverse effects were only mentioned in the Discussion (none reported).
Other bias	☐	☒	☐	Authors state baseline characteristics showed *"similar values",* however some differences were apparent (homeopathy group older, more likely to be working, less likely to sleep alone, more likely to be affected by nightly arousals, less likely to have pleasant thoughts disrupting sleep onset).
Notes	Designed as a pilot study.			

	Outcome measures (dichotomous)	Total number of participants in study = 34				
		Intervention group Total no. in group = 18 (14 analysed)		**Control group** Total no. in group = 16 (14 analysed)		
		Events	**Total**	**Events**	**Total**	**P value**
	Adverse effects	From discussion: *"No adverse effects were noted in the current study."*				

	Outcome measures (continuous)	Total number of participants in study = 34						
		Intervention group Total no. in group = 18 (14 analysed)			**Control group** Total no. in group = 16 (14 analysed)			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Total arousal levels over 28 day period (PSAS) (mean)	*"From day 16 until the completion of the study, however, the experimental group was consistently less aroused before bed"*						
	Reduction over time in somatic and cognitive arousals (PSAS)	Significant reduction for homeopathy group: P<0.001 No significant change for placebo group: P=0.463						
	Arousal levels at day 28 (PSAS)	10.36	IQR	14	17.7	IQR	12	0.023

	(median)		NR			NR		
	Improvement in sleep onset latency (sleep diary) (mean)	Significant improvement for homeopathy group: P=0.011 No significant change for placebo group: P=0.206						
	Sleep onset latency at day 28 (sleep diary) (median) (minutes)	10.35	IQR NR	13	17.39	IQR NR	14	0.016

*PSAS: The scale has 16 questions organised into 2 subscales for cognitive and somatic arousal. Each question has 5 varying degrees of severity 1 (not at all) to 5 (extremely); PSAS score ranges from 16 to 80, with elevated scores indicating the presence and severity of PI.

Abbreviations: IQR: interquartile range; n: number; NR: not reported; PI: psychophysiological onset insomnia; PSAS: Pre-sleep Arousal Scale; SD: standard deviation

Homeopathy data extraction form: Hellhammer et al. 2013

Reference: Hellhammer J, Schubert M. Effects of a homeopathic combination remedy on the acute stress response, well-being, and sleep: a double-blind, randomized clinical trial. Journal of Alternative and Complementary Medicine 2013, 19:161-169.

Study design: Randomised controlled trial.

Affiliation/source of funds: The authors acknowledge the financial support of Dr. Loges & Co. GmbH for this study.
Conflicts of interest: No competing financial interests exist.

Participants and setting
Setting: *"single center study conducted at study sites of a contract research organization (Daacro) in Germany"* November 27, 2009 to December 22, 2009.
Inclusion criteria: Women aged 30 to 50 years that were employed full-time who experienced physical symptoms without organic findings when stressed. Symptoms included uneasiness, nervousness, attention deficit, tension, fatigue, sleep disorders, headaches, lack of concentration, and gastro-intestinal disorders.
Exclusion criteria: Smoking, alcohol/drug addiction, pregnancy, any acute or chronic diseases, any medication interfering with study outcome measures, lack of good health assessed by a physician and laboratory parameters, any other study participation during the past 6 months, and/or the lack of internet access at home.

Intervention
Homeopathy: dysto-loges S (sold in pharmacies over the counter in Germany) tablets containing Passiflora incarnata TM (mother tincture, 13 mg) along with Gelsemium D4 (39 mg), Reserpinum D6 (31.2 mg), Coffea D6 (33.3 mg), and Veratrum D6 (33.3 mg).
All participants were asked to take three tablets daily for 14 days, one tablet before each meal (breakfast, lunch, and dinner) (holding it in their mouth until dissolved, without consuming caffeinated drinks or essential oils at the same time); on the last study day (day 15), participants took three tablets before breakfast and an additional three tablets upon arrival at the study site.
Total number randomised: n=20

Comparison
Control: Placebo tablets (which only contained the inactive components of dysto-loges S (i.e., corn starch, lactose monohydrate, and magnesium stearate)). Test and placebo substances were identical in odour, taste, and colour.
Total number randomised: n=20

Outcomes: The primary study endpoint was the stress-induced change of cortisol levels. Secondary biological endpoints were plasma cortisol, ACTH, catecholamines, and heart rates. Secondary psychological endpoints were perceived stress, anxiety, insecurity, mood, calmness, alertness, and life and sleep quality (state anxiety (STAI X1); multidimensional mood states (MDBF); visual analogue scales (VAS) for stress, anxiety, insecurity; visual analogue scales for sleep quality (VIS)).

Very brief summary of <u>study authors'</u> main findings/conclusions: *"This study provides preliminary evidence for beneficial effects of dysto-loges S on sleep quality. Improvement of sleep quality was positively associated with a normalized neuroendocrine stress response during acute stress, whereas an altered hormonal response was observed in participants with impaired sleep. We hypothesize that the test product may possibly reduce NE release."*				
Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	Computer generated randomisation sequence; the randomisation schedule was concealed from the study manager, assistant and medical staff.
Allocation concealment *(selection bias)*	☒	☐	☐	*"Packaging and labelling of the study medication was done by the Pharmacy of the University Clinic Mainz, Germany. Daacro received the prepacked bottles, which were numbered according to the randomization sequence…. Information concerning the allocation of participants was sequentially numbered and sealed in envelopes that were kept by the CEO of the contract research organisation."*
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	Use of placebo to blind participants and study personnel.
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	As above.
Incomplete outcome data *(attrition bias)*	☒	☐	☐	One participant (homeopathy group) withdrew from the study due to personal problems; 39 participants completed this study; all 40 included in the intention-to-treat analyses.
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	Insufficient information to determine risk of reporting bias; no access to trial protocol/registration.
Other bias	☐	☐	☒	Groups comparable at baseline for the limited number of characteristics presented. The authors note that *"interpretations are limited by the fact that NE levels were not assessed before the treatment period. Thus, one cannot exclude that NE levels in the treatment group were lower even before substance intake."*
Notes				

		Total number of participants in study = 40

	Outcome measures (dichotomous)	Intervention group Total no. in group = 20		Control group Total no. in group = 20		
		Events	**Total**	**Events**	**Total**	**P value**
	Secondary					
	Adverse events	0	20	0	20	NA
	Compliance	*"Compliance was very good; one participant violated the study protocol by taking one instead of three tablets per day at home."*				

	Outcome measures (continuous)	Total number of participants in study = 40						
		Intervention group Total no. in group = 20			Control group Total no. in group = 20			
		Mean	**95% CI**	**Total**	**Mean**	**95% CI**	**Total**	**P value**
	Primary							
	Salivary cortisol in response to TSST (mmol/L)	*	*	20	*	*	20	0.651
	Secondary biological outcomes	*"There was no significant difference between verum and placebo treatment regarding stress-induced saliva and plasma cortisol levels, ACTH, and E levels… group comparison of heart rates revealed no differences."*						
	Plasma cortisol in response to TSST (nmol/L)	*	*	20	*	*	20	0.741
	ACTH in response to TSST (pg/mL)	*	*	20	*	*	20	0.674
	Epinephrine in response to TSST (pg/mL)	*	*	20	*	*	20	0.523
	Noreinephrine in response to TSST (pg/mL)	*"Participants treated with the homeopathic combination remedy had significantly lower NE levels as compared to the placebo group before and after the TSST."*						0.023
	Heart rate in response to TSST (bpm)	*	*	20	*	*	20	0.614
	Secondary psychological outcomes in response to stress test	*"Values of psychological parameters did not significantly differ between verum and placebo"*						
	State anxiety (STAI) in response to TSST	*	*	20	*	*	20	0.651
	Positive mood (MDBF) in response to TSST	*	*	20	*	*	20	0.105
	Alertness (MDBF) in response to TSST	*	*	20	*	*	20	0.111
	Calmness (MDBF) in response to TSST	*	*	20	*	*	20	0.446
	Stress perception in response to TSST (VAS) (mm)	*	*	20	*	*	20	0.758
	Anxiety in response to TSST (VAS) (mm)	*	*	20	*	*	20	0.754
	Insecurity in response to TSST (VAS) (mm)	*	*	20	*	*	20	0.871
	Secondary psychological outcomes concerning sleep and life quality	*"There were no significant group differences in stress perception and stress symptoms, easefulness, and concentration as well as in time needed for falling asleep and in awakening at night."*						
	Perceived stress (PSS)	*	*	20	*	*	20	0.718
	No. stress symptoms after 1 week, 2	*	*	20	*	*	20	0.545

	weeks (VIS)							
	Concentration after 1 week, 2 weeks (VIS) (mm)	*	*	20	*	*	20	0.943
	Easefulness after 1 week, 2 weeks (VIS) (mm)	*	*	20	*	*	20	0.647
	Time falling asleep after 1 week, 2 weeks (VIS) (min)	*	*	20	*	*	20	0.261
	Waking up at night after 1 week, 2 weeks (VIS)	*	*	20	*	*	20	0.501
	Having a good night after 1 week, 2 weeks (VIS) (mm)	*	*	20	*	*	20	0.549
	Sleep quality	*"Participants of the verum group had significantly improved sleep after the treatment period (p = 0.010, R2 = 0.21; Table 2, Fig. 3). Sleep quality improved by around 30% in the verum group, and 21% of between group variance in sleep quality were accounted for by the treatment. In contrast, sleep quality did not differ between baseline and after treatment in the placebo group."*						

*Paper presents data as placebo and verum mean (95% CI) for each outcome listed above (including at various time-points after the TSST) in Tables 2 and 3 of manuscript

Abbreviations: ACTH: adrenocorticotrophic hormone; bpm: beats per minute; CI: confidence interval; L: litre; MDBF: multidimensional mood states; mg: milligrams; mL: millilitres; mm: millimetres; n: number; NE: norepinephrine; NA: not applicable; nmol: nanomole; pg: pictograms; PSS: perceived stress scale; STAI: State-Trait-Anxiety Questionnaire; TSST: Trier Social Stress Test; VAS: visual analogue scales; VIS: visual analogue scales for sleep quality

Homeopathy data extraction form: Issing et al. 2005

Reference: Issing W, Klein P, Weiser M. The homeopathic preparation Vertigoheel versus Ginkgo biloba in the treatment of vertigo in an elderly population: a double-blinded, randomized, controlled clinical trial. Journal of Alternative and Complementary Medicine 2005, 11(1):155-160.
Study design: Randomised controlled trial.
Source of funds: unconditional grant from Biologische Heilmittle Heel GmbH, Germany. **Conflicts of interest:** none reported.
Participants and setting **Setting:** 13 German centres practising either alternative medicine or both alternative and conventional medicine **Inclusion criteria:** Caucasian patients between the ages of 60 and 80 years with previously diagnosed vertigo or at least one of the following symptoms of vertigo: blackouts, unsteadiness, grogginess, light-headedness', torpor, 'seeing stars', or flickering, blurred or impaired vision. The primary inclusion criteria included the occurrence of at least three episodes of vertigo per day in the week prior to the study or constant vertigo. With a median intensity of vertigo episodes between 2 and 4 on a 5-point assessment scale; a total score of at least 20 in a specially designed dizziness questionnaire; a score of at least 20 points in the Tinetti mobility test; and no aural impediments. Patients were also required to have normal blood pressure at enrolment (systolic between 110 and 160 mm Hg, diastolic between 70 and 90 mm Hg). **Exclusion criteria:** participation in another clinical study within 30 days prior to enrolment; lactose intolerance; known serious chronic or malignant disease or neurologic disorders; treatment with an antivertigo agent, antiemetic, corticosteroid, agent affecting circulation, antihistamine, migraine medication, streptomycin, gentamycin sedatives, psychoactive medication in the 7 days prior to the study, anticoagulation therapy

(including salicylate) in the 4 weeks prior to the start of the study.

Intervention

Homeopathy: Vertigoheel; two tablets three times daily for 8 weeks.
(1 tablet of Vertigoheel contains 201 mg of Cocculus indicus D4, 30 mg Conium maculatum D3, 30 mg Ambra grisea D6, and 30 mg petroleum D8).
Total number randomised: n = 87 randomised, n=79 analysed

Comparison

Control: Ginkgo biloba; one tablet plus one placebo tablet three times daily for 8 weeks.
(tablets contain 40 mg dried extract from Ginkgo biloba leaves standardised to 24% ginkgo flavone glycosides and 6% terpene lactones).
Total number randomised: n = 83 randomised, n=75 analysed

Outcomes: Timing: visit 2 (15 days ± 2); visit 3 (day 29 ± 3); visit 4 (day 43 ± 3); visit 5 (day 57 ± 4).
"efficacy assessments"; patient diaries; adverse events.
Final visit: blood pressure; heart rate; physician and patient global assessment of efficacy and tolerability; compliance.
Primary outcome: combined assessment of overall quality of life and mean daily frequency, intensity of duration of vertigo episodes (recorded in a patient diary) after 6 weeks of treatment (visit 4)
Duration of vertigo episodes was assessed on a five-point scale (0 to 4) when 0 was ≤ 2 minutes and 4 = continuous vertigo.
Secondary outcomes: total score and physical and psychological subscores in the dizziness questionnaire; mean daily frequency, duration and intensity of vertigo episodes over 8 weeks (on a 5-point scale; 0 = none; to 4 = very strong); overall therapeutic effect (patient and doctor assessments); attempts at walking a line; and Unterberger's stepping test (assessed on a scale of very good, good, moderate, poor, unsuccessful). Safety was evaluated by monitoring adverse events and overall assessment of tolerability patient and doctor assessments). Compliance was assessed as the percentage of planned dosage of tablets or capsules taken by patients.

Very brief summary of study authors' main findings/conclusions:
Vertigoheel is an appealing alternative to established Ginkgo biloba therapy for atherosclerosis-related vertigo.

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☐	☒	Not reported.
Allocation concealment *(selection bias)*	☐	☐	☒	*"randomly allocated."*
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	*"all tablets were of a similar size and colour"* (but see 'Other bias' below).
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	Not mentioned, but probably done.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	8/87 in the Vertigoheel group lost to follow-up: 1 discontinued; 7 protocol deviations (violation of inclusion/exclusion criteria, administration of prohibited concomitant medication, poor compliance or making visit 4 outside the specified time window). 8/83 in the Ginkgo biloba group lost to follow-up: 2 did not receive study

				drug; 1 discontinued; 5 protocol deviations (see above).
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	Some results only reported narratively or incompletely; 'combined test' not fully defined or reported; measures of statistical significance (such as p values) not always reported.
Other bias	☐	☐	☒	Some gender imbalance between groups (25% males in Vertigoheel group and 41% in Ginkgo biloba group); differences between tablets not explained (so impact on un-blinding unable to be assessed).
Notes: lower boundary of confidence interval was set at > 0.36 for rejecting the null hypothesis of inferiority.				

	Outcome measures (dichotomous)	Total number of participants in study = 154				
		Intervention group Total no. in group = 79		**Control group** Total no. in group = 75		
		Events	**Total**	**Events**	**Total**	**P value**
	Secondary					
	Global assessments (patient and doctor)	*"no noteworthy differences between Vertigoheel and G. biloba"*				
	Medication rated as 'very good' by patients	19	79	12	75	NR
	Medication rated as 'very good' by doctors	20	79	13	75	NR
	Tolerability of study medication - patients	70	79	59	75	NR
	Tolerability of study medication - doctors	73	79	61	75	NR
	Patient and doctor assessments	*"were consistent (within 5%) in each category"*				
	Adverse events	Suspected relationship to study medication: Vertigoheel: one case of abdominal pain and nausea Ginkgo biloba: two cases – abdominal pain, flatulence Two unrelated serious adverse events: pancreatic carcinoma; femoral fracture (as the result of an accident)				

	Outcome measures (continuous)	Total number of participants in study = 154						
		Intervention group Total no. in group = 79			**Control group** Total no. in group = 75			
		Mean	**SD***	**Total**	**Mean**	**SD***	**Total**	**P value**
	Primary							
	Dizziness questionnaire score: week 6 (maximum dizziness = 50)	15.5	9.7	79	15.1	9.0	75	0.480**
	Mean frequency of episodes per day over last 7 days: week 6	2.1	3.5	79	2.5	4.0	75	0.549**
	Duration of episodes score: week 6 (maximum: 4 = continuous vertigo)	0.7	1.1	79	1.1	1.2	75	0.602**
	Intensity of episodes score: week 6 (maximum: 4 = very strong)	1.0	0.7	79	1.2	0.8	75	0.563**
	Secondary							

	Line walking (mean increases from baseline); %	8.0	12.9	79	6.6	12.6	75	NR
	Unterberger's stepping test and rotation: mean rotation at week (degrees)	13.6	19.9	79	13.4	19.1	75	NR
	Combined test							0.05 (in favour of Vertigo-heel)#
	Psychological or physical symptoms of dizziness	*"no difference…between Vertigoheel and G. biloba at any timepoint in the study"*						
	Compliance (%) - tablets -capsules	 96.9 97.5	 4.2 4.6	 79 79	 98.2 98.1	 3.7 4.2	 75 75	NR

*not stated, but assumed to be SD (also evidence of skew for many outcomes)
**probability of superiority of Vertigoheel over Ginkgo biloba
#lower boundary of CI was 0.448, above the 0.36 boundary; indicating Vertigoheel was not inferior to Gingko biloba

Abbreviations: CI: confidence interval; mg: milligrams; mm Hg: millimetres of mercury; n: number; NR: not reported; ns: not significant; SD: standard deviation

Homeopathy data extraction form: Khuda-Bukhsh et al. 2011

Reference: Khuda-Bukhsh AR, Banerjee A, Biswas SJ, Karmakar SR, Banerjee P, Pathak S, et al. An initial report on the efficacy of a millesimal potency Arsenicum Album LM 0/3 in ameliorating arsenic toxicity in humans living in a high-risk arsenic village. Zhong Xi Yi Jie He XueBao: Journal of Chinese Integrative Medicine 2011, 9(6):596-604.

Study design: Randomised controlled trial.

Source of funds: *"Grateful acknowledgements are made to Boiron Lab, Byon, France, for the financial support granted to Prof. Anisur Rahman Khuda-Bukhsh for this work…"*
Conflicts of interest: *"The authors declare that they have no competing interests."*

Participants and setting

Setting: The village of Dasdiya, in Haringhata block under Nadia District, West Bengal India (an arsenic-contaminated village, where no arsenic-free drinking water is available).
Inclusion criteria: People with initial signs or symptoms or arsenic poisoning (from the same socio-economic background, with weak general health, suffering from liver or alimentary system disorders, insomnia, complained of muscle of joint pain, and showing visible signs of arsenic toxicity such as a burning sensation of eyes and skin, rain drop pigmentation).
Exclusion criteria: People with noticeably poor state of health or with advanced cancer (or terminal patients).

Intervention

Homeopathy: Arsenicum Album (fifty millesimal potency) LM 0/3 (a homeopathic remedy). Two tiny globules of the verum (or placebo) were dissolved in 100 mL of distilled water and mixed with 2 mL of ethyl alcohol 2%. Participants were advised to give 10 up and down jerks to the bottle before taking 10 drops of the remedy twice daily (once on an empty stomach in the morning and once in the evening at least an hour after/before food) for 2 months.
Total number randomised: n=unclear, n=9 analysed

Comparison
Control: Placebo tablets (as above).
Total number randomised: n=unclear, n=5 analysed)

Outcomes: blood arsenic concentration; other biochemical/pathophysiological parameters (acid phosphatase; alkaline phosphatase; aspartate aminotransferase; alanine aminotransferase; lipid peroxidase; reduced glutathione; blood glucose; creatinine; total cholesterol; high-density lipoprotein cholesterol; low-density lipoprotein cholesterol; triacylglycerol; erythrocyte sedimentation rate; packed cell volume; haemoglobin; antinuclear antibody titre; metalloproteinase).

Very brief summary of study authors' main findings/conclusions: *"Ars Alb LB 0/3 shows potential for use in high-risk arsenic villages as an interim treatment for amelioration of arsenic toxicity until more extensive medical treatment and facilities can be provided to the numerous victims of arsenic poisoning."*

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☐	☒	No detail provided on random sequence generation.
Allocation concealment *(selection bias)*	☐	☒	☐	25 *"similar"* bottles containing Ars Alb LM 0/3 and another 25 containing placebo, marked with *"numerical codes (not disclosed to the researchers or the human volunteers)"* were kept on a tray and subjects could take any bottle of their choice.
Blinding of participants and personnel *(performance bias)*	☐	☐	☒	While a placebo was used, it is not clear that the bottles and treatments were identical. There was a high rate of loss to follow up in the study (and perhaps more so in the placebo group) indicating that blinding may not have been successful.
Blinding of outcome assessment *(detection bias)*	☐	☐	☒	Unclear if group allocation was known at time of outcome assessment.
Incomplete outcome data *(attrition bias)*	☐	☒	☐	28 participants were 'randomised' (took a bottle); though only 14 returned for follow up at 2 months (50%). The numbers in each group at the start of the study are not stated.
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	Insufficient information to determine risk of reporting bias; some discrepancy between results text and result in Table 3 for biochemical parameters (i.e. results text indicates some significant differences between groups which are not reported in the Table). For other outcomes reported in text comments like *"not statistically significant"* or *"slightly lower"* were made (with no p values etc. reported).

Other bias	☐	☐	☒	Insufficient information available to determine risk of other bias. No baseline characteristics (apart for baseline values for outcomes assessed) reported.
Notes				

	Outcome measures (dichotomous)	Total number of participants in study = 28				
		Intervention group Total no. in group = unclear		**Control group** Total no. in group = unclear		
		Events	**Total**	**Events**	**Total**	**P value**
	ANA titer positive	5	9	2	5	NS
	ANA titer negative	1	9	2	5	NS
	ANA titer in borderline	3	9	1	4	NS

	Outcome measures (continuous)	Total number of participants in study = 24						
		Intervention group Total no. in group = unclear			**Control group** Total no. in group = unclear			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Arsenic content in urine (µg/mL)	54.08	10.64	9	50.72	11.50	5	NS
	Arsenic content in blood (µg/mL)	3.27	1.29	9	7.39	4.71	5	NS
	Biochemical parameters							
	AcP (nmol/(g protein.min))	46.7	0.5	9	47.1	1.7	5	*
	AlkP (nmol/(g protein.min))	114.7	1.6	9	120.2	5.5	5	*
	ALT (nmol/(g protein.min))	12.4	3.9	9	13.5	3.8	5	*
	AST (nmol/(g protein.min))	8.2	2.3	9	5.7	1.7	5	*
	LPO (nmol MDA/mL sample)	6.17	0.41	9	5.02	1.29	5	*
	GSH (nmol/mL sample)	25.83	0.89	9	23.98	0.85	5	*
	GGT (IU/L)	5.22	0.66	9	3.85	0.57	5	*
	G6PD (IU/L)	2.11	0.51	9	2.82	0.66	5	*
	Pathophysiological parameters							
	Blood glucose (mg/L)	826.9	49.2	9	993.3	36.8		NS
	Hb (g/L)	107.0	5.1	9	102.0	7.9		NS
	ESR (mm/h)	11.09	4.14	9	7.70	2.53		NS
	Total cholesterol (mg/L)	1579.1	98.6	9	1711.8	103.5		NS
	HDL-C (mg/L)	481.4	56.3	9	524.5	75.6		NS
	LDL-C (mg/L)	87.9	11.6	9	99.9	13.5		NS
	Triacylglycerol (mg/L)	1271.0	168.5	9	908.5	147.8		NS
	Creatinine (mg/L)	7.5	3.3	9	7.3	3.8		NS
	PCV (%)	32.7	2.26	9	37.4	2.95		NS
	Lymphocyte viability (%)	81.25	0.98	9	77.06	0.54	5	<0.01
	Matrix metalloproteinase	*"In the verum-fed subjects, the band intensities were slightly lower than those in the placebo-fed subjects within 2 months of treatment."*						

**"The differences, where compare between placebo and verum after 2 months of administration, were mostly significant when analyzed by two-sample t test while others were non-significant (Table*

3." Significance of difference for each outcome not reported in Table 3, which indicated no significant differences between placebo and verum at 2 months.

Abbreviations: AcP: acid phosphatase; AlkP: alkaline phosphatase; ALT: alanine aminotransferase; ANA: anti-nuclear antibody; AST: aspartate aminotransferase; ESR: erythrocyte sedimentation rate; g: grams; GGT: gamma glutamyl transferase; GSH: reduced glutathione; G6PD: glucose-6-phosphate dehydrogenase; Hb: haemoglobin; HDL-C: high-density lipoprotein cholesterol; IU: international unit; LDL-C: low-density lipoprotein cholesterol; LPO: lipid peroxidase; MDA: malonaldehyde; mg: milligrams; mm: millimetres; mL: millilitres; n: number; nmol: nanomole; NS: *"not statistically significant" (or "non-significant");* PCV: packed cell volume; SD: standard deviation

Homeopathy data extraction form: Kulkarni et al. 1988

<table>
<tr><td colspan="5">Reference: Kulkarni A, Nagarkar BM, Burde GS. Radiation protection by use of homoeopathic medicines. Hahnemannian Homoeopathic Sandesh 1988, 12:20-23.</td></tr>
<tr><td colspan="5">Study design: Randomised controlled trial</td></tr>
<tr><td colspan="5">Source of funds: Radiotherapy Department, Bombay Hospital, Bombay.
Conflicts of interest: Not detailed.</td></tr>
<tr><td colspan="5"><u>Participants and setting</u>
Setting: Bombay Hospital, Bombay.
Inclusion criteria: Patients undergoing radiotherapy.
Exclusion criteria: None stated.</td></tr>
<tr><td colspan="5"><u>Intervention 1</u>
Cobaltum 30: "Cobaltum and Causticum were the homeopathic drugs selected because they mimic various symptoms of radiation reaction." Patients were instructed to take 3 pills from the give bottle, once every morning on an empty stomach. The pills were taken throughout the entire course of radiotherapy.
Total number randomised: n=26
<u>Intervention 2</u>
Causticum 30: As above.
Total number randomised: n=28</td></tr>
<tr><td colspan="5"><u>Comparison</u>
Placebo:
Total number randomised: n=28</td></tr>
<tr><td colspan="5">Outcomes: Average grading of reactions (18 points radiation reaction profile, checked once weekly throughout course of radiotherapy; 0-5 = very minimal radiation reactions; 6-10 = moderate but tolerable reactions; 11+ = severe degree of reactions, usually warranting interruption of the radiotherapy).</td></tr>
<tr><td colspan="5">Very brief summary of <u>study authors'</u> main findings/conclusions: "It is our conclusion that homeopathic medicine i.e. Cobaltum and Causticum significantly reduce the degree of radiation reactions...It certainly improves patient's compliance to continue radiation treatments as per the treatment plan."</td></tr>
<tr><td colspan="5">Risk of bias assessment</td></tr>
<tr><td rowspan="2">Domain</td><td colspan="3">Risk of bias</td><td rowspan="2">Support for judgement</td></tr>
<tr><td>Low</td><td>High</td><td>Unclear</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>☐</td><td>☐</td><td>☒</td><td>Quote: "patients were randomly allocated" – no further details provided.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>☐</td><td>☐</td><td>☒</td><td>No detail provided.</td></tr>
<tr><td>Blinding of participants and personnel</td><td>☒</td><td>☐</td><td>☐</td><td>Placebo used.</td></tr>
</table>

(performance bias)				
Blinding of outcome assessment *(detection bias)*	☐	☐	☒	Unclear whether outcome assessors were blind to group allocation.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	82 patients were randomised. Losses to follow up or exclusions not detailed. No mention of intention-to-treat analyses.
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	Only the 'average' radiation reactions were presented (no measure of variation provided; and no measures of statistical significance provided); however in the discussion the authors state that there was no *"significant reduction"* in tumour regression for the homeopathy group (placebo group not mentioned).
Other bias	☐	☐	☒	Insufficient methodological detail provided to determine risk of other bias.
Notes				

	Outcome measures (dichotomous)	Total number of participants in study = 82						
		Intervention 1 Total no. in group = 26		**Intervention 2** Total no. in group = 28		**Control group** Total no. in group = 28		
		Events	**Total**	**Events**	**Total**	**Events**	**Total**	**P value**
	Tumour regression rates	*"We did not observe any significant reduction of tumour regression rates in the patients on homeopathic medicines."*						

	Outcome measures (continuous)	Total number of participants in study = 82									
		Intervention 1 Total no. in group = 26			**Intervention 2** Total no. in group = 28			**Control group** Total no. in group = 28			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Average grading of radiation reactions	4.7	NR	26	5.4	NR	28	8.5	NR	28	From conclusion: *"homeopathic medicines i.e. Cobaltum and Causticum significantly reduce the degree of radiation reactions."*
	Average grading of radiation reactions (head and neck)	6.75	NR	26	7.9	NR	28	9	NR	28	NR
	Average grading of radiation reactions (thorax)	5.5	NR	26	3.5	NR	28	8.75	NR	28	NR
	Average grading	5.7	NR	26	5.2	NR	28	7.5	NR	28	NR

	of radiation reactions (pelvis)										

Abbreviations: n: number; NR: not reported; SD: standard deviation

Homeopathy data extraction form: Manchanda et al. 1997

Reference: Manchanda RK, Mehan N, Bahl R, Atey R. Double blind placebo controlled clinical trials of homeopathic medicines in warts and molluscum contagiosum. CCRH Quarterly Bulletin (1997) 19:25-29.				
Study design: Randomised controlled trial.				
Affiliation: Nehru Homeopathic Medical College and Hospital. **Conflicts of interest:** Not detailed.				
Participants and setting **Setting:** Nehru Homeopathic Medical College and Hospital from May 1996 to April 1997. **Inclusion criteria:** People with warts (verruca vulgaris, verruca plana, verruca filiformis, verruca plantaris, verruca genitalis) or molluscum contagiosum of any age. **Exclusion criteria:** People on immunosuppressive drugs or having active treatment for other diseases.				
Intervention **Homeopathy:** Pre-coded drugs Thuja, Ruta, Calcarea carb and Causticum for 15 days; the drugs of 30 potency were given three times daily; 200 potency were given twice daily and 1 M potency were given once daily. **Total number randomised: n=unclear**				
Comparison **Control:** Placebo**.** **Total number randomised: n=unclear**				
Outcomes:				
Very brief summary of study authors' main findings/conclusions: *"The results of active drug group are far better than the placebo group. This again reconfirms the observation made in previous project report that homeopathic medicines are quite effective in the treatment of warts and molluscum contagiosum."*				
Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☐	☒	Described as *"double blind placebo controlled study, parallel design"* with no further details provided.
Allocation concealment *(selection bias)*	☐	☐	☒	Not described.
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	A placebo was used; and study was described as *"double blind."*
Blinding of outcome assessment *(detection bias)*	☐	☐	☒	No detail regarding blind outcome assessment.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	20 participants *"dropped out"*; unclear from which groups the patients dropped out from, and the reasons for dropping out. Unclear if intention-to-treat analyses performed.

Selective outcome reporting? *(reporting bias)*	☐	☒	☐	The only outcome was *"improved."* The numbers per group were not clearly reported.
Other bias	☐	☐	☒	It is unclear whether the groups were similar at baseline. Lack of methodological detail provided in published report.
Notes				

	Outcome measures (dichotomous)	Total number of participants in study = 124				
		Intervention group Total no. in group = Unclear (n = 104 across the two groups)		**Control group** Total no. in group = Unclear (n = 104 across the two groups)		
		Events	**Total**	**Events**	**Total**	**P value**
	Primary					
	Improved	52, 81%	Unclear	12, 19%	Unclear	NR

Abbreviations: n: number: NR: not reported

Homeopathy data extraction form: Maronna et al. 2000

Reference: Porcher-Spark A. Comparison of the efficacy and tolerance of Zeel® comp. and diclofenac for the oral treatment of gonarthrosis: results of a double blind equivalence study [Summary of trial published in German: Maronna U, Weiser M, Klein P. Orale Behandlung der Gonarthrose mit Zeel comp. - Ergebnisse einer doppelblinden Äquivalenzstudie versus Diclofenac. Orthopädische Praxis. 2000, 36(5)] International Journal for Biomedical Research and Therapy 2000, 29(3):157–158. AND Strosser W, Weiser M. Osteoarthritis patients regain mobility. International Journal for Biomedical Research and Therapy 2000, 29(6):295–299.
Study design: Randomised controlled trial.
Affiliation/source of funds: Institute for Antihomotoxic Medicine and Basic Regulation Research, Baden-Baden, Germany. **Conflicts of interest:** Not described.
Participants and setting **Setting:** 13 orthopaedic practices. **Inclusion criteria:** Men and women suffering from mild to moderate osteoarthritis of the knee (ICD-10: M17.9) for at least six months; diagnosis confirmed either clinically or radiologically according to criteria established by Altman or Kellgren; scoring at least 5 and not more than 16 on Lequesne's index of pain and functionality **Exclusion criteria:** Patients with serious hepatic, renal, cardiac, endocrine and/or haematological diseases, asthma or chronic obstructive pulmonary disease were excluded.
Intervention **Homeopathy:** One tablet of Zeel comp (homeopathic complex preparation) and a diclofenac placebo three times per day. Zeel is a homeopathic medication containing ingredents: Toxicodendron quecifolium e summitatibis, Arnica montana, Solanium dulcamara, Sanguiaria Canadensis and sulphur. Patients were treated for a 10 week study period. **Total number randomised: n=60**
Comparison

Control: One tablet of diclofenac 25 and a Zeel comp. placebo tablet three times per day. **Total number randomised: n=61**				
Outcomes: WOMAC (Western Ontario and McMaster Colleges) Osteoarthritis Index (parameters: pain (5 questions), stiffness (2 questions) and physical activity and restriction of physical functions (17 questions)) assessed at 2, 4, 6 and 10 weeks on 10 cm VAS (0 = no pain or limitation; 10 = severe pain or limitation); patient reported efficacy; patient reported tolerance.				
Very brief summary of <u>study authors'</u> main findings/conclusions: "*According to the data obtained by the scientists, both Zeel comp. and diclofenac led to a statistically significant improvement in the [osteoarthritis] symptoms." "In both treatment groups, significant and clinically relevant improvements in mobility and functionality of the affected knee joint were noted over the ten weeks of treatment. In addition, patients received greater independence and thus also greater self-sufficiency. Therapy with Zeel comp. proved equivalent to treatment with diclofenac."*				
Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☐	☒	Study described as *"randomized".*
Allocation concealment *(selection bias)*	☐	☐	☒	Quote: *"test preparations whose identity was concealed by the double-blind technique"*; no further details provided.
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	Placebos were given to both groups in addition to their active treatment.
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	As above; subjective outcomes assessed by patients who were blind.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	125 patients *were "admitted to study"* – four patients were excluded during the run-in phase (before randomisation). 7 patients in the intervention group were excluded *"three already taking the test medication were excluded from the intent-to-treat population; and four additional patients were excluded from the per protocol population."*
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	Insufficient information to permit judgement of ''High' or 'Low' risk. Information taken from published translations.
Other bias	☐	☐	☒	Insufficient information to determine other risk of bias: *"These two treatment groups were demographically and anamnestically comparable when the study began."*
Notes	Study described as a *"double blind equivalence study."*			

	Outcome measures (dichotomous)	Total number of participants in study = 121		
		<u>Intervention group</u> Total no. in group = 60	**<u>Control group</u>** Total no. in group = 61	

		Events	Total	Events	Total	P value
	Patient assessment of efficacy at end of study ('very good' or 'good')	25	53	31	61	NR
	Patient assessment tolerance ('very good' or 'good')	>85%	53	>85%	61	NR

	Outcome measures (continuous)	Total number of participants in study = 121						
		Intervention group Total no. in group = 60			**Control group** Total no. in group = 61			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**Mann-Whitney statistic**
	WOMAC Osteoarthritis Index	After 2 and 4 weeks, a marked improvement was first observed in the diclofenac group; after 6 weeks, there was no longer a difference between groups *"statistical analysis of the data showed the therapeutic equivalence of the two test medications."*						
	Total index: reduction after 2 weeks	-0.4		53	-1.0		61	0.36
	Total index: reduction after 4 weeks	-0.9		53	-1.6		61	0.41
	Total index: reduction after 6 weeks	-1.3		53	-1.7		61	0.46
	Total index: reduction after 10 weeks	-1.7		53	-2.1		61	0.46
	Pain index: reduction after 2 weeks	-0.2		53	-1.0		61	0.38
	Pain index: reduction after 4 weeks	-0.8		53	-1.5		61	0.44
	Pain index: reduction after 6 weeks	-1.1		53	-1.5		61	0.47
	Pain index: reduction after 10 weeks	-1.5		53	-2.0		61	0.45
	Stiffness index: reduction after 2 weeks	-0.5		53	-1.1		61	0.43
	Stiffness index: reduction after 4 weeks	-1.0		53	-1.9		61	0.41
	Stiffness index: reduction after 6 weeks	-1.5		53	-2.1		61	0.46
	Stiffness index: reduction after 10 weeks	-2.1		53	-2.4		61	0.47
	Functionality index: reduction after 2 weeks	-0.4		53	-0.9		61	0.42
	Functionality index: reduction after 4 weeks	-1.0		53	-1.5		61	0.43
	Functionality index: reduction after 6 weeks	-1.4		53	-1.6		61	0.48
	Functionality index: reduction after 10 weeks	-1.7		53	-2.0		61	0.46
	Data also presented for 17 items of the functionality index at 2 weeks, 4 weeks, 6, weeks, 10 weeks	*"At the latest, equivalence was established between the two groups after six weeks."*						

Abbreviations: cm: centimetres; n: number; NR: not reported; SD: standard deviation; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Homeopathy data extraction form: Mourão et al. 2013

Reference: Mourão LC, Moutinho H, Canabarro A. Additional benefits of homeopathy in the treatment of chronic periodontitis: A randomized clinical trial. Complement Therapies in Clinical Practice 2013, 19:246-250.

Study design: Randomised controlled trial

Source of funds: *"Funding Sources of funding and such as supply of drugs: School Farmacy – Institute Hahnemanniano do Brazil – IHB"*
Conflicts of interest: *"The authors declare that they have no conflicts of interest."*

Participants and setting
Setting:
Inclusion criteria: Patients of both genders, aged 35 to 70 years, with chronic periodontitis: the presence of clinical attachment level ≥ 3 mm in proximal sites of 2 non-adjacent teeth; bone loss confirmed by periapical radiographs; bleeding on probing; probing depth > 3 mm.
Exclusion criteria:

Intervention
Homeopathy: Conventional non-surgical periodontal therapy and homeopathy. The medicines used were selected according to the similia principle. 1) Depurative medicine (presents an elective action on the tissue/organ malfunction which prevents elimination or substances produced/introduced into the body): Berberis 6CH (2 tablets, twice daily, 45 days). 2) Acute drug (in low concentrations to cover all signs/symptoms of local lesions): Mercurius solubilis/Belladonna/Hepar sulphur 6CH (2 tablets, 3 times a day, 15 days). 3) Nosodes (used for chronic stimulation of the individual's energy): Pyrogenium 200 CH (single weekly dose, 2 weeks).
Total number randomised: n=20

Comparison
Control: Conventional non-surgical periodontal therapy. First visit (60 min): personal oral hygiene instructions; brief description of periodontal disease and its local and systemic effects and supragingival scaling. Other visits: consultations for sub ingival scaling and root planning – the number of consultations needed to obtain clinical outcome was standardised to 4 (one per quadrant); if there was no tooth in a quadrant the number of visits was reduced.
Total number randomised: n=20

Outcomes: Main outcome: Clinical attachment level (CAL); clinical parameters: probing depth (PD); plaque index (PI); bleeding on probing (BOP); serological parameters: LDL cholesterol; HDL cholesterol; total cholesterol; triglycerides; glucose; uric acid.

Very brief summary of study authors' main findings/conclusions: *"The findings of this 3-month follow-up study concluded that H M, as an adjunctive to CPT can provide additional benefits in the treatment of CP."*

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☐	☒	*"All subjects were randomly selected…";* no further detail provided.
Allocation concealment *(selection bias)*	☐	☐	☒	No detail provided.
Blinding of participants and personnel *(performance bias)*	☐	☒	☐	Trial described as *"Single-blind"* with no blinding of participants.
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	*"All clinical and serologic analyses were recorded by a "blind" examiner."*
Incomplete outcome data *(attrition bias)*	☐	☐	☒	Insufficient reporting of attrition/exclusions to permit

				judgement.
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	Insufficient information to determine risk of reporting bias (i.e. no access to a trial protocol or online trial registration). The values reported in text for clinical parameters and in Table 2 do not correspond. The Discussion notes that homeopathy has *"no known side effects"* however did not report on side effects in the study.
Other bias	☐	☐	☒	No baseline characteristics reported. Insufficient information to determine other risk of bias.
Notes				

	Outcome measures (continuous)	Total number of participants in study = 40						
		Intervention group Total no. in group = 20			**Control group** Total no. in group = 20			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value***
	Primary							
	CAL (from baseline to day 90)	*"After 90 days there was a significant gain in CPT-T (+0.51 mm…In CPT-C the difference found was not significant (-0.15 mm, Table 2)"*						H group: 0.001; C group: 0.232
	Secondary							
	PD (from baseline to day 90)	*"After 9- days, the PD decreased significantly in both groups (-0.34 mm and -0.15 mm, for CPT-T and CPT-C respectively) (Table 2)"*						H group: <0.001; C group: 0.002
	PI (from baseline to day 90)	*"Comparing baseline and the 90-day values, there was a significant reduction in both groups (Table 2)"*						H group: <0.001; C group: <0.001
	BOP (from baseline to day 90)	*"There was a significant reduction in both groups, comparing baseline and the 90-day values (Table 2)"*						H group: <0.001; C group: <0.001
	*Serological parameters***							
	Cholesterol LDL (90 days)	118.52	4.39	NR	125.72	31.67	NR	H group: 0.001; C

								group: 0.315
	Cholesterol HDL (90 days)	52.57	7.22	NR	51.29	8.99	NR	H group: 0.073; C group: 0.663
	Cholesterol total (90 days)	185.81	43.99	NR	191.43	28.21	NR	H group: 0.001; C group: 0.010
	Triglycerides (90 days)	108.57	42.27	NR	138.00	56.43	NR	H group: 0.003; C group: 0.042
	Glucose (90 days)	89.29	5.44	NR	93.15	6.00	NR	H group: <0.001; C group: 0.018
	Uric acid (90 days)	4.74	0.96	NR	5.05	1.19	NR	H group: <0.001; C group: 0.043

*All p values presented are for intra-group comparisons (i.e. from baseline to 90 days)
**"Intra group comparisons showed a significant reduction in total cholesterol, triglycerides, glucose and uric acid in both CP groups (Table 3). However a significant reduction in LDL cholesterol was only observed in CPT-T (Table 3)."*

Abbreviations: BOP: bleeding on probing; C: control; CAL: clinical attachment level; CP: chronic periodontitis; CPT: conventional periodontal treatment; CPT-C: conventional periodontal therapy control group; CPT-T: conventional periodontal treatment and homeopathy group; H: homeopathy; HDL: high-density lipoprotein; LDL: low-density lipoprotein; min: minutes; mm: millimetres; n: number; NR: not reported; PD: probing depth; PI: plaque index; SD: standard deviation

Homeopathy data extraction form: Naidoo and Pellow 2013

Reference: Naidoo P, Pellow J. A randomized placebo-controlled pilot study of Cat saliva 9cH and Histaminum 9cH in cat allergic adults. Homeopathy 2013, 102:123–129.
Study design: Randomised controlled trial (pilot study).
Source of funds: Not stated. **Conflicts of interest:** Not stated.
Participants and setting **Setting:** The Homeopathic Health Training Centre, at the Doornfontein campus, University of Johannesburg,

South Africa and at Weleda pharmacy (Fourways, Johannesburg).
Inclusion criteria: Participants with a positive skin prick test (SPT), who were living with a cat for a period of 6 months or more, who suffered from allergy-like symptoms (i.e. sneezing, red itchy eyes, skin rash, runny itchy stuffy nose, scratchy throat, wheezing and redness of the skin where a cat has scratched, licked or bitten) when in the presence of a cat or when exposed to cat dander.
Exclusion criteria: Individuals who were pregnant or lactating, using any other medication or intervention for allergies (including previous immunotherapy for cat allergy), or who were immuno-compromised were excluded from the study.

Intervention
Homeopathy: Cat Saliva 9cH and Histaminum 9cH (combined in a single tablet) on lactose tablets. Participants were given 25 mL bottles containing 56 tablets each (given a second bottle of medication at week 2) and were instructed to dissolve two tablets under the tongue twice daily (morning and night).
Participants attended a follow-up consultation at the end of week 2 and at the end of week 4.
Total number randomised: n=15

Comparison
Control: Placebo (unmedicated lactose tablets); identical in taste and appearance to the homeopathic complex.
Total number randomised: n=15

Outcomes: SPT (wheal diameter (mm); extent of flare reaction (mm); degree of itchiness).

Very brief summary of study authors' main findings/conclusions: *"The homeopathic medicine reduced the sensitivity reaction of cat allergic adults to cat allergen, according to the SPT. Future studies are warranted to further investigate the effect of Cat saliva and Histaminum and their role as a potential therapeutic option for this condition."*

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☐	☒	*"The medication was randomized by Natura Laboratories, using the simple random sampling method;* no further details.
Allocation concealment *(selection bias)*	☐	☐	☒	Bottles were labelled in the same manner. No information provided on the numbering (i.e. not stated whether *"sequentially numbered").*
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	Use of an identical placebo to blind participants and study personnel (the medication was manufactured and randomised by Natura Laboratories and labelled in the same manner).
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	Though not specifically stated that outcome assessors were blinded, considered likely with the use of the identical placebo.
Incomplete outcome data *(attrition bias)*	☒	☐	☐	All 30 participants completed the study; no losses to follow up/exclusions.
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	Unclear whether results (in Tables 4 and 5) for the SPT are adjusted for baseline values, or why they differ from the values presented in Tables 2 and 3. Units for level of itchiness not

				clear. Adverse effects mentioned only in the discussion *"The remedies were well tolerated and no adverse effects were noted".*
Other bias	☐	☐	☒	No data reported on baseline characteristics of the participants (except for baseline data for the wheal diameter of the SPT for cat allergen).
Notes	Pilot study			

	Outcome measures (continuous)	Total number of participants in study = 30						
		Intervention group Total no. in group = 15			**Control group** Total no. in group = 15			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Primary							
	Wheal diameter score (mm)	4.40	2.36	15	5.50	2.12	15	0.007
	Secondary							
	Flare reaction scale (mm)	2.22	1.09	15	3.07	0.88	15	0.000
	Level of itchiness	2.57	1.68	15	3.43	1.03	15	0.002

Abbreviations: mL: millilitres; mm: millimetres; n: number; SD: standard deviation; SPT: skin prick test

Homeopathy data extraction form: Pach et al. 2011

Reference: Pach D, Brinkhaus B, Roll S, Wegscheider K, Icke K, Willich SN, et al. Efficacy of injections with Disci/Rhus toxicodendron compositum for chronic low back pain – A randomized placebo-controlled trial. PLoS One 2011, 6:e26166.

Study design: Randomised controlled trial.

Source of funds: The study was sponsored by WALA Heilmittel GmbH.
Conflicts of interest: No competing interests.

Participants and setting

Setting: Nine study centres with various specialisations (family medicine, internal medicine, orthopaedics, rehabilitation, university outpatient clinics) in Germany, from August 2007 to June 2008.
Inclusion criteria: People aged 30 to 75 years, male or female, with low back pain for at least 12 months (chronic), who had already received standard therapy, with average back pain intensity of at least 40 mm on VAS (0-100 mm) in last seven days at baseline, with no other treatment except oral NSAIDs and muscle relaxants within four weeks prior to study entry, who gave informed consent. Women of childbearing potential were only included if they used effective contraception.
Exclusion criteria: previous or current treatment with Disci preparations, treatment other than NSAIDs or peripherally acting analgesics, routine use of analgesics for other diseases, protrusion or prolapsed intervertebral discs (one or more) with neurological symptoms, previous spinal surgery , suspected infectious spondylopathy, low back pain because of malignant or infectious disease, organic causes of back pain such as ankylosing spondylitis, Reiter syndrome and Behcet' syndrome, congenital deformities of the spine (without minor lordosis, kyphosis, scoliosis), suspected osteoporosis with compression fracture, suspected spinal stenosis, spondylolysis or spondylolisthesis, physiotherapy in the last four weeks prior or planned during the trial, the initiation of a new treatment for low back pain, complementary treatment in the last four weeks prior to or planned during the trial, inability to participate in the trial effectively, alcohol or substance abuse,

participation in another clinical trial, severe chronic or acute disease which did not allow study participation, bleeding disorders or oral anticoagulation treatment, pregnancy and breast feeding, current application for a benefit, involvement in planning or coordination of the study, and hypersensitivity against drug components**.**

Intervention

Homeopathy: 10 mL Disci/Rhus toxicodendron compositum (verum) (a composite medication consisting of 11 different diluted agents) injected in 5 to 10 small dosages subcutaneously with a 0.4 mm needle into painful sites on the lower back (12 treatment sessions within eight weeks: twice per week for the first four weeks (with at least one day without therapy between sessions) and one treatment per week for the second four weeks (with at least three days without therapy between sessions). Treatment duration was eight weeks; follow up was after 26 weeks.

In all three groups, rescue pain medication with peripherally acting analgesics (also paracetamol) or NSAIDs, but not pain medication acting on the central nervous system, was permitted and their intake was documented in diaries.

Total number randomised: n=51

Comparison

Placebo: Injection with isotonic saline solution which contained sodium chloride, sodium hydrogen carbonate, and water and was not distinguishable from the verum solution (via identical regimen to treatment group).

Total number randomised: n=48

Comparison

No treatment: Patients in the no treatment group received no additional intervention during the study period.

Total number randomised: n=51

Outcomes: Primary outcome: average low back pain intensity over the last 7 days on VAS (0-100 mm; 0 = no pain; 100 = worst imaginable pain) after 8 weeks. Secondary outcomes: VAS at 26 weeks; the following outcomes at 8 and 26 weeks: back function (HFAQ); quality of life (SF-36); pain disability scale (PDI); pain perception scale (SES). Patient diaries were used to calculate the number of days with medication between weeks 5-8; safety and blinding were also evaluated.

Very brief summary of study authors' main findings/conclusions: *"The homeopathic preparation was not superior to placebo. Compared to no treatment injections resulted in significant and clinical relevant chronic back pain relief."*

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	Randomisation sequence was computer generated, with stratification for centres.
Allocation concealment *(selection bias)*	☒	☐	☐	Randomisation envelopes were prepared by two individuals not involved in the study; envelopes were opaque, sequentially numbered and sealed, each containing and randomisation number.

Blinding of participants and personnel *(performance bias)*	☒	☐	☐	Trial was *"partly double blind"* – no blinding for no treatment group. Quote: *"In the verum and in the placebo group both physicians and patients were blinded to group assignment. In addition, both participating statisticians were blinded for data analysis."* After 8 weeks of treatment, patients and physicians were asked to guess treatment intervention; treatment with verum could not be identified more often than expected by chance.
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	As above.
Incomplete outcome data *(attrition bias)*	☒	☐	☐	At 8 week follow up (primary outcome): 1/51 (2%) participant from the verum refused further participation; 4/48 (8%) in the placebo group refused participation and 1/48 (2%) dropped out because of surgery; 2/51 (4%) in no treatment group were excluded (spinal stenosis and 'everything incomprehensible'). At 26 week follow up 1/50 (2%) from verum group, 3/43 (9%) from placebo group and 2/49 (4%) from no treatment group refused to complete the questionnaires. The primary analysis population was the intention to treat population; an additional per-protocol analysis was performed.
Selective outcome reporting? *(reporting bias)*	☒	☐	☐	Outcomes clearly defined, and pre-specified in accompanying protocol.
Other bias	☐	☐	☒	For most baseline characteristics groups were comparable at baseline, with the exception of gender, height, and two scales of the SF-36. All treatment groups received the therapy free of charge; *"the no treatment group received therapy after the study."*
Notes				

	Outcome measures (dichotomous)	Total number of participants in study = 150						
		Homeopathy group Total no. in group = 51		**Placebo group** Total no. in group = 48		**No treatment group** Total no. in group = 51		
		Events	**Events**	**Events**		**Events**	**Total**	**P value**

	Secondary							
	Adverse events: any	37	51	34	48	NR	NR	NR
	Adverse events: haematoma	8	51	5	48	NR	NR	0.546
	Adverse events: common cold	9	51	5	48	NR	NR	0.379
	Adverse events: pain	17	51	17	48	NR	NR	0.814

	Outcome measures (continuous)	Total number of participants in study = 150									
		Homeopathy group Total no. in group = 51			**Placebo group** Total no. in group = 48			**No treatment group** Total no. in group =51			
		Mean	**95% CI**	**Total**	**Mean**	**95% CI**	**Total**	**Mean**	**95% CI**	**Total**	**P value**
	Primary										
	Pain intensity in last 7 days at 8-week follow up (on VAS, 0-100) adjusted	37.0	25.3-48.8	50	41.8	30.1-53.	49	53.0	41.8-64.2	43	V vs. NT: 0.001 V vs. P: 0.350
	Pain intensity in last 7 days at 8-week follow up (on VAS, 0-100) unadjusted	36.6	27.8-45.4	50	52.6	46.2-59.1	49	43.4	33.3-53.4	43	V vs. NT: 0.001 V vs. P: 0.244
	Secondary										
	Pain intensity in last 7 days at 26-week follow up (on VAS, 0-100) adjusted	36.6	25.4-47.8	50	35.5	24.2-46.9	49	45.0	34.1-55.9	43	V vs. NT: 0.085 V vs. P: 0.837
	Days with rescue medication (weeks 1-4)	3.9	1.1-6.8	50	2.8	-0.1-5.7	49	8.8	6.0-11.6	43	V vs. NT: <0.001 V vs. P: 0.396
	Days with rescue medication (weeks 5-8)	3.7	1.2-6.3	50	3.3	0.8-5.9	49	8.2	5.7-10.7	43	V vs. NT: 0.001 V vs. P: 0.785
	Days with rescue medication (weeks 1-8)	7.7	2.5-12.9	50	6.0	0.7-11.4	49	17.1	12.0-22.2	43	V vs. NT: <0.001 V vs. P: 0.532
	Affective pain at 8 weeks (SES)	44.0	41.7-46.3	50	43.5	41.0-46.2	49	44.9	42.5-47.3	43	V vs. NT: 0.590 V vs. P:

	Outcome measures (continuous)	Total number of participants in study = 150									
		Homeopathy group Total no. in group = 51			**Placebo group** Total no. in group = 48			**No treatment group** Total no. in group =51			
		Mean	**95% CI**	**Total**	**Mean**	**95% CI**	**Total**	**Mean**	**95% CI**	**Total**	**P value**
											0.795
	Affective pain at 26 weeks (SES)	42.9	40.0-45.7	50	41.4	38.3-44.4	49	42.1	39.3-45.0	43	V vs. NT: 0.686 V vs. P: 0.420
	Sensory pain at 8 weeks (SES)	45.3	43.3-47.3	50	46.1	44.0-48.2	49	45.0	43.0-47.0	43	V vs. NT: 0.811 V vs. P: 0.594
	Sensory pain at 26 weeks (SES)	45.5	42.8-48.1	50	43.7	41.0-46.3	49	44.8	42.2-47.4	43	V vs. NT: 0.680 V vs. P: 0.277
	PDI at 8 weeks	22.7	19.3-26.2	50	21.4	17.7-25.1	49	25.9	22.5-29.3	43	V vs. NT: 0.200 V vs. P: 0.598
	PDI at 26 weeks	18.1	14.0-22.3	50	21.4	17.2-25.6	49	22.7	18.7-26.7	43	V vs. NT: 0.046 V vs. P: 0.173
	Back function (HFAQ) at 8 weeks	68.3	64.0-72.6	50	68.4	63.8-73.0	49	64.8	60.5-69.1	43	V vs. NT: 0.261 V vs. P: 0.969
	Back function (HFAQ) at 26 weeks	69.0	62.8-75.2	50	67.4	61.0-73.8	49	64.8	58.8-70.9	43	V vs. NT: 0.226 V vs. P: 0.660
	Physical component score at 8 weeks (SF-36)	37.1	34.9-39.2	50	39.8	37.5-42.1	49	35.4	33.3-37.5	43	V vs. NT: 0.278 V vs. P: 0.089
	Physical component score at 26 weeks (SF-36)	38.2	35.0-41.5	50	40.9	37.5-44.2	49	36.5	33.3-39.7	43	V vs. NT: 0.326

	Outcome measures (continuous)	Total number of participants in study = 150									
		Homeopathy group Total no. in group = 51			**Placebo group** Total no. in group = 48			**No treatment group** Total no. in group =51			
		Mean	**95% CI**	**Total**	**Mean**	**95% CI**	**Total**	**Mean**	**95% CI**	**Total**	**P value**
											V vs. P: 0.163
	Mental component score at 8 weeks (SF-36)	8.5	46.0-50.9	50	47.5	44.9-50.1	49	50.9	48.4-53.3	43	V vs. NT: 0.174 V vs. P: 0.609
	Mental component score at 26 weeks (SF-36)	51.2	48.9-53.5	50	48.9	46.4-51.4	49	51.5	49.1-53.9	43	V vs. NT: 0.861 V vs. P: 0.185
	Physical functioning at 8 weeks (SF-36)	59.6	55.2-64.1	50	64.0	59.2-68.09	49	59.8	55.3-64.3	43	V vs. NT: 0.955 V vs. P: 0.196
	Physical functioning at 26 weeks (SF-36)	63.4	56.7-70.0	50	66.3	59.5-73.2	49	60.1	53.6-66.6	43	V vs. NT: 0.370 V vs. P: 0.439
	Role physical at 8 weeks (SF-36)	47.8	38.3-57.3	50	56.6	57.0-46.8	49	47.1	37.7-45.0	43	V vs. NT: 0.919 V vs. P: 0.198
	Role physical at 26 weeks (SF-36)	54.7	42.0-67.3	50	60.5	47.4-73.7	49	49.7	37.3-62.1	43	V vs. NT: 0.508 V vs. P: 0.458
	Bodily pain at 8 weeks (SF-36)	48.0	42.6-53.5	50	46.8	40.9-52.7	49	40.0	34.5-45.5	43	V vs. NT: 0.041 V vs. P: 0.767
	Bodily pain at 26 weeks (SF-36)	53.3	45.2-61.4	50	50.2	41.9-58.5	49	46.1	38.1-54.0	43	V vs. NT: 0.085 V vs. P: 0.483
	General health perception at 8 weeks	53.7	49.7-57.750	50	54.2	49.9-58.5	49	52.9	48.9-56.9	43	V vs. NT:

	Outcome measures (continuous)	Total number of participants in study = 150									
		Homeopathy group Total no. in group = 51			**Placebo group** Total no. in group = 48			**No treatment group** Total no. in group =51			
		Mean	**95% CI**	**Total**	**Mean**	**95% CI**	**Total**	**Mean**	**95% CI**	**Total**	**P value**
	(SF-36)										0.773 V vs. P: 0.878
	General health perception at 26 weeks (SF-36)	54.8	50.2-59.4	50	57.1	52.1-62.1	49	51.9	47.2-56.5	43	V vs. NT: 0.321 V vs. P: 0.465
	Vitality at 8 weeks (SF-36)	45.5	41.0-50.0	50	51.1	46.3-56.0	49	44.5	40.0-49.0	43	V vs. NT: 0.759 V vs. P: 0.096
	Vitality at 26 weeks (SF-36)	50.1	45.0-55.3	50	51.7	46.3-57.0	49	49.2	44.2-54.3	43	V vs. NT: 0.764 V vs. P: 0.614
	Social functioning at 8 weeks (SF-36)	73.9	68.5-79.3	50	75.4	69.6-81.3	49	76.7	71.3-82.2	43	V vs. NT: 0.472 V vs. P: 0.712
	Social functioning at 26 weeks (SF-36)	81.5	76.5-86.5	50	78.7	73.2-84.3	49	78.2	73.0-83.3	43	V vs. NT: 0.363 V vs. P: 0.470
	Role emotional at 8 weeks (SF-36)	75.5	65.9-85.1	50	62.5	52.1-72.9	49	74.4	64.5-84.3	43	V vs. NT: 0.874 V vs. P: 0.072
	Role emotional at 26 weeks (SF-36)	80.8	71.7-89.9	50	71.6	61.4-81.7	49	80.7	71.2-90.1	43	V vs. NT: 0.982 V vs. P: 0.182
	Mental health at 8 weeks (SF-36)	64.9	60.7-69.1	50	68.2	63.7-72.8	49	70.9	66.7-75.2	43	V vs. NT: 0.047 V vs. P: 0.283
	Mental health at 26	70.2	65.8-	50	67.9	63.0-	49	70.1	65.6-	43	V vs.

	Outcome measures (continuous)	Total number of participants in study = 150									
		Homeopathy group Total no. in group = 51			**Placebo group** Total no. in group = 48			**No treatment group** Total no. in group =51			
		Mean	**95% CI**	**Total**	**Mean**	**95% CI**	**Total**	**Mean**	**95% CI**	**Total**	**P value**
	weeks (SF-36)		74.6			72.8			74.6		NT: 0.970 V vs. P: 0.487

Abbreviations: CI: confidence interval; HFAQ: Hannover Functional Ability Questionnaire; mL: millilitres; mm: millimetres; n: number; NSAID: non-steroidal anti-inflammatory drug; NR: not reported; NT: no treatment group; P: placebo; PDI: pain disability index; SES: pain perception scale; SF-36: quality of life (Medical Outcome Study-Short Form 36); V: verum; VAS: visual analogue scale

Homeopathy data extraction form: Pellow and Swanepoel 2013

Reference: Pellow J, Swanepoel M. A randomised pilot study on the efficacy of milking cream and a homeopathic complex topical cream on diaper dermatitis. Health SA Gesondheid 2013; 18(1):680.

Study design: Randomised controlled trial (pilot study).

Source of funds: *"This work was financed and supported by the University of Johannesburg. The contents of this work are solely the responsibility of the authors and do not represent the official views of UJ."*
Conflicts of interest: *"The authors declare that they have no financial or personal relationship(s) which may have inappropriately influenced them in writing this article."*

Participants and setting
Setting: The Homeopathic Health Training Centre, at the Doornfontein campus of the University of Johannesburg.
Inclusion criteria: Children with diaper dermatitis (DD), between the ages of 3 months to 24 months, who were wearing disposable diapers on a daily basis.
Exclusion criteria: Children not using diapers continuously; with any other known dermatological disease; with an allergy or sensitivity to disposable diapers or skin care products; using any chronic or ongoing medications that might have affected the outcome of the study; or with a known allergy to any of the ingredients in the treatment or control creams were excluded from the study.

Intervention
Homeopathy: Homoeopathically medicated milking cream (parents were given a 200 g tub of milking cream containing Atropa belladonna 6cH 3%, Sulphuricum acidum 6cH 3% and Calendula officinalis D1 3%). The researcher demonstrated the application of the cream in the presence of the participants' parents or guardians at the end of the initial consultation, and parents were asked to apply the cream to the affected area during the normal diaper changing routine, as well as after every bath for 7 days. They were asked not to change the normal diaper changing routine, nappy brand, wet-wipe brand or the child's diet during the study period. If any other cream/intervention was used, they were asked to notify the researcher. Follow up took place on days 2, 4, 7, and 10.
Total number randomised: n=20

Comparison
Control: Milking cream (containing chlorhexidine (an antiseptic), vitamin E (which has anti-inflammatory activity and maintains cell membrane structure) and lanolin (which has emollient effects and increases wound healing rates)). Parents were given a 200 g tub as above.
Total number randomised: n=20

Outcomes: Severity of DD (4-Point Grading Scale) looking at ulceration, scaling, rash papules, rash, oedema, redness, macules and continuous redness in 10 areas, adding to a total score of 40 (the higher the rating, the more sever the rash); total percentage area affected (Modified Lund and Browder Chart looking at the same 10 areas, referred to as the total nappy area).				
Very brief summary of <u>study authors'</u> main findings/conclusions: *"The results showed that both the homeopathic complex cream as well as the unmedicated milking cream by itself had an ameliorating effect on DD in infants and could serve as a safe and effective alternative treatment for this condition. Evidence also showed that the treatment group outperformed the control group in certain affected areas, and seemed to have a more rapid resolution of symptoms. Further investigation is warranted."*				
Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☐	☒	*"Participants were allocated to either Group A (n = 20) or Group B (n = 20) using matched pairs according to severity in order to ensure equal distribution in both groups."*
Allocation concealment *(selection bias)*	☐	☐	☒	No detail provided.
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	Trial described as *"double-blind";* considered likely that participants were blinded.
Blinding of outcome assessment *(detection bias)*	☐	☐	☒	Blinding of outcome assessors not stated.
Incomplete outcome data *(attrition bias)*	☒	☐	☐	1/20 participant in the homeopathy group withdrew (gastroenteritis); 2/20 participants in the control group withdrew (diarrhoea; unknown); therefore 37/40 participants included in the analyses.
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	No results were presented for 5 of the 10 areas; quote: *"It was evident that five of the 10 areas were most commonly affected in all participants – both buttocks, the genitals and the inner thighs –and the results for these areas are given below. The number of participants affected in the other five areas was too small for statistical analysis, however it was noted that there was an improvement in DD symptoms in these regions for both groups over the seven days."* Adverse effects mentioned in Discussion only.
Other bias	☐	☐	☒	Gender and age were reported to be *"similar between the group groups."* No further details provided.
Notes	Pilot study.			

		Total number of participants in study = 40

	Outcome measures (dichotomous)	Intervention group Total no. in group = 20		Control group Total no. in group = 20		
		Events	**Total**	**Events**	**Total**	**P value**
	Adverse effects (reported in Discussion only)	*"no adverse effects were noted by any participants', parents or guardians in either group."*				

	Outcome measures (continuous)	Total number of participants in study = 40						
		Intervention group Total no. in group = 20			Control group Total no. in group = 20			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Genital region, % area affected (Modified Lund and Browder Chart) (day 2)	32.5	NR	19	26.11	NR	18	NR
	Genital region, % area affected (Modified Lund and Browder Chart) (day 4)	16.05	NR	19	19.44	NR	18	NR
	Genital region, % area affected (Modified Lund and Browder Chart) (day 7)	6.84	NR	19	6.67	NR	18	0.950
	Genital region, rash severity score (4-Point Grading Scale) (day 2)	0.75	NR	19	0.78	NR	18	NR
	Genital region, rash severity score (4-Point Grading Scale) (day 4)	0.37	NR	19	0.47	NR	18	NR
	Genital region, rash severity score (4-Point Grading Scale) (day 7)	0.11	NR	19	0.17	NR	18	0.593
	"Both groups had a statistically-significant reduction in mean percentage of area affected and rash severity of the genital region by day 7 (p = < 0.001)". *"Inter-group analysis, however, revealed no statistically-significant differences between the two groups for percentage area affected (p = 0.950) or for rash severity (p = 0.593) by day 7, indicating that the treatment group did not outperform the control group."*							
	Right inner thigh, % area affected (Modified Lund and Browder Chart) (day 2)	24.5	NR	19	24.55	NR	18	NR
	Right inner thigh, % area affected (Modified Lund and Browder Chart) (day 4)	8.95	NR	19	14.44	NR	18	NR
	Right inner thigh, % area affected (Modified Lund and Browder Chart) (day 7)	0.53	NR	19	7.78	NR	18	0.113
	Right inner thigh, rash severity score (4-Point Grading Scale) (day 2)	0.5	NR	19	0.67	NR	18	NR
	Right inner thigh, rash severity score (4-Point Grading Scale) (day 4)	0.21	NR	19	0.33	NR	18	NR
	Right inner thigh, rash severity score (4-Point Grading Scale) (day 7)	0.03	NR	19	0.17	NR	18	0.125
	"Both groups had a statistically-significant reduction in mean percentage of area affected and rash severity of the right inner thigh region by day 7 (p = < 0.001)". *"Inter-group analysis, however, indicated no statistically-significant differences between the two groups for*							

	either the percentage area affected (p = 0.113) or the rash severity (p = 0.125) by day 7, indicating that the treatment group did not outperform the control group."							
	Left inner thigh, % area affected (Modified Lund and Browder Chart) (day 2)	16	NR	19	28.33	NR	18	NR
	Left inner thigh, % area affected (Modified Lund and Browder Chart) (day 4)	4.21	NR	19	20.56	NR	18	0.003
	Left inner thigh, % area affected (Modified Lund and Browder Chart) (day 7)	1.58	NR	19	11.11	NR	18	0.033
	Left inner thigh, rash severity score (4-Point Grading Scale) (day 2)	0.58	NR	19	0.61	NR	18	NR
	Left inner thigh, rash severity score (4-Point Grading Scale) (day 4)	0.11	NR	19	0.44	NR	18	0.004
	Left inner thigh, rash severity score (4-Point Grading Scale) (day 7)	0.03	NR	19	0.22	NR	18	0.029
	"Both groups showed a statistically-significant reduction in percentage area affected by day 7 (p = < 0.001)… The mean rash severity of the left inner thigh region of both groups improved over the seven days (treatment group p = < 0.001; control group p = 0.001)." *"Inter-group analysis revealed statistically-significant differences on days 4 (p = 0.003) and 7 (p = 0.033) for percentage of area affected, and on days 4 (p = 0.004) and 7 (p = 0.029) for rash severity, indicating that the treatment group outperformed the control group."*							
	Right buttock, % area affected (Modified Lund and Browder Chart) (day 2)	42.5	NR	19	55	NR	18	NR
	Right buttock, % area affected (Modified Lund and Browder Chart) (day 4)	21.05	NR	19	42.78	NR	18	0.010
	Right buttock, % area affected (Modified Lund and Browder Chart) (day 7)	11.58	NR	19	26.11	NR	18	0.024
	Right buttock, rash severity score (4-Point Grading Scale) (day 2)	1.18	NR	19	1.75	NR	18	0.048
	Right buttock, rash severity score (4-Point Grading Scale) (day 4)	0.61	NR	19	1.42	NR	18	0.005
	Right buttock, rash severity score (4-Point Grading Scale) (day 7)	0.34	NR	19	0.83	NR	18	0.019
	"Both groups had a statistically-significant reduction in mean percentage of area affected and rash severity of the right buttock region by day 7 (p = < 0.001)". *"Inter-group analysis revealed statistically-significant differences on day 4 (p = 0.010) and day 7 (p = 0.024) for percentage of area affected, and on days 2 (p = 0.048), 4 (p = 0.005) and 7 (p = 0.019) for rash severity, indicating that the treatment group outperformed the control group."*							
	Left buttock, % area affected (Modified Lund and Browder Chart) (day 2)	45.5	NR	19	53.89	NR	18	NR
	Left buttock, % area affected (Modified Lund and Browder Chart) (day 4)	21.58	NR	19	45.56	NR	18	0.006
	Left buttock, % area affected	10.53	NR	19	27.78	NR	18	0.010

	(Modified Lund and Browder Chart) (day 7)							
	Left buttock, rash severity score (4-Point Grading Scale) (day 2)	1.18	NR	19	1.69	NR	18	0.067
	Left buttock, rash severity score (4-Point Grading Scale) (day 4)	0.63	NR	19	1.53	NR	18	0.002
	Left buttock, rash severity score (4-Point Grading Scale) (day 7)	0.34	NR	19	0.83	NR	18	0.010
	"Both groups had a statistically-significant reduction in mean percentage of area affected and rash severity by day 7 (p = < 0.001)". *"Inter-group analysis revealed statistically-significant differences on days 4 (p = 0.006) and 7 (p = 0.010) for percentage of area affected, and on days 2 (p = 0.067), 4 (p = 0.002) and 7 (p = 0.010) for rash severity, indicating that the treatment group outperformed the control group."*							

Abbreviations: DD: diaper dermatitis; g: grams; n: number; NR: not reported; SD: standard deviation

Homeopathy data extraction form: Pomposelli et al. 2009

Reference: Pomposelli R, Piasere V, Andreoni C, Costini G, Tonini E, Spalluzzi A, et al. Observational study of homeopathic and conventional therapies in patients with diabetic polyneuropathy. Homeopathy 2009, 98(1):17-25.

Study design: Prospective cohort study

Source of funds: *"The study was financed by a grant from "Belladonna" Association (Milan, Italy), a medical non-profit cultural association having the statutory purpose of supporting the research in homeopathy, and in part by Italian Ministry of Research (60%). Homeopathic medicines were provided free by Siffra (Strada in Chianti, Italy)."*

Conflicts of interest: *"Homeopathic medical doctors (R. Pomposelli, MD, C. Andreoni, MD, G. Costini, MD, and E. Tonini, MD) worked on a voluntary basis and did not receive supplementary compensation for the research. The doctors of the Quarenghi Clinic were A. Spalluzzi, MD (Diabetologist), D. Rossi, MD (Neurophysiologist) and C. Quarenghi, MD, (Internist). Dr. V. Piasere, MD, has received a grant from Belladonna Association. P. Bellavite, MD, and M.E. Zanolin are Professors at University of Verona (School of Medicine). No affiliation nor financial relationship of any author with the drug companies existed."*

Participants and setting

Setting: Quarenghi Clinic, S. Pellegrino, Bergamo, Italy

Inclusion criteria: Patients with a diagnosis of diabetic polyneuropathy were included, with the exclusion of other possible causes of polyneuropathy attending the Quarenghi Clinic.

Exclusion criteria: Patients with neoplasia, acquired immune deficiency syndrome (AIDS), chronic inflammatory diseases (e.g. Crohn's Disease, rheumatoid arthritis), patients with a history of or currently suffering from alcohol abuse, Alzheimer's disease, patients who were mentally unstable or for any reason incapable of completing the questionnaires, patients with homeopathic therapies already in progress, macrocytic anaemia due to folic acid and B12 deficiencies. Patients were withdrawn from the study if deviation from protocol occurred, for life threatening conditions, and according to patient's choice or inability to attend the Clinic.

Intervention

Homeopathy: Individualised homeopathic therapy – patients received homeopathic prescription from one of the four medical doctors (with a minimum 6 years' experience in homeopathy). Follow up required 2-3 further visits in 1 year with the same doctor.

Total number included: n=45

Comparison

Control: Conventional therapy alone (e.g. diet, insulin or oral hypoglycaemic agent, physiotherapy).

Total number included: n=32				
Outcomes: Primary outcome: diabetic neuropathy symptom (DNS) score (scored by the physician) 0 (polyneuropathy absent) to 4 (one point for the presence of each of the following symptoms more than once per week in the last two weeks: (a) unsteadiness in walking; (b) burning, pain or weakness in the legs or feet; (c) tingling sensation in the legs and feet; (d) areas of numbness, insensibility in the legs or feet). Secondary outcomes: quality of life (patient completed questionnaire) (SF-36 score comprising 8 dimensions. The score in each dimension ranges from 0 (worst possible) to 100 (optimal)).				
Very brief summary of <u>study authors'</u> main findings/conclusions: *"Complementary homeopathic therapy of diabetic neuropathy was feasible and promising effects in symptoms cores and cost savings were observed."*				
Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☒	☐	No randomisation.
Allocation concealment *(selection bias)*	☐	☒	☐	As above.
Blinding of participants and personnel *(performance bias)*	☐	☒	☐	No blinding of participants and study personnel.
Blinding of outcome assessment *(detection bias)*	☐	☒	☐	No blinding of outcome assessment.
Incomplete outcome data *(attrition bias)*	☐	☒	☐	45 patients included in the homeopathy group and 32 in the conventional treatment group. 13/45 (29%) patients withdrew from the homeopathy group (6 voluntary unspecified withdrawals (practical difficulties in attending additional appointments); 2 could not be contacted; 1 heart disease; 1 stroke; 1 cognitive decline; 1 neoplasia); and 3/32 (9%) from conventional treatment group (1 deceased; 1 neoplasia; 1 could not be contacted). An intention to treat analysis took into account the 'drop outs' considering them as cases that had not improved.
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	For a number of outcomes in text statements are made without the presentation of data; e.g.: *"No significant changes were observed in either the values for the peroneal motor nerve and for the ulnar motor nerve (data not shown)." "Means of body weight and blood pressure (systolic and diastolic) did not show differences between the two groups or variations over the period of*

				observation (data not shown).”
Other bias	☐	☒	☐	Notable baseline imbalances between groups.
Notes (Newcastle-Ottawa Scale considerations)	Selection: Eligible patients were all consecutive patients attending the Clinic during the recruitment period. The patient was informed as to the possible treatment options. Comparability: groups were *“sufficiently similar”* in regards to DNS severity scores and electroneurophysiological data, but differences were present in regards to other variables including quality of life scores in some domains, consumption of medicines, and severity of clinical condition (greater severity of the clinical conditions of the patients in the homeopathy group). Due to the small sample size, difference baseline values and drop-puts, the outcomes for patients were not statistically compared. Outcome ascertainment: outcome assessment not conducted blind (conducted by doctors and patients), and high loss to follow up in homeopathy group in an already small sample.			

	Outcome measures (dichotomous)	Total number of participants in study = 77				
		Intervention group Total no. in group = 45		**Control group** Total no. in group = 32		
		Events	**Total**	**Events**	**Total**	**P value**
	Secondary					
	Serious adverse effects directly attributable to the homeopathic medicines	0	45	N/A	N/A	N/A

	Outcome measures (continuous)	Total number of participants in study = 77						
		Intervention group Total no. in group = 45			**Control group** Total no. in group = 32			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Primary							
	DNS score baseline	1.40	1.21	45	1.26	1.06	32	6 months vs. baseline: homeopathy: 0.016; conventional treatment: 0.350. 12 months vs. baseline: homeopathy: 0.146; conventional treatment: 0.182
	DNS score 6 months	1.07	1.25	45	1.06	1.15	32	
	DNS score 12 months	1.22	1.27	45	0.94	1.21	32	
	Secondary							
	Electrophysiological conductivity studies of sensory nerves (12 months vs. baseline): sural nerve	*	*	**	*	*	**	Homeopathy: 0.26 Conventional treatment: 0.93
	Electrophysiological	*	*	**	*	*	**	Homeopathy:

	conductivity studies of sensory nerves (12 months vs. baseline): right ulnar nerve							0.38 Conventional treatment: 0.80
		"No significant changes were observed in either the values for the peroneal motor nerve and for the ulnar motor nerve (data not shown)."						
	Fasting blood glucose (6 months vs. baseline)	*	*	**	*	*	**	Homeopathy: 1.00 Conventional treatment: 0.68
	Fasting blood glucose (12 months vs. baseline)	*	*	**	*	*	**	Homeopathy: 1.00 Conventional treatment: 0.50
	"Means of body weight and blood pressure (systolic and diastolic) did not show differences between the two groups or variations over the period of observation (data not shown)."							
	Quality of life (physical function) (baseline vs. 6 months and vs. 12 months)	*	*	**	*	*	**	Homeopathy group: 0.019 (12 months) Conventional treatment: 0.189 (12 months)
	Quality of life (role limitations) baseline vs. 6 months and vs. 12 months)	*	*	**	*	*	**	Homeopathy group: NS Conventional treatment: NS
	Quality of life (bodily pain) baseline vs. 6 months and vs. 12 months)	*	*	**	*	*	**	Homeopathy group: NS Conventional treatment: NS
	Quality of life (general health) baseline vs. 6 months and vs. 12 months)	*	*	**	*	*	**	Homeopathy group: NS Conventional treatment: NS
	Quality of life (vitality) baseline vs. 6 months and vs. 12 months)	*	*	**	*	*	**	Homeopathy group: NS Conventional treatment: NS
	Quality of life (social function) baseline vs. 6 months and vs. 12 months)	*	*	**	*	*	**	Homeopathy group: 0.04 (6 months) Conventional treatment: NS
	Quality of life (role limitations) (baseline vs. 6 months and vs. 12 months)	*	*	**	*	*	**	Homeopathy group: < 0.05 (6 months) Conventional treatment: NS
	Quality of life (mental health) baseline vs. 6 months and vs. 12 months)	*	*	**	*	*	**	Homeopathy group: 0.052 (6 months)

								Conventional treatment: NS

*Means (and standard error of the mean/standard deviations) at each time point (baseline, 6 months, 12 months) are presented in the manuscript in tables/figures
**numbers vary according to time point (baseline, 6 months, 12 months) and are presented in the manuscript tables/figures

Abbreviations: DNS: diabetic neuropathy symptom; n: number; NA: not applicable; NS: not significant; SD: standard deviation; SF-36: quality of life (Medical Outcome Study-Short Form 36)

Homeopathy data extraction form: Relton et al. 2012

Reference: Relton C, O'Cathain A, Nicholl J. A pilot 'cohort multiple randomised controlled trial' of treatment by a homeopath for women with menopausal hot flushes. Contemporary Clinical Trials 2012, 33:853-859.
Study design: Randomised controlled trial (note: this was a pilot 'cohort multiple randomised controlled trial').
Source of funds: One of the authors (CR) was supported by a pre-doctoral training fellowship award from the Department of Health's National Coordinating Centre for Research Capacity Development. *"All work has been independent from the funders in every way."* **Conflicts of interest:** Not detailed.
Participants and setting **Setting:** Six National Health Service general practices in a large city in the North of England. **Inclusion criteria:** A cohort of women with menopausal hot flushes was recruited. From this cohort, through questionnaires, the 'eligible trial group' was identified – women were included if they were aged 45 to 65, reported 14 or more menopausal hot flushes/night sweats per week, and consented to fill in further questionnaires and for their anonymised data to be used for looking at the benefit of treatment of hot flushes. **Exclusion criteria:** Women were excluded if they were taking hormone replacement therapy and did not intend to stop, were using immune-suppressants or chemotherapy, homeopathy or acupuncture.
Intervention **Homeopathy:** Post-randomisation, offer group patients were told they had been selected at random are were given information about the trial treatment they were being offered. The intervention was the offer of treatment from one of 2 study homeopaths (one was medically qualified; one was a professional homeopath); both practiced individualised homeopathy. Treatment consisted of a maximum of 5 consultations and the use of homeopathic medicines (from 2 pharmacies). Homeopaths reported using 18 different homeopathic medicines (some were a one off dose, and others were to be taken twice daily every day). **Total number randomised: n=24 (17 accepted offer)**
Comparison **Control:** No offer of treatment. **Total number randomised: n=24**
Outcomes: Primary outcome measure of clinical effectiveness: Hot Flush Frequency and Severity Scale (HFFSS). Secondary outcomes: Greene Climacteric Scale (GCS) (which asked patients how bothered they were by each of 21 menopausal symptoms); the primary symptom and wellbeing scores of Measure Your Medical Outcome Profile (MYMOP); EQ-5D to measure generic quality of life; Medication Change Questionnaire; visits to hospital; visits to GP surgery; visits to other health professionals; days off work.
Very brief summary of study authors' main findings/conclusions: (Conclusions not related to homeopathic treatment, and rather in relation to the study design).
Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation	☒	☐	☐	A random number sheet was

(selection bias)				generated by the statistician on a one to one basis using block randomisation with blocks of 8.
Allocation concealment *(selection bias)*	☒	☐	☐	The random numbers were put into sealed numbered envelopes. Eligible questionnaires were assigned a study number by an independent administrated, blind to patient data and whether group A or B was the offer of treatment. The numbered envelopes corresponding to each woman's study numbered was opened to reveal the group they were assigned.
Blinding of participants and personnel *(performance bias)*	☐	☒	☐	No blinding.
Blinding of outcome assessment *(detection bias)*	☐	☒	☐	As above.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	Outcome data were available for 24/24 (100%) women in the no offer group and 20/24 (83%) in the offer group. Not all participants filled out each outcome (numbers for outcomes in offer group ranged from 18-20).
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	Insufficient information to determine risk of bias (i.e. no access to a trial protocol/registration).
Other bias	☐	☐	☒	Baseline characteristic were well-matched, apart from that the HFFSS standard deviation in the 'offer group' was 3 times that of the 'no offer group'.
Notes	Of the 'offer group' (offered homeopathy) 17/24 accepted and had one or more consultations with a homeopath; women received from 1 to 5 appointments.			

	Outcome measures (continuous)	Total number of participants in study = 48						
		Intervention group Total no. in group = 24			**Control group** Total no. in group = 24			
		Mean change	**SD**	**Total**	**Mean change**	**SD**	**Total**	**P value**
	Primary*							
	Hot flush frequency severity score (difference between 36 week and baseline score)	-6.89	13.7	20	-1.16	3.90	23	NR
	Secondary*							
	GCS total score (0-63) (difference between 36 week and baseline score)	-1.95	7.16	20	1.83	6.19	23	NR

	MYMOP primary symptom score (0-6) (difference between 36 week and baseline score)	-0.50	1.25	18	0.09	0.90	23	NR
	MYMOP wellbeing score (0-6) (difference between 36 week and baseline score)	0.05	1.51	19	-0.22	1.48	23	NR
	EQ-5D quality of life (0-1) (difference between 36 week and baseline score)	0.07	0.13	20	-0.03	0.18	22	NR
	All medication (difference between 36 week and baseline score)	-0.80	2.24	20	0.61	2.33	23	NR
	Prescribed medication (difference between 36 week and baseline score)	1.10	4.49	20	1.50	2.27	23	NR
	Self-prescribed medication (difference between 36 week and baseline score)	-0.45	1.15	20	0.38	1.41	23	NR

*For all outcomes except the EQ-5D, lower scores indicate better health

Abbreviations: GCS: Greene Climacteric Scale; EQ-5D: generic quality of life measure; HFFSS: hot flush frequency and severity score; MYMOP: Measure Your Medical Outcome Profile; n: number; NR: not reported; SD: standard deviation

Homeopathy data extraction form: Robertson et al. 2007

Reference: Robertson A, Suryanarayanan R, Banerjee A. Homeopathic Arnica montana for post-tonsillectomy analgesia: a randomised placebo control trial. Homeopathy 2007, 96(1):17-21.
Study design: Randomised controlled trial
Source of funds: *"We did not receive any funding from any external source."* The funding came from the ENT department; the Arnica tablets and placebo were provided free by Weleda (UK) Ltd. **Conflicts of interest:** *"All authors declare that they have no competing interests."*
Participants and setting **Setting:** Leister Royal Infirmary between November 2002 and June 2003. **Inclusion criteria:** Patients aged over 18 undergoing tonsillectomy. **Exclusion criteria:** Patients who had tonsillectomy in combination with other surgery or for a potential malignancy were excluded, as were patients on systemic steroids or antihistamines.
All patients: Tonsillectomies were performed by different surgeons, but by blunt dissection. Intra-operative analgesia was morphine 10 mg and/or a non-steroidal analgesic. All patients were discharged on the first post-operative day, with standardised analgesia (Cocodamol 8/500 2 tablets, 6 hourly as required and diclofenac 50 mg 8 hourly as required. **Intervention** **Homeopathy:** Sucrose tablets impregnated with Arnica 30C; patients were instructed to take 2 tablets, 6 times on the first post-operative day, and the 2 tablets twice a day for the next 7 days. **Total number randomised: n=93 randomised, n=53 analysed**
Comparison **Control:** Identical sucrose tablets (but not coated impregnated with ethanol only). **Total number randomised: n=97 randomised, n=58 analysed**
Outcomes: Primary outcome: change in pain scores (50 mm visual analogue scale (VAS)) recorded by the patient on a questionnaire over 14 days post-operatively. Secondary outcomes: analgesia consumption; visits to the general practitioner or hospital; antibiotic use; the day on which swallowing returned to normal; day returned to work.
Very brief summary of study authors' main findings/conclusions: *"The results of this trial suggest that Arnica*

montana given after tonsillectomy provides a small, but statistically significant, decrease in pain scores compared to placebo."				
Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	Computer generated code.
Allocation concealment *(selection bias)*	☒	☐	☐	*"The patients were given a randomly numbered (computer generated code held by independent pharmacist) bottle containing either the Arnica or placebo tablets."* The bottles were identical except for the identification number.
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	Patients and the prescribing doctor were blinded.
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	As above (predominately subjectively measured outcomes).
Incomplete outcome data *(attrition bias)*	☐	☒	☐	Of 190 patients randomised, 111 returned questionnaires (58.4%); 41.6% of patients were lost to follow up. Reasons for losses not reported.
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	P values not reported when non-significant results seen, or reported as <0.05 for significant results. For the mean drop in pain score from day 1 – 14, only mean values presented per group (no standard deviations). For return to work, median values presented with no measure of variance (i.e. interquartile range).
Other bias	☐	☐	☒	The only baseline characteristic reported by group was age. Different surgeons performed the tonsillectomies and there was variation in the intra-operative analgesia.
Notes				

	Outcome measures (dichotomous)	Total number of participants in study = 190				
		Intervention group Total no. in group = 93		**Intervention group** Total no. in group = 93		
		Events	**Total**	**Events**	**Total**	**P value**
	Secondary					
	Complications					
	Visit to general practitioner	31	53	36	58	NS
	Antibiotic use (required full course post-operatively)	22	53	26	58	NS

	Secondary haemorrhage	2	53	4	58	0.78

	Outcome measures (continuous)	Total number of participants in study = 190						
		Intervention group Total no. in group = 93			**Control group** Total no. in group = 97			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value***
	Primary							
	Pain score day 1 (VAS)	33.8	9.5	53	32.9	11.3	58	NS
	Pain score day 2 (VAS)	34	8.2	53	34	12.2	58	NS
	Pain score day 3 (VAS)	34.7	10.1	53	33.9	10.6	58	NS
	Pain score day 4 (VAS)	33.8	10.8	53	32.7	11.5	58	NS
	Pain score day 5 (VAS)	36.2	9.9	53	32.9	12.4	58	NS
	Pain score day 6 (VAS)	34.8	10.7	53	33	12.1	58	NS
	Pain score day 7 (VAS)	31.2	11	53	29.5	12.9	58	NS
	Pain score day 8 (VAS)	26.2	12.5	53	26.1	12.3	58	NS
	Pain score day 9 (VAS)	21.1	10.9	53	22.9	12	58	NS
	Pain score day 10 (VAS)	15.1	9.5	53	19.1	12	58	<0.05
	Pain score day 11 (VAS)	11.5	8.7	53	15.1	12.2	58	<0.05
	Pain score day 12 (VAS)	9.7	9.0	53	12	11.3	58	NS
	Pain score day 13 (VAS)	7.9	7.1	53	10.4	12.2	58	NS
	Pain score day 14 (VAS)	5.5	6.8	53	9	11.4	58	<0.05
	Drop in pain score from day 1 to 14 (VAS)	28.3	NR	53	23.8	NR	58	<0.05
	Secondary							
	Analgesia consumption							
	Cocodamol consumption day 1	6.2	2.5	53	5.7	2.2	58	NS
	Cocodamol consumption day 2	6	2.8	53	6	2.3	58	NS
	Cocodamol consumption day 3	6.6	2.5	53	5.9	2.5	58	NS
	Cocodamol consumption day 4	6	2.6	53	5.8	2.4	58	NS
	Cocodamol consumption day 5	6.5	2.5	53	5.9	2.7	58	NS
	Cocodamol consumption day 6	6.1	2.7	53	5.6	2.7	58	NS
	Cocodamol consumption day 7	5.5	3.1	53	5.4	2.9	58	NS
	Cocodamol consumption day 8	5.2	3.2	53	5	2.8	58	NS
	Cocodamol consumption day 9	4.7	3.2	53	4.5	2.8	58	NS
	Cocodamol consumption day 10	3.9	3.1	53	3.6	2.7	58	NS
	Cocodamol consumption day 11	3	3.1	53	2.7	2.8	58	NS
	Cocodamol consumption day 12	2.5	3.1	53	2.2	2.6	58	NS
	Cocodamol consumption day 13	2.2	2.9	53	1.7	2.4	58	NS
	Cocodamol consumption day 14	1.7	2.8	53	1.2	2.1	58	NS
	Cocodamol consumption day total	65.8	NR	53	61.2	NR	58	NS
	Diclofenac consumption day 1	2.4	1	53	2.2	1	58	NS
	Diclofenac consumption day 2	2.5	1.1	53	2.6	0.9	58	NS
	Diclofenac consumption day 3	2.6	0.8	53	2.5	0.9	58	NS
	Diclofenac consumption day 4	2.6	0.9	53	2.6	0.8	58	NS
	Diclofenac consumption day 5	2.6	0.9	53	2.7	0.7	58	NS
	Diclofenac consumption day 6	2.5	1	53	2.5	1	58	NS
	Diclofenac consumption day 7	2.2	1.2	53	2.4	1	58	NS
	Diclofenac consumption day 8	1.9	1.3	53	2	1.2	58	NS
	Diclofenac consumption day 9	1.6	1.3	53	1.8	1.2	58	NS

	Diclofenac consumption day 10	1.2	1.3	53	1.5	1.3	58	NS
	Diclofenac consumption day 11	0.8	1.2	53	0.9	1.2	58	NS
	Diclofenac consumption day 12	0.5	1.1	53	0.7	1.1	58	NS
	Diclofenac consumption day 13	0.5	1	53	0.5	0.9	58	NS
	Diclofenac consumption day 14	0.4	1	53	0.4	0.9	58	NS
	Diclofenac consumption day total	24.2	NR	53	25.3	NR	58	NS
	Other							
	Return to work (median) (days)	> 14 in both groups (range 4 to > 14)						NS
	Return to normal swallowing (median) (days)	13	NR	53	12	NR	58	NS

*Actual p values not reported – reported as either *"no significant differences"* or *"p<0.05"*

Abbreviations: mg: milligrams; mm: millimetres; n: number; NS: no significant difference; SD: standard deviation; VAS: visual analogue scale

Homeopathy data extraction form: Saha et al. 2013

Reference: Saha S, Koley M, Hossain SI, Mundle M, Ghosh S, Nag G, et al. Individualized homoeopathy versus placebo in essential hypertension: A double-blind randomized controlled trial. Indian Journal of Research in Homoeopathy 2013, 7:62-71.

Study design: Randomised controlled trial.

Source of funds: *"Nil."*
Conflicts of interest: *"None declared."*

Participants and setting

Setting: The Outpatient Clinic for hypertensive patients at the Mahesh Bhattacharya Homoeopathy Medical College and Hospital, Howrah, West Bengal, India, between April 2011 and February 2012.
Inclusion criteria: Patients 1) suffering from essential hypertension (pre-hypertensive: SBP 120-139 mm Hg, DBP 80-89 mm Hg, stage I hypertensive: SBP 140-159 mm Hg, DBP 90-99 mm Hg; and stage II hypertensive: SBP ≥60 mm Hg, DBP ≥100 mm Hg); 2) aged 18 to 65 years; 3) of both sexes; 4) with at least a 6 month history of suffering; 5) whose history, examination, and routine investigations revealed no evidence of obvious secondary causes; and 6) giving written informed consent.
Exclusion criteria: Diagnosis or findings from history uncertain; physical exam/routine investigations produced suspicion of a secondary cause of hypertension; diagnosed cases of secondary hypertension; anti-hypertensive therapy for at least six months; malignant hypertension (SBP >200 mm Hg and DBP >140 mm Hg) with clinical features of hypertensive encephalopathy, cardiac decompensation, and rapidly declining renal function; isolated systolic hypertension; labile hypertension; not strictly conforming to the criteria given by the Joint National Committee; presence of severe concomitant disease; failure of vital organs/systems; presence of systemic or infectious diseases; immunocompromised cases; diagnosed cases of developmental defects or congenital abnormalities; pregnant patients or those breastfeeding or likely to become pregnancy; patients with a history of drug/alcohol abuse.

Intervention

Homeopathy: Individualised homeopathy: a range of homeopathic potencies were used as per the requirement, decided by the treating physicians. Each dose, administered orally (in centesimal potencies) consisted of a single drop of medicine in 83.1% ethanol in 10 mL distilled water and was served in an amber-coloured glass vial; these were directed to be taken once daily. For 50 millesimal potencies, a single medicated globule was dissolved in 60 mL distilled water with 2 drops of 83.1% ethanol, divided into 10 equal doses; each dose was directed to be taken after 10 equal downward strokes into half a cup of normal water, from which a single teaspoon was to be taken and the rest discarded.
Total number randomised: n=70

<u>Comparison</u> **Control:** Placebo (identical in appearance) served in identical amber-coloured glass vials, administered as above. **Total number randomised: n=80**				
Outcomes: Changes in SBP and/or DBP at 3 months and 6 months (lowering of SBP by a minimum of 15 mm Hg and DBP by a minimum of 6 mm Hg was considered 'improved'); any adverse events.				
Very brief summary of <u>study authors'</u> main findings/conclusions: *"Finally our data suggest that individualized homoeopathy treatment may have significantly beneficial effects different from placebo in patients suffering from essential hypertension."*				
Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	A coin-toss method was used.
Allocation concealment *(selection bias)*	☒	☐	☐	*"Randomization codes ('h' = heads, 't' = tail) were mentioned on the prescription of each participant by the treating physicians and were sent to the pharmacist. The pharmacist was instructed to serve either medicine or placebo to the groups as per the mentioned codes on the prescription."*
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	Trial was *"double-blind"* (participants; treating physicians and outcome assessors) with the pharmacist allocating treatment as per the patients 'code'). Blinding was checked during the trial by asking the patients in which group they believed they were in.
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	Outcome assessor was blinded.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	There were 18/150 (12%) dropouts/discontinuations: 6/70 in the homeopathy group (self-withdrawal: 2; irregular: 3; hepatitis: 1); and 12/80 in the placebo group (self-withdrawal: 8; irregular: 3; deterioration: 1). Therefore 64 analysed in homeopathy group; 68 in control group). *"Missing values were calculated by the maximum likelihood method of estimation of the lambda parameter of normal distribution."*
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	While the trial registration number is reported, on searching, the trial appears to have been retrospectively registered outcome data not reported for some of the secondary outcomes

				detailed in the trial registration (1. Clinical improvement in symptom scores; 2. Halt of the disease progress and complications 3. Prevention of relapse); and the trial registration notes that: "*the protocol needed amendments and the study was terminated prematurely"*; however no information about protocol amendments or that the trial was terminated previously, was provided in the published trial manuscript.
Other bias	☐	☐	☒	Baseline demographic, clinical and pathological-biochemical data were presented, and characteristics were similar between groups (only significant difference was in weight, with the homeopathy group on average ~ 0.5 kg heavier). Insufficient information to determine other important sources of bias.
Notes				

	Outcome measures (dichotomous)	Total number of participants in study = 150				
		Intervention group Total no. in group = 70		**Control group** Total no. in group = 80		
		Events	**Total**	**Events**	**Total**	**P value**
	Primary					
	BP improved at 6 months (lowering of SBP by a minimum of 15 mm Hg and DBP by a minimum of 6 mm Hg was considered 'improved')	54	64	9	68	0.000
	Secondary					
	Serious adverse events (*"a single case of hepatitis in the verum group and one case of deterioration of condition in control group; however, those cannot be attributed to causality."*)	1	64	1	68	NR
	"Mild-to-moderate homoeopathic aggravation, as per homoeopathic principles, was observed."	Unclear	64	NA	NA	NA

	Outcome measures (continuous)	Total number of participants in study = 150						
		Intervention group Total no. in group = 70			**Control group** Total no. in group = **80**			
		Mean	**95% CI**	**Total**	**Mean**	**95% CI**	**Total**	**P value**
	Primary							
	SBP change at 3 months (mm Hg)	-16.6	-9.9, -23.3	64	2.2	-7.2, 2.8	68	0.0001*

	SBP change at 6 months (mm Hg)	-26.6	-21.5, -31.7	64	3.6	-8.7, 1.5	68	
	DBP change at 3 months (mm Hg)	-7.3	-4.1, -10.5	64	1.6	-3.6, 0.4	68	0.0001*
	DBP change at 6 months (mm Hg)	-11.8	-9.2, -14.4	64	1.6	-3.6, 0.4	68	
	(Post-hoc independent t test)							
	SBP at 3 months (mm Hg)	145.1	19.0	64	162.9	15.3	68	0.001
	SBP at 6 months (mm Hg)	135.1	18.3	64	164.3	15.8	68	0.001
	DBP at 3 months (mm Hg)	92.8	8.5	64	100.1	6.1	68	0.001
	DBP at 6 months (mm Hg)	88.3	6.7	64	100.1	5.8	68	0.001

**"Repeated measures ANOVA was performed comparing data obtained at baseline, at 3 months and 6 months which also revealed significant difference between the two groups both in SBP [F=77.2]; and DBP[F=63.2]; P=0.0001."*

Abbreviations: BP: blood pressure; CI: confidence interval; DBP: diastolic blood pressure; kg: kilograms; mL: millilitres; mm: millimetres; mm Hg: millimetres of mercury; NA: not applicable; SBP: systolic blood pressure

Homeopathy data extraction form: Saruggia and Corghi 1992

Reference: Saruggia M, Corghi E. Effects of homoeopathic dilutions of China rubra on intradialytic symptomatology in patients treated with chronic haemodialysis. British Homoeopathic Journal 1992, 81(2):86-88.				
Study design: Randomised controlled trial (crossover trial).				
Source of funds: Not stated. **Conflicts of interest:** Not stated.				
Participants and setting **Setting:** Italy. **Inclusion criteria:** Patients with end-stage renal failure on chronic haemodialysis treatment (three times per week). Patients were aged 18 to 76 years; 17 males and 18 females. **Exclusion criteria:**				
Intervention **Homeopathy:** Cinchona rubra (China) in homeopathic dilutions; 3 lactose granules of China ruba 9 CH on waking and in the evening, for two weeks. **Total number randomised: n=unclear** (crossover trial so assumed all 35 patients received treatment; during stage 2 or stage 3)				
Comparison **Control:** Placebo (same regimen as homeopathy group). *"The active and placebo treatments were indistinguishable."* **Total number randomised: n=unclear** (crossover trial so assumed all 35 patients received placebo; during stage 2 or stage 3)				
Outcomes: Symptoms (assessed by questionnaire: nausea, vomiting, headache, asthenia, muscle cramps).				
Very brief summary of study authors' main findings/conclusions: *"Statistically significant improvements of asthenia, lethargy and headache were detected on active treatment compared to placebo. There was no significant change in nausea and vomiting."*				
Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	

Random sequence generation *(selection bias)*	☐	☐	☒	After an initial run-in phase the patients were *"randomized into two double-blind groups."*
Allocation concealment *(selection bias)*	☐	☐	☒	As above; no further details provided.
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	Trial described as *"double-blind"* with the use of a placebo.
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	Patients were the outcome assessors (symptom questionnaire).
Incomplete outcome data *(attrition bias)*	☐	☐	☒	Data are presented for 819 questionnaires; 21 were not returned or were not valid. Unclear from which groups
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	For the symptoms, the results have been presented according to the *"819 valid questionnaires"* received from the 35 patients. Unclear how the symptoms were scored and whether the values presented are means, and no measures of variance presented. Muscle cramps were pre-specified as a symptom to be assessed; however no data were reported for this symptom.
Other bias	☐	☒	☐	Insufficient information to determine other risk of bias; no baseline characteristics presented. No 'wash-out period' described, and thus the trial is at high risk of a carry-over effect.
Notes				

	Outcome measures (continuous)	Total number of participants in study = 35						
		Intervention group Total no. in group = unclear			**Control group** Total no. in group = unclear			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Nausea	1.90	NR	NR	2.00	NR	NR	0.26*
	Vomiting	1.94	NR	NR	2.09	NR	NR	0.37*
	Headache	1.80	NR	NR	2.04	NR	NR	0.03*; 0.02^
	Lethargy	1.64	NR	NR	2.29	NR	NR	0.003*; 0.013^
	Asthenia	1.49	NR	NR	2.28	NR	NR	0.0001*; 0.0005^

*Friedmann's test p value (comparing run-in with treatment and placebo)

^Wilcoxon's rank sum test p value (comparing treatment with placebo)

Abbreviations: n: number; NR: not reported; SD: standard deviation

Homeopathy data extraction form: Schmidt 1996

Reference: Schmidt C A. Double blind, placebo-controlled trial: arnica montana applied topically to subcutaneous mechanical injuries. Journal of the American Institute of Homeopathy 1996, 89(4):186-193.				
Study design: Randomised controlled trial				
Source of funds: Not stated. **Conflicts of interest:** Not stated.				
Participants and setting **Setting:** *"Two trials were conducted, each at the end of an annual running race in Central Park, New York City…"* **Inclusion criteria:** *""holiday runners" who were not accustomed to running and who were clearly tires and sore after the 3.5 mile race… the vast majority of subjects in our trial consisted of such special-occasion runners… Subjects were accepted among any person acknowledging muscle soreness attributed to the race or anticipating muscle soreness due to the same."* **Exclusion criteria:**				
Intervention 1 **Homeopathy:** Arnica montana 6C administered in the form of petroleum jelly. Subjects were given a ¼ teaspoon of the treatment in a disposable plastic package. Written and verbal instructions were provided to apply the ointment immediately to the sorest area on the exposed skin; to not apply to broken skin; and to not take other remedies for at least one hour. **Total number randomised: n=unclear randomised, n=46 analysed** **Intervention** **Homeopathy:** Arnica montana 1X administered in the form of petroleum jelly. As above. **Total number randomised: n=unclear randomised, n=44 analysed**				
Comparison **Control:** Placebo (petroleum jelly). As above. **Total number randomised: n=unclear randomised, n=51 analysed**				
Outcomes: *"How would you rate the condition of your injury after using the ointment"* (0 = no improvement; 10 = complete improvement in the condition of muscle)				
Very brief summary of study authors' main findings/conclusions: *"Both potencies of Arnica showed results clearly superior to that of the placebo under test conditions."*				
Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☐	☒	No information provided.
Allocation concealment *(selection bias)*	☐	☐	☒	Subjects were given a plastic package marked with one of 3 letters coded to the 3 groups. No further information provided.
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	*"To maintain objectivity and a true double-blind standard the master researcher who assigned the code was not present for either of the races and did not participate in the follow-up... and did not participate in any way in this project other than the coding of the ointments."*

Blinding of outcome assessment *(detection bias)*	☒	☐	☐	As above. Participant assessment of outcomes.
Incomplete outcome data *(attrition bias)*	☐	☒	☐	There were 337 subjects to follow up; 141 (42%) were able to be contacted who had used the ointment and followed the research protocol: *"The information of subjects not contacted within 72 hours was discarded."* Reasons for losses/exclusions were not reported by group, but included: failed telephone communication; lost ointment; lack of need/desire to use ointment; distaste and/or disgust for aesthetically unsatisfying ointment; forgetting to use ointment.
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	The only outcome reported was the patients' subjective assessment of the condition of injury after using the ointment on a scale of 0-10.
Other bias	☐	☒	☐	No assessment of baseline characteristics: runners were not screened for 'usual level of physical activity'; *"In general the first runners to finish the race walked comfortably past our research team uninterested in our offers."* Additional differences in the treatment of patients according to group: pairs of researchers distributed one kind of treatment each and gave information to and gathered information from these subjects. The authors state that *"Two different trials"* were conducted but that the results are not reported separately because the race days were *"identical in many ways."*
Notes				

	Outcome measures (continuous)	Total number of participants in study = 337 (141 analysed)									
		Arnica 1X group Total no. in group = 44			**Arnica 6C group** Total no. in group = 46			**Control group** Total no. in group = 51			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Primary										
	Condition of injury after treatment (0-10 scale)	6.22	2.66	44	5.23	2.94	46	2.57	3.71	51	*

**"Both potencies of Arnica showed results clearly superior to that of the placebo under test conditions."*

Abbreviations: n: number; SD: standard deviation

Homeopathy data extraction form: Sencer et al. 2012

Reference: Sencer SF, Zhou T, Freedman LS, Ives JA, Chen Z, Wall D, et al. Traumeel S in preventing and treating mucositis in young patients undergoing SCT: a report of the Children's Oncology Group. Bone Marrow Transplant 2012, 47:1409-1414.				
Study design: Randomised controlled trial				
Source of funds: *"This research is supported by the CCOP Grant… Chair's Grant… and the Statistics and Data Center Grant… of the Children's Oncology Group from the National Cancer Institute, National Institutes of Health, Bethesda, MD, USA."* **Conflicts of interest:** *"Drs. Ives and Oberbaum previously had consulting relationships with Heel Incorporated, but currently none of the authors have any financial relationships with HEEL or any other conflicts."*				
Participants and setting **Setting:** Somewhat unclear – reports *"April 2004 to December 2006 at 1 out of 28 COG member institutions and at 2 Israeli institutions"* however later reports *"of the 28 participating centers…"* **Inclusion criteria:** 3-25 year olds undergoing myeloablative HSCT, allogenic or autologous for malignant and non-malignant conditions. **Exclusion criteria:** Patients receiving a non-myeloablative HSCT, those taking glutamine or vancomycin oral paste, and any individuals allergic or sensitive to Echinacea were excluded.				
Intervention **Homeopathy:** Traumeel (complex homeopathy remedy containing 14 medicinal plants and minerals in very low concentrations) in 2.2 mL glass ampoules. Treatment began on the day before transplant and ended when patients met completion criteria or not later than the 20th day after transplant. Five times a day, a pharmacist drew the contents of the ampoules into an oral syringe; patients were instructed to rinse the mouth vigorously with the study medication, retain it for 30 second and then swallow. Patients were instructed not to eat/drink for 30 min after each dose. **Total number randomised: n=99 randomised, n=98 analysed**				
Comparison **Control:** Placebo (normal saline) (identical in appearance and taste). **Total number randomised: n=96 randomised, n=92 analysed**				
Outcomes: Main outcome: sum of modified Walsh scored for mucositis (scored daily from day -1 to 20 day after HCST) (assessed as AUC). Other outcomes: 5-grade WHO oral-toxicity scale; amount of narcotic equivalents used per day; days of total parenteral feeding; days of nasogastric feeding; adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events v. 3.0; mortality up to 30 days after termination of protocol therapy; venocclusive disease of the liver; acute GVHD and invasive infection within 100 days post-transplant.				
Very brief summary of study authors' main findings/conclusions: *"We could not confirm that Traumeel is an effective treatment for mucositis in children undergoing HSCT."*				
Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	Block randomisation with stratification.
Allocation concealment *(selection bias)*	☒	☐	☐	The study medications were identified by serial number only. The code was kept by Heel (the drug company) and the COG statistician. Patient allocation was communicated to

				McKesson Bioservices Corporation who dispensed the study drug.
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	Blinded with the use of an identical placebo.
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	As above.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	195 patients randomised; 5 were 'ineligible' (1 in Traumeel group did not start the study; 4 in placebo group: 2 took glutamine; 1 did not received myeloablation; 1 not clear). For 106/190 (56%) patients there was full data (Walsh score on 22 days); 35/190 (18%) had 4 or fewer missing scores, 24/190 (13%) had 5-10 missing scores, 25/190 (13%) had more than 11 score missing, 9/190 (5%) has no follow-up data. The 9 patients with no follow-up data were excluded from analyses (4 in Traumeel group; 5 in placebo group). Missing follow-up data were imputer by linear interpolation when 3 consecutive days or less were missing; *"other missing scores were imputed randomly 10 times from scores of similar patients with complete data, and the method of multiple imputation was applied to the 10 full data sets so created."* For some outcome, denominators were not clear; for others they varied without sufficient explanation for missing data/exclusions.
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	Insufficient information to determine risk of reporting bias (i.e. no access to trial protocol/registration).
Other bias	☐	☐	☒	Baseline characteristics similar between groups, however there was an indication of more males and fewer females in the placebo group (p: 0.06). Authors note in their Discussion potential confounding factors, such as differences across study sites in how the medication was administered; variation between institutions in who was completing the daily forms etc.
Notes				

	Outcome measures (dichotomous)	Total number of participants in study = 195 (5 not eligible = 190)				
		Intervention group Total no. in group = 98		**Control group** Total no. in group = 92		
		Events	**Total**	**Events**	**Total**	**P value**
	Secondary					
	Patients with nasogastric feeding	11	98	9	92	0.75
	Mortality proportion to 31 days after termination of protocol therapy	17	98	13	92	0.54
	Venocclusive disease of the liver	5	86	4	76	0.88
	Acute GVHD	18	86	14	76	0.69
	Adverse events: gastrointestinal	14	98	17	92	0.43
	Adverse events: cardiac	5	98	2	92	0.45
	Adverse events: bleeding	2	98	1	92	0.99
	Adverse events: infection	11	98	8	92	0.56
	Adverse events: pain in lip, mouth, joint or back	8	98	4	92	0.63

	Outcome measures (continuous)	Total number of participants in study = 195 (5 not eligible = 190)						
		Intervention group Total no. in group = 98			**Control group** Total no. in group = 92			
		Mean*	**SE**	**Total**	**Mean***	**SE**	**Total**	**P value^**
	Primary							
	AUC of Walsh score (all patients)	76.7	5.5	94	67.3	6.3	87	0.13
	AUC of Walsh score (compliant < 30% days)	90.3	12.3	26	67.9	16.3	17	0.18
	AUC of Walsh score (compliant 30-65% days)	88.4	13.8	13	99.4	18.5	8	0.75
	AUC of Walsh score (compliant 65-99% days)	82.4	9.4	20	81.4	9.9	32	0.66
	AUC of Walsh score (compliant 100% days)	59.4	8.3	35	43.3	9.3	30	0.07
	Secondary							
	AUC of WHO oral mucositis score	24.4	1.80	91	21.6	2.07	80	0.24
	Total doses (in equivalent mg/kg) of morphine	17.7	3.1	NR	28.5	10.9	NR	0.2
	Number of days of total parenteral nutrition	15.3	0.56	NR	15.2	0.65	NR	0.90

*Mean and SE estimated by multiple imputation

^Mann-Whitney test adjusted for multiple imputation

Abbreviations: AUC: area under the curve; COG: Children's Oncology Group; GVHD: graft-versus-host-disease; HSCT: haematopoietic stem cell therapy; min: minutes; mL: millilitres; n: number; NR: not reported; SCT: stem cell therapy; SE: standard error; WHO: World Health Organization

Homeopathy data extraction form: Steinsbekk et al. 2005

Reference: Steinsbekk A, Fønnebø V, Lewith G, Bentzen N. Homeopathic care for the prevention of upper respiratory tract infections in children: a pragmatic, randomized, controlled trial comparing randomized homeopathic care and waiting-list controls. Complementary Therapies in Medicine 2005, 13:231-238.

Study design: Randomised controlled trial.

Source of funds: Norwegian Research Council.
Conflicts of interest: Not stated.

Participants and setting

Setting: Trondheim, Norway. September 2002 to June 2003 and January to June 2004. *"The trial took place in two periods to limit the study to the winter months with a high incidence of URTI: September 2002 to June 2003 and January to June 2004. Patients attending the casualty department were recruited; leaflets were also distributed to local child health centres, and an advertisement placed in the newspaper."*
Inclusion criteria: Children less than 10 years of age who had been to a medical doctor for URTI (how often or the number of episodes were not criteria). URTI was defined as having a health problem to which the consulting doctor gave an International Classification of Primary Care code of H01 (ear pain), H71 (acute otitis media), H72 (glue ear), H74 (chronic otitis media), R72 (streptococcal infection), R74 (URTI), R75 (sinusitis) or R76 (tonsillitis).
Exclusion criteria: Concomitant serious disease or daily use of medicines such as antibiotics, steroids (except for inhalators) and cytotoxic agents, use of homeopathic medicines in the 3 months.

Intervention

Homeopathy: Children were offered an immediate appointment with a homeopath and asked to fill in symptom diaries for 12 weeks. Children were allocated sequentially to one of 5 homeopaths (three worked in a centre with other homeopaths, 2 were in sole practice; 1 was male, 4 were female, with experience ranging from 2-27 years). The homeopaths made an independent choice of medication and could prescribe any homeopathic medicine(s) at any potency. The medicine was posted to the patient from a homeopathic dispensary; parents were told they could contact the study team if they had any questions, to minimise interactions. All participants were informed that they could use any other treatment of their own choice except any form of homeopathic medication, and that they should seek help from their general practitioner as needed.
Total number randomised: n=82 randomised, n=68 analysed

Comparison

Control: Children randomised to a waiting list group as a control were told they would get an appointment after filling out their symptom diary for 12 weeks.
Total number randomised: n=87 randomised, n=74 analysed

Outcomes: Primary outcome: median total symptom score for URTI during the 12 weeks. Patient diaries were used (completed by the child's parents); the daily diary asked: whether the child had been ill with URTI; had other illness; used antibiotics; used analgesic/antipyretic drugs; visited a medical doctor; whether someone had been absent from work due to child's illness; whether child had taken the homeopathic medicines. On the days the child was ill with URTI, the parents filled in a separate symptom diary (nine symptoms could be recorded, with a daily possible total score ranging from 0-11; the total symptom score was the sum of scores for each day). Parents were asked if there were noises coming from the chest.

Very brief summary of study authors' main findings/conclusions: *"In this study, there was a clinically relevant effect of individualised homeopathic care in the prevention of URTI in children."*

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	Quote*: "computer-generated randomisation with stratification for three age groups (0 < 3, 3 < 6 and 6 <*

				10 years) in blocks whose size was concealed."
Allocation concealment *(selection bias)*	☒	☐	☐	Randomisation was by telephone/fax to an independent trial service office.
Blinding of participants and personnel *(performance bias)*	☐	☒	☐	Trial was *"open,"* with no blinding.
Blinding of outcome assessment *(detection bias)*	☐	☒	☐	As above.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	27 (16%) patients either did not return any data (diary) or withdrew after random allocation (14/82 (17%) in homeopathic care group and 13/87 (15%) in control group), leaving 68 in the homeopathic care group and 74 in the waiting-list control. 9 patients in the homeopathic care group and 2 in the control group were lost to follow up, and did not return data for the whole study *("Those lost to follow-up in both groups tended to have higher symptoms scores and more days with URTI than those who completed the study, although this was not statistically significant when missing values were replaced with the mean for the period they had participated.")*
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	Insufficient information to permit judgement of 'High' or 'Low' risk.
Other bias	☐	☐	☒	The groups were comparable at baseline for demographic variables and health history. Of 193 patients who returned consent forms, 169 were randomised (after they returned the initial questionnaire); those who did not start the study were older (no other differences were reported).
Notes	*"All participants were informed that they could use any other treatment of their own choice except any form of homeopathic medication, and that they should seek help from their general practitioner as needed."*			

	Outcome measures (dichotomous)	Total number of participants in study = 169 were randomised, 142 analysed				
		Intervention group Total no. in group = 82 (68 analysed)		**Control group** Total no. in group = 87 (74 analysed)		
		Events	**Total**	**Events**	**Total**	**P value**
	Secondary					
	Had days with URTI	54	68	69	74	0.016

	Had days with other illness	34	68	34	74	0.629
	Used antibiotics	9	68	12	74	0.617
	Used analgesic/antipyretic	28	68	32	74	0.803
	Consulted a medical doctor	19	68	26	74	0.357
	Had parents with work absence when ill	25	68	33	74	0.343
	Adverse effects	15 (22.1%) of patients in the homeopathic care group self-reported adverse effects; all were mild and transient				

	Outcome measures (continuous)	Total number of participants in study = 169 were randomised, 142 analysed						
		Intervention group Total no. in group = 82 (68 analysed)			**Control group** Total no. in group = 87 (74 analysed)			
		Median	**95% CI**	**Total**	**Median**	**95% CI**	**Total**	**P value**
	Primary							
	Total symptom score	24	11.4, 35.6	68	44	32.1, 60.8	74	0.026
	Secondary							
	Days with URTI	8	4, 11.6	68	13	9.1, 15	74	0.006
	Days with antibiotic	0	0, 0	68	0	0, 0	74	0.611
	Days with analgesic/antipyretic	0	0, 1	68	0	0, 1	74	0.728
	Visits to medical doctor	0	0, 0	68	0	0, 0	74	0.531
	Days with other illness	0.5	0, 2	68	0	0, 1	74	0.865
	Days with noises from chest	0	0, 1	68	0	0, 3	74	0.189
	Days with work absence due to ill child	0	0, 0	68	0	0, 1	74	0.177

Abbreviations: CI: confidence interval; n: number; URTI: upper respiratory tract infection

Homeopathy data extraction form: Taylor and Jacobs 2011

Reference: Taylor JA, Jacobs J. Homeopathic ear drops as an adjunct to standard therapy in children with acute otitis media. Homeopathy 2011, 100:109-115.
Study design: Randomised controlled trial
Source of funds: The study was funded by the Standard Homeopathic Company, Los Angeles, California. *"The sponsor modified and approved the study protocol. The sponsor had no role in the collection, analysis and interpretation of the data or in wiring the manuscript."* **Conflicts of interest:** *"One author (JJ) has been a paid consultant for the study sponsor."*
Participants and setting **Setting:** The University of Washington Medical Center Pediatric Care Center, February 2008 to February 2009. **Inclusion criteria:** Children 6 months to 11 years old diagnosed with AOM; with distinctly abnormal tympanic membrane(s) with significant discomfort related to AOM; with an otoscopy scale score of ≥ 4; with parents who indicated that the symptom severity on the faces scale (AOM-FS) was 4 or greater (corresponding to a 'moderate problem' or more). **Exclusion criteria:** Children with a chronic medical condition, who had received antibiotics within the previous 2 days, had a diagnosis of AOM during the preceding 30 days, or who had a perforated tympanic membrane were

excluded. Children who had received any homeopathic medicine during the previous 30 days were not enrolled.

Intervention

Homeopathic ear drop solution in addition to standard care: Parents of children randomised to the ear drops were instructed to administer 3 to 4 homeopathic ear drops up to 3 times per day as needed for relief of AOM symptoms for a maximum of 5 days. The homeopathic ear drops (Hylands Earache Drops) were commercially available in the United States and contained a combination of six homeopathic remedies: Pulsatilla, Chamomilla, Sulphur, Calcarea carbonica, Belladonna, and Lycopodium, all in the 30c potency.

Total number randomised: n=59 randomised*, n=44 analysed

*Note: 120 children were randomised in total, however 1 child was excluded for being too old (not reported from which group the child was excluded)

Comparison

Standard care: *"the examining provider determined the appropriate treatment for the patient. This included an immediate prescription for an oral antibiotic, or a delayed antibiotic prescription, as well as treatments for otalgia such as acetaminophen, ibuprofen, or topical benzocaine ear drops. These treatments, solely determined by the examining provider based on the clinical presentation, constituted standard therapy."*

Total number randomised: n=60 randomised*, n=50 analysed

*Note: 120 children were randomised in total, however 1 child was excluded for being too old (not reported from which group the child was excluded)

Outcomes: Primary outcomes: ETG-5 scores (ear treatment group symptom questionnaire) (at each assessment, 1-10), occurrence of adverse events. Secondary outcomes: AOM-FS scores at each assessment 1-10; use of medications to treat symptoms of AOM; return visits to heath care providers; FSIIR (functional status II-revised scale) scores (at 12-15 day follow up).

Very brief summary of study authors' main findings/conclusions: *"This study suggests that homeopathic ear drops were moderately effective in treating otalgia in children with AOM and may be most effective in the early period after a diagnosis of AOM. Pediatricians and other primary health care providers should consider homeopathic ear drops a useful adjunct to standard therapy."*

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	*"Group assignment (ear drops or standard therapy alone) was determined by use of a computer generated randomization schedule. Randomization was stratified by antibiotic treatment plan (immediate or delayed therapy) and in blocks of 4."*
Allocation concealment *(selection bias)*	☐	☐	☒	Not described.
Blinding of participants and personnel *(performance bias)*	☐	☒	☐	No blinding; placebo would have been feasible.
Blinding of outcome assessment *(detection bias)*	☐	☒	☐	No blinding (subjective outcomes assessed by parents).
Incomplete outcome data *(attrition bias)*	☐	☐	☒	Of the 120 children randomised, 1 was excluded for being *"too old, inadvertently enrolled".* 59 were allocated to homeopathy, 60 to standard care. Symptom diaries were

				available for 75% (44/59) of the homeopathy group and 83% (50/60) of the standard care group. 95% (56/59) of the homeopathy group and 95% (57/60) of the standard care group completed the 12-15 day follow up. Children whose parents returned diaries were significantly less likely to live in a household with a cigarette smoker and more likely to have a mother who was a college graduate. For ETG-5 scores and AOM-FS scores numbers per group for each assessment not detailed (only total number across groups).
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	No access to a trial protocol to assess selective reporting. Only means (no standard deviations) reported for ETG-5 and AOM-FS scores. Data for use of symptomatic medications only reported on day 3, when 'significant' difference between groups observed.
Other bias	☐	☐	☒	Baseline characteristics were only reported for participants who returned symptom diaries. Though randomisation was stratified by antibiotic plan, 90/120 children received immediate antibiotic prescriptions; 30/120 received a delayed antibiotic prescription.
Notes				

	Outcome measures (dichotomous)	Total number of participants in study = 119				
		Intervention group Total no. in group = 44		**Control group** Total no. in group = 50		
		Events	**Total**	**Events**	**Total**	**P value**
	Primary					
	Adverse events – vomiting	5	44	10	50	0.25
	Adverse events – rash	3	44	5	50	0.58
	Adverse events – diarrhoea	3	44	12	50	0.02
	Adverse events – hyper behaviour	3	44	11	50	0.04
	Adverse events – headache	7	44	6	50	0.58
	Adverse events – lethargy	13	44	15	50	0.96
	Adverse events – other symptom	19	44	22	50	0.94
	Secondary					
	Use of symptomatic medications (acetaminophen, ibuprofen, topical benzocaine) on day 3	4	44	14	50	0.02
	Use of symptomatic medications on	*"No other statistically significant differences were noted"*				

	other days (up to 5 days)					
	One or more return visit to healthcare provider at 12-15 day follow up	13	56	8	57	0.21
	Prescriptions filled at 12-15 days (for patients whose provider had recommended delayed antibiotic approach)	1	14	5	14	0.17
	Side effects	One or more side effects (pain, crying, irritability, itchiness, redness, diarrhoea) noted after 11.1% (22/198) doses in 18.1% (8/44) children in the homeopathy group				

	Outcome measures (continuous)	Total number of participants in study = 119						
		Intervention group Total no. in group = 59			**Control group** Total no. in group = 60			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Primary							
	ETG-5 score at assessment 1	14.2	NR	*	16.5	NR	*	0.19
	ETG-5 score at assessment 2	10.5	NR	*	14.1	NR	*	0.04
	ETG-5 score at assessment 3	6.1	NR	*	10.8	NR	*	0.003
	ETG-5 score at assessment 4	6.7	NR	*	8.7	NR	*	0.35
	ETG-5 score at assessment 5	6.1	NR	*	7.0	NR	*	0.91
	ETG-5 score at assessment 6	2.5	NR	*	7.3	NR	*	0.46
	ETG-5 score at assessment 7	3.8	NR	*	5.8	NR	*	0.25
	ETG-5 score at assessment 8	3.3	NR	*	3.7	NR	*	0.83
	ETG-5 score at assessment 9	2.8	NR	*	3.7	NR	*	0.24
	ETG-5 score at assessment 10	2.3	NR	*	3.4	NR	*	0.36
	Secondary							
	AOM-FS score at assessment 1	4.0	NR	*	4.3	NR	*	0.43
	AOM-FS score at assessment 2	3.4	NR	*	3.6	NR	*	0.28
	AOM-FS score at assessment 3	2.7	NR	*	3.0	NR	*	0.31
	AOM-FS score at assessment 4	2.5	NR	*	2.8	NR	*	0.31
	AOM-FS score at assessment 5	2.4	NR	*	2.4	NR	*	0.82
	AOM-FS score at assessment 6	2.1	NR	*	2.3	NR	*	0.67
	AOM-FS score at assessment 7	1.9	NR	*	2.1	NR	*	0.62
	AOM-FS score at assessment 8	1.7	NR	*	1.9	NR	*	0.73
	AOM-FS score at assessment 9	1.7	NR	*	1.7	NR	*	0.84
	AOM-FS score at assessment 10	1.5	NR	*	1.3	NR	*	0.97
	FSII scores at 12-15 day follow up	81.4	NR	56	81.5	NR	57	0.97

*Numbers at each assessment (1-10) were reported in Table 2 (for ETG-5 scores) and Table 3 (for AOM-FS scores) of the manuscript as a total across both groups only

Abbreviations: AOM: acute otitis media; AOM-FS: Acute Otitis Media-Faces Scale*;* ETG-5*:* ear treatment group symptom questionnaire; FSIIR: functional status II revised scale; n: number; NR: not reported; SD: standard deviation

Homeopathy data extraction form: Totonchi and Guyuron 2007

Reference: Totonchi A, Guyuron B. A randomized, controlled comparison between arnica and steroids in the

management of postrhinoplasty ecchymosis and edema. Plastic and Reconstructive Surgery 2007, 120(1):271-274

Study design: Randomised controlled trial

Source of funds: Not stated.
Conflicts of interest: *"The authors have no financial interest or commercial affiliation with any product, devise or drug mentioned in this article."*

Participants and setting
Setting:
Inclusion criteria: Patients who had undergone a primary rhinoplasty with osteotomy (male or female; from 15 to 65 years).
Exclusion criteria: None stated.

Intervention 1
Homeopathy: Arnica 3 times a day for 4 days.
Total number randomised: n=unclear
Intervention 2
Corticosteroids: 10 mg intravenous dexamethasone intra-operatively followed by a 6 day oral tapering dose of methyl-prednisone.
Total number randomised: n=unclear

Comparison
Control: No treatment.
Total number randomised: n=unclear

Outcomes: Extent of ecchymosis (0-5); colour density of ecchymosis (0-4); severity of ecchymosis (0-3).

Very brief summary of study authors' main findings/conclusions: *"We conclude from this study that both arnica and corticosteroids are efficacious in significantly reducing postrhinoplasty edema within 2 days after surgery, with its resolution within 8 days. However, the trend (p = 0.06) for increased ecchymosis on day 2 and a delay in its resolution after administration of corticosteroids renders the benefits of corticosteroids questionable."*

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☐	☒	*"Patients were randomized into three groups."* No further detail provided.
Allocation concealment *(selection bias)*	☐	☐	☒	Not detailed.
Blinding of participants and personnel *(performance bias)*	☐	☒	☐	No blinding (control group received no treatment, and arnica and dexamethasone given according to different regimens).
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	Digital photographs were obtained on post-operative days 2 and 8 and were reviewed by 3 blind panellists.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	Insufficient information to determine risk of attrition bias.
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	Numbers randomised to each of the 3 groups not reported; for the outcomes, only means are reported (i.e. no standard deviations).
Other bias	☐	☐	☒	No baseline characteristics reported. Insufficient information to determine other risk of bias.

Notes	

	Outcome measures (continuous)	Total number of participants in study = 48									
		Homeopathy group Total no. in group = unclear			**Corticosteroid group** Total no. in group = unclear			**Control group** Total no. in group = unclear			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Extent of ecchymosis post-operative day 2	2.90	NR	NR	2.88	NR	NR	3.31	NR	NR	0.19
	Intensity of ecchymosis post-operative day 2	2.06	NR	NR	2.52	NR	NR	2.29	NR	NR	0.06
	Severity of oedema post-operative day 2	1.19	NR	NR	1.02	NR	NR	1.96	NR	NR	<0.0001 (control group significantly higher than other groups)
	Extent of ecchymosis post-operative day 8	1.42	NR	NR	2.73	NR	NR	2.17	NR	NR	<0.05 (corticosteroid group significantly higher than other groups)
	Intensity of ecchymosis post-operative day 8	0.92	NR	NR	1.85	NR	NR	1.02	NR	UK	<0.0 05 (corticosteroid group significantly higher than other groups)
	Severity of oedema post-operative day 8	0.15	NR	NR	0.08	NR	NR	0.25	NR	NR	0.25
	Difference in extent of ecchymosis from post-operative day 2 to day 8	1.48	NR	NR	0.56	NR	NR	1.15	NR	NR	<0.05 (homeopathy and control groups significantly higher than corticosteroid group)
	Difference in intensity of ecchymosis from post-operative day 2 to day 8	1.15	NR	NR	0.67	NR	NR	1.27	NR	NR	<0.05 (homeopathy and control groups significantly higher than corticosteroid group)
	Difference in severity of oedema from post-operative day 2 to day 8	1.04	NR	NR	0.94	NR	NR	1.71	NR	NR	<0.0001 (control group significantly higher than treatment groups)

Abbreviations: mg: milligrams; n: number; NR: not reported; SD: standard deviation

Homeopathy data extraction form: Villanueva et al. 2012

Reference: Villanueva DFD, Rodríguez AP, García LRG, Osés CAM. Use of homeopathic formula in malnourished children. International Journal of High Dilution Research 2012, 11(38):25-32.

Study design: Randomised controlled trial

Source of funds: Not detailed.
Conflicts of interest: Not detailed.

Participants and setting
Setting: San Juan Policlinic, Ranchuelo County, Cuba from November 2004 to December 2005.
Inclusion criteria: Malnourished children aged between 1 and 19 years old with a weight-height ratio below the 3rd percentile.
Exclusion criteria: Presence of encephalopathy, malformations, severe mental retardation.

Intervention
Homeopathy: Homeopathic complex (Calcarea fluorica 30 cH, Calcarea carbonica 30 cH, Calcarea phosphorica 30 cH).
Total number randomised: n=50

Comparison
Control: Patients in control and homeopathy group were prescribed a diet adjusted to their age and gender, and a poly-vitamin (1 tablet per day for children older than 9, and half a tablet per day for children younger than 9). No placebo used.
Total number randomised: n=49

Outcomes:

Very brief summary of study authors' main findings/conclusions: *"The homeopathic complex used proved to be effective as adjuvant in the treatment of malnourished children, as shown by the significant proportion of children who shifted from a condition below the 3rd percentile to normal weight in the treated group."*

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	*"The sample was randomly divided into two groups by means of simple random sampling using software Mathcad 14.0."*
Allocation concealment *(selection bias)*	☐	☐	☒	Not detailed.
Blinding of participants and personnel *(performance bias)*	☐	☒	☐	No blinding.
Blinding of outcome assessment *(detection bias)*	☐	☒	☐	No blinding.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	The methods detail exit criteria: *"children who moved to other areas or did not comply with treatment,"* however did not report whether there were any 'exits.'
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	Insufficient information to permit judgement of 'High or 'Low' (i.e. no access to trial protocol/registration); only outcome reported was 'recovery of the normal weight' (10th to 90th percentile).
Other bias	☐	☐	☒	Baseline characteristics were presented for the total population

				(not according to group allocation), apart from age; for age it appeared that there may be more participants age 5-9 and less aged 10 to 14 in the homeopathy group (50% vs. 35% and 18% vs. 37%), however the paper reports: *"There were no significant differences between both groups (data not shown)."*
Notes				

	Outcome measures (dichotomous)	Total number of participants in study = 99				
		Intervention group Total no. in group = 50		**Control group** Total no. in group = 49		
		Events	**Total**	**Events**	**Total**	**P value**
	Recovery to normal weight	42	50	15	49	<0.001
	Recovery to normal weight (age 1-4 years)	9	10	1	11	0.007
	Recovery to normal weight (age 5-9 years)	22	25	4	17	<0.001
	Recovery to normal weight (age 10-14 years)	7	9	9	18	0.035
	Recovery to normal weight (age 15-19 years)	4	6	1	3	0.157

Abbreviations: n: number

Homeopathy data extraction form: Weiser et al. 1998

Reference: Weiser M, Strosser W, Klein P. Homeopathic vs conventional treatment of vertigo: a randomized double-blind controlled clinical study. Archives of Otolaryngology--Head and Neck Surgery 1998, 124(8):879-885.
Study design: Randomised controlled trial (*"confirmative equivalence trial"*)
Source of funds: Not specifically detailed, though: *"The study was conducted by a contract research organization to exclude the possibility of sponsor bias."* **Conflicts of interest:** Not detailed.
Participants and setting **Setting:** 15 study centres (general practices) in Germany between November 1995 and November 1996. **Inclusion criteria:** Acute or chronic vertigo symptoms of various origins (including Meniere disease and vasomotor vertigo), a minimum of 3 vertigo attacks during the week before the study began, and an assessment of intensity of vertigo attacks by the patient between 2 and 4 on a 5-point rating scale. **Exclusion criteria:** Chronic vertigo (longer than 6 months) if specifically treated during the 4 weeks before the study began; vertigo caused by psychovegetative disorders (to avoid possible noncompliance); vertigo caused by a tumour or coffee, tea, tobacco, alcohol or drug abuse; vertigo caused by inflammation from an underlying disease; myocardial infarction within the 6 months before the study began; severe metabolic disease; gastroduodenal ulcer; pheochromocytoma; bronchial asthma. Other concomitant vertigo or antiemetic medication, corticosteroids or antihistamines, migraine medication, psychoactive drugs and vascular drugs were not allowed during the study (7 day wash-out phase before the

study begun).

Intervention

Homeopathy: Homeopathic preparation (Vertigoheel, Heel Inc, Albuquerque, NM) containing ambra grisea D6, anamitra cocculus D4, conium maculatum D3, and petroleum rectificatum D8; and placebo. The patients took 15 drops, 3 times a day of the active drug, plus the corresponding placebo for 42 consecutive days.
Total number randomised: n=59

Comparison

Control: Betahistine hydrochloride (18 mg per day in 3 divided doses) and placebo.
Total number randomised: n=60

Outcomes: Primary outcomes: frequency, duration and intensity of vertigo attacks – assessed at visit 1 (baseline) and for each study day in a diary. The mean daily duration was assessed on a 5-point rating scale, with 0 = 0-2 minutes, 1 = 2-10 minutes, 2 = 11-60 minutes, 3 = 1-6 hours; 4 = more than 6 hours. The mean daily intensity was assessed on another 5-point rating scale (0 = no discomfort, 1 = slight discomfort, 2 = moderate discomfort, 3 = severe discomfort, 4 = very severe discomfort). Secondary outcomes: quality of life (Medical Outcome Study-Short Form 36); severity of vertigo-specific symptoms and general impairment of daily life (questionnaire based on the Neuro-Otologische Daternerfassung Claussen test – a specific anamnestic rating scale for patients with vertigo; scores were transformed to a scale of 0 = maximum number of symptoms, 100 = no symptoms); patients' and investigators' global assessments of efficacy (5-point rating scale; 1 = no complaints; 5 = deterioration); adverse events, clinical laboratory data and vital signs (to assess adverse effects); patients' and investigators' assessment of overall tolerability (1 = excellent; 4 = poor).

Very brief summary of study authors' main findings/conclusions: *"Concerning the main efficacy variable, therapeutic equivalence between the homeopathic remedy and betahistine could be shown with statistical significance (confirmative analysis). Both remedies reduced the frequency, duration, and intensity of vertigo attacks during a 6-week treatment period. Also, vertigo-specific complaints were significantly reduced in both treatment groups."*

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	Computer-generated randomisation list.
Allocation concealment *(selection bias)*	☐	☐	☒	Method(s) not described in sufficient detail.
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	*"Double-blind"* controlled trial. Because of the difference in taste between the homeopathic remedy and betahistine, corresponding placebos were produced to be identical in taste, shape and smell.
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	As above (predominately patient assessed outcomes).
Incomplete outcome data *(attrition bias)*	☐	☐	☒	119 patients (59 in homeopathy group 60 in betahistine group) were randomised. The data for 2 patients were *"inconsistent and not comprehensible and, therefore, were excluded from the study. Major protocol deviations (violations of inclusion or exclusion criteria, compliance, premature study*

				termination because of patient's personal reasons, or unavailable for follow-up) led to the exclusion of 12 patients from analysis intended per protocol analysis." In total, 14 losses/exclusions; 53/59 (homeopathy group) and 52/60 (betahistine group) patients available for analyses – numbers for primary outcomes not specifically reported – assumed 53 and 52.
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	For some secondary outcomes, no outcome data reported, and rather, general statements made in results text: *"Mean relevant changes from baseline were not observed in either treatment group…."* and *"for more than 70% of the patients a significant improvement with absolutely no complaints was reported by the investigators."*
Other bias	☐	☐	☒	Insufficient information to determine other risk of bias. Demographic and anamnestic characteristics that were reported were comparable between groups at baseline.
Notes	Study described as a *"confirmative equivalence trial."*			

	Outcome measures (dichotomous)	Total number of participants in study = 119				
		Intervention group Total no. in group = 59		**Control group** Total no. in group = 60		
		Events	**Total**	**Events**	**Total**	**P value**
	Secondary					
	Worsening of symptoms (investigators' assessments)	0	Unclear*	1	Unclear*	NR
	Worsening of symptoms (patients' assessments)	0	Unclear*	3	Unclear*	NR
	"In both groups, for more than 70% of the patients a significant improvement with absolutely no complaints was reported by the investigators."					
	"Fifty-seven adverse events (29 in the homeopathic group and 28 in the betahistine group) during the clinical trial were reported for 31 patients"					
	Causal relationship of an adverse event assessed by investigator as very probable or probable	2 (nausea, tremor of the hands)	Unclear*	1 (headache combined with very strong vertigo)	Unclear*	NR
	"For more than 90% of the patients, a good or excellent tolerability of the homeopathic remedy or betahistine was reported by the investigators."					

	Outcome measures (continuous)	Total number of participants in study = 119						
		Intervention group Total no. in group = 59 (maximum of 53 analysed)			**Control group** Total no. in group = 60 (maximum of 52 analysed)			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Primary							
	Frequency of vertigo attacks (change: last 7 days of treatment minus baseline)	-5.3	13.3	Unclear: 53	-3.3	2.1	Unclear: 52	0.53
	Duration of vertigo attacks (change: last 7 days of treatment minus baseline)	-1.2	1.2	Unclear: 53	-1.0	1.4	Unclear: 52	0.51
	Intensity of vertigo attacks (change: last 7 days of treatment minus baseline)	-1.9	0.8	Unclear: 53	-1.9	0.8	Unclear: 52	0.50
	Secondary							
	Vertigo-specific questionnaire** (set 1) (change after 42 days minus baseline)	28.6	17.2	51	25.8	22.8	52	0.53
	Vertigo-specific questionnaire** (set 2) (change after 42 days minus baseline)	29.2	23.6	52	28.7	24.9	52	0.50
	Vertigo-specific questionnaire** (set 3) (change after 42 days minus baseline)	19.0	11.3	52	16.8	13.5	52	0.54
	Vertigo-specific questionnaire** (set 4) (change after 42 days minus baseline)	11.8	8.9	52	12.5	13.2	52	0.51
	Physical health							
	Physical functioning (change: last 7 days of treatment minus baseline)	18.7	25.4	51	16.9	29.5	51	0.55
	Role limitations attributed to physical problems (change: last 7 days of treatment minus baseline)	27.0	43	51	24.5	44.2	50	0.52
	Bodily pain (change: last 7 days of treatment minus baseline)	7.1	26.3	51	13.9	28.8	51	0.42
	General health (change: last 7 days of treatment minus baseline)	6.6	16.5	51	11.5	19.7	50	0.44
	Mental health							
	Vitality (change: last 7 days of treatment minus baseline)	9.1	16.9	51	11.7	16.1	51	0.45
	Role limitations attributed to emotional problems (change: last 7 days of treatment minus baseline)	30.7	45.1	51	22.7	48.3	50	0.54
	Social functioning (change: last 7 days of treatment minus baseline)	8.6	21.3	51	14.2	20.8	51	0.43
	Mental health (change: last 7 days of	6.4	15.8	51	8.5	16.1	51	0.46

	treatment minus baseline)							
	Global assessment of efficacy by investigators	NR	NR	NR	NR	NR	NR	0.63
	Global assessment of efficacy by patients	NR	NR	NR	NR	NR	NR	0.76
	Global tolerance assessments of the investigators	NR	NR	NR	NR	NR	NR	0.46
	Global tolerance assessments of the patients	NR	NR	NR	NR	NR	NR	0.18
	"Mean relevant changes from baseline were not observed in either treatment group, neither for the clinical laboratory variables nor for the vital signs variables."							

*117 patients of the 119 randomised were assessed in regards to safety – unclear number per group
**Summary score of questionnaire transformed to a scale from 0 to 100; 0 = maximum of symptoms; 100 = no symptoms. Set 1: direct vertigo symptoms; set 2: intensity of vertigo during special exercises; set 3: vertigo-associated symptoms; set 4: restrictions in daily life activities

Abbreviations: mg: milligrams; n: number; NR: not reported

Homeopathy data extraction form: Wolschner et al. 2001

Reference: Wolschner U, Strösser W, Weiser M, Klein P. Treating vertigo - homeopathic combination remedy therapeutically equivalent to dimenhydrinate. Biologische Medezin 2001, 30(4):184-190.
Study design: Prospective cohort study.
Source of funds: Not detailed. **Conflicts of interest:** Not detailed.
Participants and setting **Setting:** 159 family practitioners and otolaryngologists in Germany participated in the study. **Inclusion criteria:** Patient suffering either vestibular or non-vestibular vertigo. **Exclusion criteria:** Parallel treatment with other antivertigo drugs was not allowed during the study (but non-pharmaceutical adjuvant therapies were permitted).
Intervention **Homeopathy:** Vertigoheel tablets (manufactured by Biologische Heilmittel Heel GmbH of Baden-Baden, Germany) containing homeopathic dilutions of *Ambra grisea*, *Anamirta cocculus*, *Conium maculatum*, and *Petroleum rectificatum* – the actual dosage was left to the discretion of the physician, as was the duration of treatment, up to a maximum of 8 weeks. (In most cases the prescribed dose was 2-3 tablets three times a day). **Total number included: n=352**
Comparison **Control:** Dimenydrinate (50 mg tablets) – the actual dosage was left to the discretion of the physician, as was the duration of treatment, up to a maximum of 8 weeks. (The standard dose (59% patients) of dimenhydrinate was 50 mg 2-3 times per day) **Total number included: n=422**
Outcomes: Degree of vertigo: average daily duration of vertigo attacks (0 – no vertigo attacks; 1 = 0-2 minutes; 2 = 2-10 minutes; 3 = 11-60 minutes; 4 = 1-6 hours; 5 = more than 6 hours); average daily severity of vertigo attacks (0 = no vertigo; 4 = very severe); average number of vertigo attacks per day. Symptoms (nausea, vomiting, attacks of perspiration, 0 = none; 3 = severe); patient compliance; tolerability (adverse effects, overall assessment by physician and end of treatment); onset of efficacy (point in time when first improvement was noted) (1 day; 2-3 days; 4-7 days; 1-2 weeks; 2-3 weeks; 3-4 weeks; 4-6 weeks; > 6 weeks; no improvement); results of therapy (overall assessment by physician end of treatment/observation (very good; good; fair; no

success;worse))				
Very brief summary of <u>study authors'</u> main findings/conclusions: *"The study confirms that Vertigoheel is a safe and effective treatment option for vertigo of varying etiology and is therapeutically equivalent to medications containing dimenhydrinate."*				
Risk of bias assessment				
Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☐	☒	☐	No randomisation.
Allocation concealment *(selection bias)*	☐	☒	☐	No randomisation.
Blinding of participants and personnel *(performance bias)*	☐	☒	☐	No blinding of participants or study personnel.
Blinding of outcome assessment *(detection bias)*	☐	☒	☐	No blinding of outcome assessment.
Incomplete outcome data *(attrition bias)*	☐	☐	☒	Unclear if there were any losses to follow up (only percentages were reported in text, with no 'n' values for each outcome).
Selective outcome reporting? *(reporting bias)*	☐	☐	☒	Unclear – insufficient information to determine risk of reporting bias.
Other bias	☐	☒	☐	Baseline imbalances were not controlled for in analyses.
Notes (Newcastle-Ottawa Scale considerations)	*"Translated from Biologische Medizin"* Selection: unclear how the two groups (exposed and un-exposed to homeopathy) were selected – 159 physicians participated and it was not detailed as to how physicians allocated treatment (therefore difficult assess whether 'non-exposed' cohort came from a similar/ the same community). Comparability: some potential baseline differences presented (in the Table and in text), however no control for these potential confounding factors (as results presented as summary statistics (averages, and percentages) only). Outcome ascertainment: outcome assessment not conducted blind (conducted by prescribing physicians), and completeness of follow up is not clear (with no losses/exclusions documented).			

	Outcome measures (dichotomous)	Total number of participants in study = 774				
		<u>Intervention group</u> Total no. in group = 352		**<u>Control group</u>** Total no. in group = 422		
		Events	**Total**	**Events**	**Total**	**P value**
	Improvement of vertigo symptoms in the first week of therapy	172 (49%)	352	261 (59%)	422	NR
	No improvement of vertigo symptoms during treatment period	14 (4%)	352	22 (5%)	422	NR
	Good or very good effect of medication (physician rated)	310 (88%)	352	385 (87%)	422	NR

	Fair effect of medication (physician rated)	32 (9%)	352	31 (7%)	422	NR
	No success of medication (physician rated)	11 (3%)	352	22 (5%)	422	NR
	Good or very good compliance (physician rated)	338 (96%)	352	441 (93%)	422	NR
	Premature termination due to inadequate efficacy	5 (1.4%)	352	19 (4.3%)	422	NR
	Adverse effects	1 (confusion)	352	1 (eczema)	422	NR
	Tolerability good or very good (physician rated)	349 (99%)	352	433 (98%)	422	NR
	Tolerability fair (physician rated)	4	352	4	422	NR
	Tolerability poor (physician rated)	0	352	2	422	NR

	Outcome measures (continuous)	Total number of participants in study = 774						
		Intervention group Total no. in group = 352			**Control group** Total no. in group = 422			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Number of vertigo attacks at 'exit examination' (after a maximum of 8 weeks)	1.0	NR	352	1.0	NR	422	NR
	Intensity of vertigo at 'exit examination' score (scale 0-4) (after a maximum of 8 weeks)	< 1 (see manuscript figure)	NR	352	< 1 (see manuscript figure)	NR	422	NR
	Duration of vertigo symptoms at 'exit examination' score (scale 0-5) (after a maximum of 8 weeks)	< 1 (see manuscript figure)	NR	352	< 1 (see manuscript figure)	NR	422	NR
	Degree of severity of nausea score at 'exit examination' (scale 0-3) (after a maximum of 8 weeks)	<0.5 (see manuscript figure)	NR	352	<0.5 (see manuscript figure)	NR	422	NR
	Degree of severity of vomiting score at 'exit examination'(scale 0-3) (after a maximum of 8 weeks)	<0.5 (see manuscript figure)	NR	352	<0.5 (see manuscript figure)	NR	422	NR
	Degree of severity of perspiration score at 'exit examination' (scale 0-3) (after a maximum of 8 weeks)	<0.5 (see manuscript figure)	NR	352	<0.5 (see manuscript figure)	NR	422	NR

Abbreviations: mg: milligrams; n: number; NR: not reported; SD: standard deviation

Homeopathy data extraction form: Zanasi et al. 2014

Reference: Zanasi A, Mazzolini M, Tursi F, Morselli-Labate AM, Paccapelo A, Lecchi M. Homeopathic medicine for acute cough in upper respiratory tractinfections and acute bronchitis: A randomized, double-blind, placebo-controlled trial. Pulmonary Pharmacology and Therapeutics 2014, 27(1);102-108.
Study design: Randomised controlled trial
Affiliation: Italian Association for Cough Study, **Conflicts of interest:** *"Publication of this article was supported by an unrestricted grant from Boiron s.r.l. (Milan, Italy)."*

Participants and setting

Setting: Outpatient clinic specifically devoted to the management of cough, located in Bologna (Italy) from January to December 2012

Inclusion criteria: People of at least 18 years of age with cough induced by URTI lasting from 3 to 5 days.

Exclusion criteria: People with pre-existing respiratory problems; who had undergone antibiotic treatment within 7 days prior to enrolment in the study; who had used antitussive agents or any other medication that might positively or negatively affect the cough symptom.

Intervention

Homeopathic syrup: Patients were instructed to take a dose of 15 mL 4 times a day for 7 days.

The composition of the homeopathic syrup was as follows: Anemone pulsatilla 6 CH, Rumex crispus 6 CH, Bryonia dioica 3 CH, Ipecacuanha 3 CH, Spongia tosta 3 CH, Sticta pulmonaria 3 CH, Antimonium tartaricum 6 CH, Myocarde 6 CH, Coccus cacti 3 CH, Drosera MT. Patients were followed up for a further 7 days.

Total number randomised: n=40

Comparison

Control: Placebo syrup made with the following excipients (which were the same ones present in the homeopathic syrup): glucose syrup, ethanol 96% (V/V) 0.340 g, benzoic acid 0.085 g, caramel 0.125 g.

Total number randomised: n=40

Outcomes: The primary endpoint: reduction of cough severity, as measured by a validated verbal category-descriptive (VCD) scores which patients reported on diary cards, at 2, 4, 7 and 14 days (0 = no cough; 5 = distressing continuous coughing that did not stop for 24 hours). *"We used the patient-compiled VCD scores because these have been shown to have the highest correlation with objectively-measured cough severity."* Secondary outcomes: laboratory examinations of viscosity of secretions at 4 days; patients subjective assessment of mucus (0 = no presence of expectorate; 3 = viscous, distressing and difficult to expectorate); side effects.

Very brief summary of study authors' main findings/conclusions: "We concluded that the homeopathic syrup employed in the study was able to effectively reduce cough severity and sputum viscosity, thereby representing a valid remedy for the management of acute cough induced by URTIs."

Risk of bias assessment

Domain	**Risk of bias**			***Support for judgement***
	Low	**High**	**Unclear**	
Random sequence generation *(selection bias)*	☒	☐	☐	*"A computer program was used to generate block randomization."*
Allocation concealment *(selection bias)*	☒	☐	☐	*"The two treatments had the same flavour and were stocked in consecutively numbered bottles of 200 mL each, that were identical in the appearance. Each patient received two bottles."*
Blinding of participants and personnel *(performance bias)*	☒	☐	☐	Identical placebo syrup used.
Blinding of outcome assessment *(detection bias)*	☒	☐	☐	As above.
Incomplete outcome data *(attrition bias)*	☒	☐	☐	No loss to follow-up and intention-to-treat analysis performed. Sputum viscosity measurements were available for only 53/80 patients (where a sufficient amount of mucus had been collected).
Selective outcome reporting?	☐	☐	☒	Insufficient information to permit

(reporting bias)				judgement of 'High' or 'Low' risk; no access to trial protocol.
Other bias	☐	☐	☒	The two groups were comparable for gender, though the homeopathic group was older on average (no other baseline characteristics detailed).
Notes				

	Outcome measures (dichotomous)	Total number of participants in study = 80				
		Intervention group Total no. in group = 40		**Control group** Total no. in group = 40		
		Events	**Total**	**Events**	**Total**	**P value**
	Primary					
	VCD cough score of 2 or more at 2 days	*	40	*	40	1.000
	VCD cough score of 2 or more at 4 days	*	40	*	40	0.048
	VCD cough score of 2 or more at 7 days	*	40	*	40	0.005
	VCD cough score of 2 or more at 14 days	*	40	*	40	0.546
	Secondary					
	Cough present at 14 days	5	40	8	40	NR
	Adverse events directly related to treatment	0	40	0	40	NA
	Side effects unrelated to treatment	2 (insomnia and cramps)	40	3 (diarrhoea, headache, and restlessness)	40	NR

	Outcome measures (continuous)	Total number of participants in study = 80						
		Intervention group Total no. in group = 40			**Control group** Total no. in group = 40			
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**P value**
	Primary							
	VCD cough score at 2 days	*	*	40	*	*	40	0.939
	VCD cough score at 4 days	*	*	40	*	*	40	<0.001
	VCD cough score at 7 days	*	*	40	*	*	40	0.023
	VCD cough score at 14 days	*	*	40	*	*	40	0.532
	Secondary							
	Sputum viscosity at day 4	*	*	25	*	*	28	0.018
	Absolute improvement in sputum viscosity (N m)	-4.50	3.99	25	-2.48	3.10	28	0.092
	Subjective evaluation of mucus	*	*	40	*	*	40	0.496

*Results presented as proportions/means with SD in Figures 2-4 in the manuscript

Abbreviations: g: grams; mL: millilitres; n: number; NA: not applicable; N m: newton metre; NR: not reported; SD: standard deviation; URTI: upper respiratory tract infection; V: volume; VCD: verbal category descriptive