Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials

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Summary

Background Homoeopathy seems scientifically implausible, but has widespread use. We aimed to assess whether the clinical effect reported in randomised controlled trials of homoeopathic remedies is equivalent to that reported for placebo.

Methods We sought studies from computerised bibliographies and contacts with researchers, institutions, manufacturers, individual collectors, homoeopathic conference proceedings, and books. We included all languages. Double-blind and/or randomised placebo-controlled trials of clinical conditions were considered. Our review of 186 trials identified 119 that met the inclusion criteria. 89 had adequate data for meta-analysis, and two sets of trial were used to assess reproducibility. Two reviewers assessed study quality with two scales and extracted data for information on clinical condition, homoeopathy type, dilution, "remedy", population, and outcomes.

Findings The combined odds ratio for the 89 studies entered into the main meta-analysis was 2·45 (95% CI 2·05, 2·93) in favour of homoeopathy. The odds ratio for the 26 good-quality studies was 1·66 (1·33, 2·08), and that corrected for publication bias was 1·78 (1·03, 3·10). Four studies on the effects of a single remedy on seasonal allergies had a pooled odds ratio for ocular symptoms at 4 weeks of 2·03 (1·51, 2·74). Five studies on postoperative ileus had a pooled mean effect-size-difference of −0·22 standard deviations (95% CI −0·36, −0·09) for flatus, and −0·18 SDs (−0·33, −0·03) for stool (both $p<0·05$).

Interpretation The results of our meta-analysis are not compatible with the hypothesis that the clinical effects of homoeopathy are completely due to placebo. However, we found insufficient evidence from these studies that homoeopathy is clearly efficacious for any single clinical condition. Further research on homoeopathy is warranted provided it is rigorous and systematic.

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See Commentaries pages 824, 825

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Introduction

Between 30 and 70% of patients in developed countries use complementary, alternative, or unconventional medicine,[1–3] even though high-quality scientific research on these practices is lacking.[4] Homoeopathy is one of the most widespread and controversial of these therapies. There are two main theoretical tenets: the principle of "similars" and the use of dilutions called "potencies".[5] The principle of similars states that patients with particular signs and symptoms can be cured if given a drug that produces the same signs and symptoms in a healthy individual. The second principle is that remedies retain biological activity if they are repeatedly diluted and agitated or shaken between each dilution. These dilutions are said to produce effects even when diluted beyond Avogadro's number in which no original molecules of the starting substance remain. How the solution "remembers" information from the original substance is speculative.[6]

Many scientists think that homoeopathy violates natural laws[7] and thus any effect must be a placebo effect.[8,9] But use of and belief in the effectiveness of homoeopathy is widespread and growing among physicians and the public,[10–13] and advocates claim that there are measurable and reproducible effects over placebo.[14] A systematic review of 107 controlled clinical trials in homoeopathy by Kleijnen et al in 1991 showed a surprising number of positive results, even among those that received high quality-ratings for randomisation, blinding, sample size, and other methodological criteria.[15] Vote counts of positive and negative trials, as used in that review, can be misleading without a quantitative summary of results. Since that study was published, at least 50 more controlled trials in homoeopathy have been reported.

We aimed to assess whether the effect seen with homoeopathic remedies is equivalent to that seen with placebo. If the hypothesis that all clinical effects of homoeopathy are due to placebo is correct, it would mean that in all properly conducted placebo-controlled trials on homoeopathy, one placebo had been compared with another. The overall results of these trials, in any disease, should vary randomly around a zero difference between groups. This placebo hypothesis would be falsified if all properly conducted comparisons of homoeopathy and placebo showed a pooled effect significantly different from zero difference, or if there is independently replicated evidence for an effect over placebo in at least one consistently applied homoeopathic approach. Of course, evidence of an effect over placebo would be stronger if both approaches showed "positive" effects and "non-believers" were involved in the trials. We have tested both of the above strategies (overall comparison and reproducibility comparisons) with quantitative meta-analytic methods.

Methods

Literature search and data sources

All published reports of controlled clinical trials of homoeopathy were collected with use of multiple sources: (1) the review by Kleijnen et al,[15] which used an extensive search strategy for

MEDLINE and EMBASE up to 1990; (2) a MEDLINE search by an information specialist from 1966 to August, 1995, with the full-text terms homeop* and homoeop*, and the MeSH terms homoeopathy, homoeopathy, and alternative medicine, and screening of all citations found; (3) contacts with homoeopathic researchers, institutions reporting on homoeopathic research, and homoeopathic manufacturers, and follow-up on suggestions from these contacts; (4) searching several extensive homoeopathic and complementary medicine registries, including those of the Woodward Foundation (USA), CISCOM (RCCM, London), AMED (British Library), HomInform (Glasgow), IDAG (Amersfoort, Netherlands), and CCRH (India), as well as several individual collections; (5) attending several homoeopathic meetings, inquiring about research and searching the conference proceedings, abstract booklets, and indices from those, from other meetings, and from homoeopathic books; (6) the references of reviews and trials found; and (7) additional searches of MEDLINE by ourselves, using additional search terms, and search of EMBASE from 1989 to October, 1995. All languages were included.

Study selection

Inclusion and exclusion criteria for study selection were predefined. All studies had to: (1) be controlled trials on people being treated or entered into a preventive trial; (2) have a parallel control group receiving placebo; (3) have an explicit statement that there was random assignment to treatment and placebo groups, or that the trial involved double-blind conditions for participants, therapists, and outcome evaluators, making unbiased treatment allocation likely; (4) be a written report, such as a journal publication, abstract, thesis, conference proceeding, unpublished report, book section, or monograph; and (5) provide sufficient information after data extraction to have outcome rates calculated for both groups.

We excluded: (1) studies from homoeopathic "provings" in which remedies are given to healthy volunteers to assess their effects; (2) physiological trials in healthy participants not aimed at treatment or prevention; (3) single-case experiments; (4) other investigations that did not use a parallel placebo group; and (5) studies in which a reasonable outcome measure for data synthesis could not be determined. Selection was done by two independent reviewers (KL, NC). Prediscussion reliability of the selection process was assessed with the κ statistic on a random selection of half the trials.[16] Final authority for selection disagreements rested with KL.

Data extraction

All data were independently extracted by KL and NC on pretested forms and entered into a spreadsheet. The extraction process included basic descriptive information and details on outcome measures and two pretested quality-assessments. Descriptive information included author, year, disease treated (or being prevented), type of homoeopathy (classical, clinical, complex, isopathic), remedies used, "potency" (dilution) used (low, medium, high), population, outcomes, number randomised and analysed, country, language of publication, publication type and source, authors' report of statistical significance, and study quality-assessments (both component and summary).

The studies were categorised into the four main types of homoeopathy and into three levels of dilution. When a single homoeopathic remedy was selected based on the total symptom picture of a patient, it was called "classical" homoeopathy which is felt by some practitioners to represent the original, most effective, and "pure" type. When one or several single remedies were administered for standard clinical situations or conventional diagnoses, it was called "clinical" homoeopathy. When multiple remedies were mixed into a standard formula (Fertigarzneimittel) to "cover" a person's symptoms and diagnoses, it was called "complex" homoeopathy. And when serial agitated dilutions were made from the causative agent in an infectious or toxicological condition (as with vaccination), it was called "isopathy". "Low potencies" were defined as those prepared on the decimal (D) scale between D1 (drug:solute in a 1:9 ratio by volume, done once) and D8 (repeated eight times) or on the centesimal (C) scale between C1 (1:99, once) and C4 (repeated four times). This "low-potency" dilution has estimated molar concentrations of potential active agents administered to the patient of between 10^{-5} and 10^{-12}. "Medium potencies" were defined as those between D9 and D23 or C5 and C11, with estimated molar concentrations administered of between 10^{-13} and 10^{-27}. "High potencies" were defined as those over D23 or C11, with estimated molar concentrations administered less than 10^{-27}.

Selection data	Number		Trials included	Inadequate data
Controlled trials	186	Number	89	30
Clinical trials	171	Sample size	118	66
Placebo trials	133	Mean study quality	4·04	3·46
Randomised and/or double-blind	119	Medline citation	25%	10%
Prevention trials	7	Reported positive	67%	70%
Sufficient data	89			
Insufficient data	30	**Quality data***		**Number** (out of 89)
Descriptive data		"High" quality		26
Clinical conditions	24	Jadad score ⩾3		40
Countries	13	Internal validity ⩾5		34
Languages	4			
Years	1943–95	**Quality components***		(out of 89)
Number of remedies	50	Allocation concealment		34
Patients		Double-blinding		81
Total number	10 523	Dropout handling		28
Mean	118	Primary outcome measure by author		21
Median	60	Clear extraction outcome obtained		69
Range	5–1306	Trials cited in MEDLINE		21
Dilution data		**Homoeopathic types**		(out of 89)
"Low dilution" (10^{-5} to 10^{-12} mol/L)	33	Classical		13
"Medium dlution" (10^{-13} to 10^{-27} mol/L)	20	Clinical		49
"High dilution" ($\leqslant 10^{-27}$ mol/L)	31	Complex		20
Mixed dilution	5	Isopathy		7

*Number of studies meeting specific quality-criteria definitions.

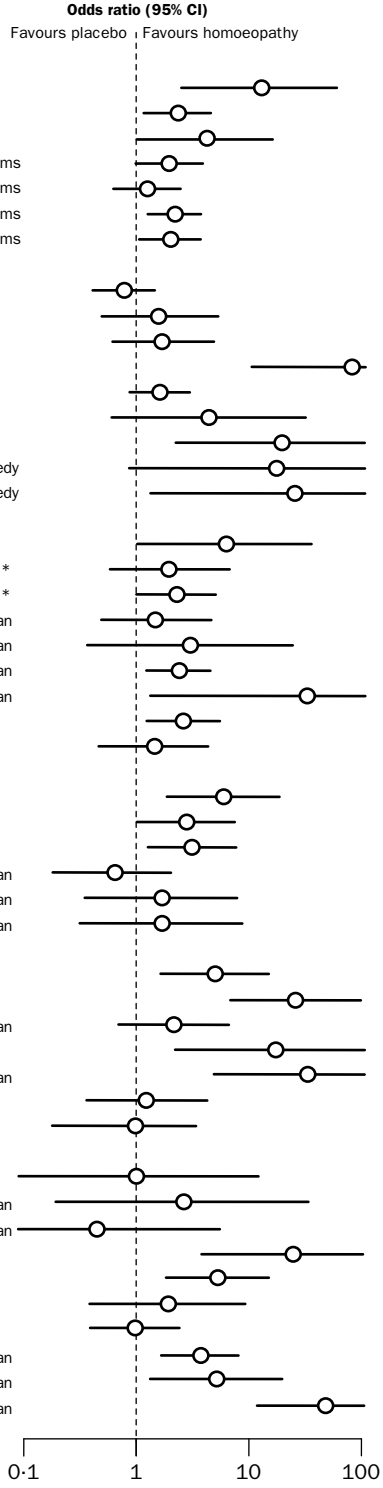
Table 1: **Clinical trials of homoeopathy**

We used a hierarchy of preset criteria for identifying preferred outcomes for the meta-analysis to ensure that the most relevant outcomes were selected from each study. First preference was any predefined main outcome-measure, defined as the outcome on which sample size was calculated. Second preference was patients' global assessment of improvement, if measured. Third preference was physicians' global assessment of improvement. Fourth preference was outcome measures that (in the judgment of the reviewers) were most important (eg, duration of illness in trials of upper respiratory tract infection). In a few studies where no clear outcome measure could be identified, outcomes were assigned to numbers on dice (2–12) which were then rolled to randomly select the outcome included in the meta-analysis.

Quality assessment

All trials were evaluated with two quality scores for internal validity. The first assessment was done with a scale developed by Jadad et al.[17] This scale has been used in pain,[17] infertility,[18] general internal medicine,[19] acupuncture,[20] and herbal treatment of depression.[21] It is one of the only systems systematically developed and tested for discrimination, face validity, and reliability.[17] It includes three items that assess random allocation, double-blinding, and the reports of dropouts and withdrawals. To assess for adequacy of concealment, handling of dropouts, baseline comparability of groups, and adequacy of inferential statistics, a second more elaborate scale for internal validity was used.[20,21] Each trial was independently scored by KL and NC, and interobserver reliability of the extraction and quality-assessment process before discussion was checked with the intraclass correlation coefficient for both scores.[22] A predefined set of

First author (ref)	n	Jadad/ IV score	Condition	Intervention	Outcome
Allergy					
Reilly (14)	28	100/93	Allergic asthma	Individual nosode C30	VAS improvement (mm)*
Reilly (97)	39	60/50	Pollinosis	Pollen C30	Global assessment patient
Reilly (98)	162	100/93	Pollinosis	Pollen C30	VAS improvement (mm)*
Wiesenauer (112)	121	80/79	Pollinosis	Galphimia D4	Improvement ocular symptoms
Wiesenauer (109)	142	80/79	Pollinosis	Galphimia D6	Improvement ocular symptoms
Wiesenauer (111)	243	60/86	Pollinosis	Galphimia C2	Improvement ocular symptoms
Wiesenauer (113)	164	60/79	Pollinosis	Galphimia D4	Improvement ocular symptoms
Dermatology					
Labrecque(78)	174	80/100	Warts	Thuya C30, Ant C5, Ac.nitr.C7	Disappearance of warts
Leaman(79)	34	40/50	Minor burns	Cantharis C200	Pain (area under curve)*
Mössinger (88)	144	40/36	Pyodermia	Hepar sulfuris D4	Days to healing (days)*
Paterson (193)	40	80/64	Skin lesions	Mustard gas C30	Depth of lesion
Paterson (293)	169	40/57	Skin lesions	Individual treatment	Depth of lesion
Paterson (393)	22	40/57	Skin lesions	Rhus tox C30	Depth of lesion
Paterson (493)	39	40/57	Skin lesions	Mustard gas C30	Depth of lesion
Schwab (1102)	13	60/71	Dermatoses	(only patients fitting) Sulphur	Predicted reactions on remedy
Schwab (2102)	16	40/71	Dermatoses	(only patients fitting) Sulphur	Predicted reactions on remedy
Gastroenterology					
Bignamini (41)	31	40/64	Anal fissure	Acidum nitricum C9	Improvement
Jacobs (73)	34	60/64	Diarrhoea	Individual treatment in C30	Duration of diarrhoea (days)*
Jacobs (72)	92	100/86	Diarrhoea	Individual treatment in C30	Duration of diarrhoea (days)*
Mössinger (186)	53	20/29	Gastritis	Nux vomica D4	Global assessment, physician
Mössinger (286)	16	20/29	Gastritis	Nux vomica D30	Global assessment, physician
Ritter (99)	147	40/50	Gastritis	Nux vomica D4	Global assessment, physician
Mössinger (90)	14	0/14	Cholecystopathia	Absinthium D2	Global assessment, physician
Rahlfs (96)	119	40/79	Irritable bowel	Asa foetida D3	Global assessment, patient
Rahlfs (95)	72	40/79	Irritable bowel	Asa foetida D1	Global assessment, patient
Musculoskeletal complaints					
Böhmer (44)	102	100/100	Sprains	Traumeel (complex)	Global assessment, patient
Zell (114)	73	100/100	Sprains	Traumeel (complex)	Joint movement
Thiel (104)	80	40/79	Haemarthrosis	Traumeel (complex)	Joint movement
Mössinger (386)	47	20/29	Cramps	Cuprum D30	Global assessment, physician
Mössinger (486)	34	20/29	Cramps	Cuprum D4	Global assessment, physician
Mössinger (586)	48	20/29	Cramps	Cuprum D200	Global assessment, physician
Neurology					
Albertini (36)	60	20/36	Dental neuralgia	Arnica C7, Hypericum C15	Global assessment, patient
Brigo (45)	60	40/79	Migraine	Individual treatment in C30	Global assessment, patient
Dexpert (55)	55	20/29	Seasickness	Cocculine (complex)	Global assessment, physician
Ponti (94)	93	20/50	Seasickness	Nux C2, Cocculus C2, Tab C2	Global assessment, patient
Master (83)	36	40/29	Aphasia	Individual treatment	Global assessment, physician
Savage (100)	40	60/64	Stroke	Arnica C30	Survival
Savage (101)	40	60/79	Stroke	Arnica M	Survival
Obstetrics & gynaecology					
Bekkering (40)	5	60/57	Menopause	Famosan (complex)	Symptom score*
Carey (47)	40	40/57	Vaginal discharge	Candida C30	Global assessment, physician
Chapman (50)	10	80/71	Premenstrual syndr	Individual treatment	Global assessment, physician
Coudert (52)	34	40/64	Childbirth	Caulophyllum C5	Labour pains
Dorfman (58)	93	60/71	Childbirth	Complex	Labour pains
Gauthier (65)	24	60/50	Menopausal compl	Lachesis C30	Global assessment, patient
Hofmeyr (70)	122	100/100	Childbirth	Arnica D6 (D30)	Perineal pain
Kubista (77)	119	40/57	Mastodynia	Mastodynon (complex)	Global assessment, physician
Lepaisant (81)	45	60/64	Premenstrual syndr	Folliculinum C9	Global assessment, physician
Ustianowski (105)	200	20/29	Cystitis	Staphisagria C30	Global assessment, physician



* Trials with continuous outcomes (converted to odds ratios)

Table 2: **Trials in meta-analysis**

**For prevention trials, presented odds ratio=1÷actual odds ratio. Jadad/IV score: actual number of quality criteria met×100÷maximum possible score. URI=upper respiratory tract infection, ENT=ear, nose, and throat, VAS=visual analogue score.

criteria for determining the highest quality trials was established which required a score of 3 or greater in the Jadad score (a cutoff recommended by him),[17-19] and a score of 5 or greater on our seven-item internal-validity score.

Quantitative data synthesis

Most of the trials used discrete outcome-measures for which the computation of an odds ratio was straightforward. 15 trials used continuous rather than discrete outcomes and provided the placebo and treatment groups' means and standard deviations on these outcomes. For these trials the difference between means divided by the pooled standard deviation was converted to the corresponding odds ratio with a relation given by Hasselblad and Hedges.[23] All dropouts were counted as non-responders (intention-to-treat analysis). Odds ratios were computed such that a result greater than one indicates greater effectiveness of homoeopathic therapy compared with placebo. The χ^2 test for heterogeneity (α=0·10) was used to assess effect-size variance among the trials.[24] Heterogeneity is expected for the first approach to the hypothesis (overall comparison analysis) but not for the

First author (ref)	n	Jadad/ IV score	Condition	Intervention	Outcome
URI, asthma, & ENT					
Bordes (42)	60	40/57	Cough	Drosetux (complex)	Global assessment, patient
Casanova (49)	300	40/57	URI	Oscillococcinum	Fever on third day (°C)*
Davies (53)	36	40/29	Prevention, URI	'Common cold' tablets	Patients with infection**
de Lange (54)	175	100/100	Recurrent URI	Individual treatment	Global assessment, patient
Ferley (61)	1270	60/79	Prevention, URI	L52 (complex)	Patients with infection**
Ferley (62)	487	60/79	URI	Oscillococcinum	Patients recovered within 48 hs
Heilmann (69)	102	40/43	Prevention, URI	Engystol (complex)	Patients with infection**
Hourst (71)	41	40/71	URI	Thuya C9+2 other remedies	Complaints
Lecocq (80)	60	40/50	URI	L52 (complex)	Global assessment, patient
Mössinger (87)	118	40/50	Pharyngitis	Phytolacca D2	Duration (days)*
Mössinger (89)	106	20/43	Running nose	Euphorbium D3	Symptoms
Mössinger (91)	44	20/50	Otitis media	Pulsatilla D2	Global assessment, physician
Nollevaux (92)	200	20/43	Prevention URI	Mucococcinum 200K	Patients with infection**
Weiser (107)	116	100/79	Chronic sinusitis	Euphorbium comp (complex)	Severity score*
Freitas (64)	64	80/79	Asthma	Blatta orientalis C6	Severity score*
Rheumatology					
Andrade (38)	44	80/79	Rheumatoid arthritis	Individual treatment	Global assessment physician
Gibson (66)	46	60/64	Rheumatoid arthritis	Individual treatment	Global assessment
Köhler (76)	176	60/43	Rheumatoid arthritis	Rheumaselect (complex)	Predefined responder criteria
Wiesenauer (110)	176	80/79	Rheumatoid arthritis	Rheumaselect (complex)	Predefined responder criteria
Shipley (103)	36	60/71	Osteoarthritis	Rhus tox. D6	Treatment preference
Fisher (63)	30	60/71	Fibrositis	Rhus tox. C6	Global assessment
Casanova (48)	60	20/29	Myalgia	Urathone (complex)	Global assessment, patient
Surgery & anaesthesiology					
Alibeu (37)	50	40/57	Agitation	Aconite C4	Physician's assessment
Aulagnier (39)	200	40/64	Postoperative ileus	Opium C9, Raph. C9, Arnica C9	Global assessment, patient
Chevrel (51)	96	40/71	Postoperative ileus	Opium C15	Time to first stool (h)*
Dorfman (57)	80	40/36	Postoperative ileus	Complex	Patients without pain
Estrangin (60)	97	40/43	Postoperative ileus	Arnica C7, China C7, Pyrog C5	Time to flatulence <2 days
GRECHO (67)	450	80/86	Postoperative ileus	Opium C15 (+C15, Raph C5)	Time to first stool (h)*
Kaziro (74)	77	60/50	Tooth extraction	Arnica C200	Pain
Kennedy (75)	128	60/57	Preventing complic	Arnica C200	Complications**
Lökken (82)	24	100/86	Tooth extraction	Individual treatment in D30	Treatment preference
Michaud (84)	49	0/14	Tooth extraction	Apis C7, Arnica C15	Oedema
Valero (106)	161	80/57	Prev postop infect	Pyrogenium C7	Infections**
Valero (106)	102	80/64	Postoperative ileus	Raphanus C7	Time to first stool (h)*
Miscellaneous					
Bourgois (43)	29	40/36	Haematomas	Arnica C5	Pain score*
Dorfman (56)	39	20/43	Haematomas	Arnica C5	Pain
Campbell (46)	46	40/36	Bruises	Arnica C30	Treatment preference
Ernst (59)	59	40/71	Varicosis	Poikiven (complex)	Pain reduction
Hariveau (68)	68	20/43	Cramps	Cuprum C15	Global assessment
Mokkapatti (85)	85	40/43	Prev conjunctivitis	Euphrasia C30	Patients with infection**
Werk (108)	108	100/57	Overweight	Helianthus tuberosus D1	Body mass index <26

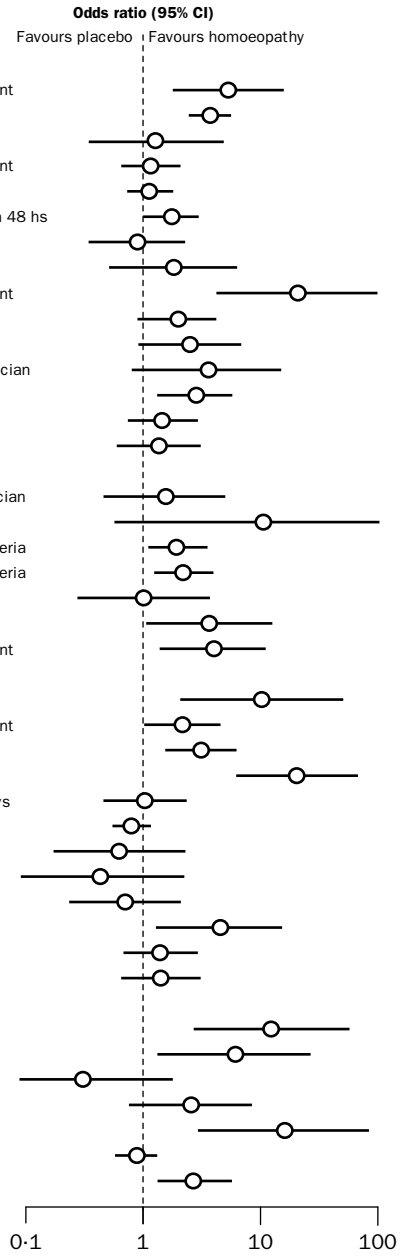


Table 2 – **continued**

second approach (testing for reproducibility). The odds ratio was used as the measure of effect in the overall comparison test of this meta-analysis because it is the most satisfactory metric in which to combine across trials with discrete outcomes.[25] Both fixed-effects[26] and the more conservative random-effects[27] methods were used to combine the log odds ratios across trials. The random effects method is more appropriate because the treatments and conditions in these studies are expected to be statistically heterogeneous even though all trials met the specific criteria necessary for answering the study hypothesis. Calculations were done with SPSS for Windows with a program used and validated in previous data sets. Results were reported as means with 95% CIs for all outcomes.

Sensitivity and subgroup analyses

Several sensitivity and subgroup analyses were done to estimate the robustness of results. These evaluated the effects of publication bias, indicators of study quality, publication source, outcome preference, and a "worst-case" situation that included the above plus only medium-potency and high-potency studies. Characteristics and significance reporting of the trials not included in the meta-analyses were compared with those included to assess generic differences between entered and not-entered study sets.

Publication-bias selection model

Publication bias is a significant problem in medicine and occurs when the chance that a trial is reported depends, to some extent, on the outcome of the trial.[28] Publication bias makes interpretation of meta-analyses difficult because the trials observed may be only a selected subset (eg, the most positive) of all trials.[29] We assumed that publication bias occurred in our data set despite extensive efforts to collect all studies. Although it is difficult to establish conclusively that publication bias is operating in any particular meta-analysis, several methods exist to test for its effects on outcome estimates. The funnel plot, a plot of the log odds ratios versus their standard errors, has been widely used to detect potential publication bias and is useful when actual treatment effects are homogeneous.[30] In addition, a statistical test for publication bias and a correction for its effects are possible

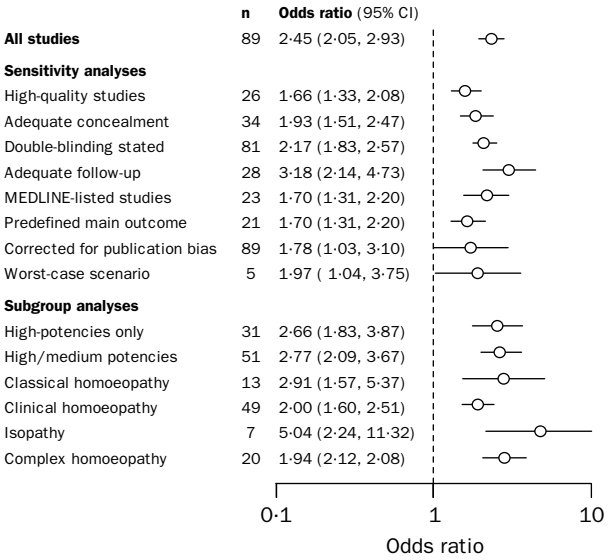


Table 3: **Pooled odds ratios and 95% CI (random-effects model)**

when models for the selection process can be estimated. A general non-parametric selection model was applied to the entire collection of studies to estimate the extent and size of undetected reports.[31,32] This analysis used a random-effects model for log odds ratios and a selection model in which the likelihood that a study was reported (the weight function) depended on the one-tailed p value.[33] The results from this model were then used to recalculate an estimate of the overall odds ratio corrected for publication bias. We also evaluated the potential effects of publication bias by calculating the number of hypothetical results that might be "in the file drawers" of researchers and therefore unavailable for pooling.[34,35]

Results

Literature search and study selection

186 trials were identified (excluding drug "provings"). Of these, one was a time-series, placebo-controlled single-case experiment, 14 involved assessment of physiological measures on healthy volunteers, and 38 did not include a placebo group, leaving 133 placebo-controlled trials evaluating treatment or prevention. Of these, three trials were not randomised, nine were unclear about randomisation and double-blinding, and in two trials a single-blind design was used but a statement on treatment allocation was lacking. Thus, 119 trials met the inclusion criteria for data extraction and quality assessment. Of these, 30 had inadequate information to allow statistical meta-analysis, leaving 89 trials that met all inclusion and exclusion criteria.[14,36-114] The 30 trials excluded because of inadequate information did not differ significantly from those included by type of homoeopathy, dilution range, country, year, or language of publication.[115-138] Excluded trials did have lower quality scores, smaller sample sizes, fewer MEDLINE-listed reports, and a slightly higher percentage of positive results (70 *vs* 67%) (table 1). Prediscussion inter-rater reliability of the selection process was good (κ=0·76) and no trial required a third rater to resolve disagreements about selection.

The 89 trials included in the first meta-analysis (overall comparison) had a mean sample size of 118 patients and median of 60 patients per study. These studies looked at twenty-four clinical categories, which included seven prevention trials, four types of homoeopathy, and fifty homoeopathic remedy classes. They came from thirteen countries, were in four languages, and were published between 1943 and October, 1995. 33 (37%) used "low" dilutions, 20 (22%) "medium" dilutions, and 31 (37%) "high" dilutions. Both medium-dilution and high-dilution categories theoretically contained too few molecules of the original drug to have any biological effect (estimated total concentration per patient below 10^{-13} mol/L). 13 (15%) trials used the "classical" model of homoeopathy, 49 (55%) the "clinical" model, 20 (22%) the "complex" model, and seven (8%) used "isopathy".

Data extraction and quality assessment

26 (29%) trials met our predefined criteria for high quality. 40 (45%) of the trials received a score of 3 or greater on the Jadad scale and 34 (38%) received a score of 5 or greater on our internal-validity scale. The mean Jadad quality-score for this trial set (n=89) was 52% of the maximum. Quality-score components for concealment of treatment allocation, double-blinding, and handling of dropouts were judged adequate in 34, 81, and 28 trials, respectively (table 1). Prediscussion inter-rater reliability of the quality-assessment scales had an intraclass correlation of 0·66 for the Jadad and 0·78 for our scale. Predefined primary-outcome measures were clear in only 21 (24%) of the trials, but in 69 (77%) of trials it was not difficult to identify a clear outcome for entry into the meta-analysis. In only four trials did disagreement in selection of the outcome measure have relevance to the effect-size estimate. In two of these trials, disagreement was because of multiple outcome-measures, so we threw dice to select the outcome for the meta-analysis.

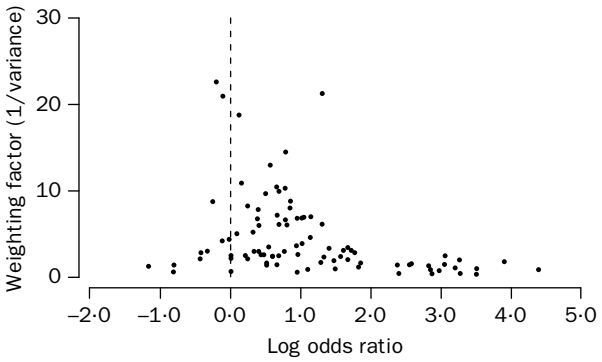
Quantitative data synthesis and sensitivity analyses

Table 2 lists all 89 studies by author, sample size quality rating, condition, intervention, outcome, and the odds ratio for each study. Table 3 shows the combined odds ratios for the 89 studies entered into the overall comparison meta-analysis and results for each subgroup and sensitivity analysis. The overall odds ratio was 2·45 in favour of homoeopathy with a 95% CI of 2·05 to 2·93 (random- effects model). The odds ratio for the 26 high-quality studies was 1·66 (1·33 to 2·08). Results from the multiple sensitivity and subgroup analyses are also listed in table 3. These analyses (including any combination of

First author	Galphimia potency	Scores method (Jadad/internal-validity)	Galphimia glauca (responder/randomised)	Placebo (responder/randomised)	Odds ratio (95% CI)
Wiesenauer[112]	D4	80/79	30/61	20/60	1·94 (0·93, 4·04)
Wiesenauer[109]	D6	80/79	28/71	24/71	1·21 (0·65, 2·24)
Wiesenauer[111]	C2	60/86	75/121	52/122	2·19 (1·31, 3·67)
Wiesenauer[113]	D4	60/79	50/82	36/82	2·00 (1·07, 3·72)
Pooled fixed effects	· ·	· ·	183/371	132/370	2·03 (1·51, 2·74)
Pooled random effects	· ·	· ·	183/371	132/370	2·20 (1·18, 4·12)

Patients with ocular symptoms rated as relieved or much better after 4 weeks (intent to treat). Trials included outpatients with acute pollinosis caused by flowering plants and grasses, history of >2 years, no additional medication with corticosteroids or antihistamines. Randomisation concealment by numbered pharmacy. Changes of eye and nose symptoms were assessed after 2 and 4 weeks. All trials had high number of dropouts and withdrawals.

Table 4: **Results of four placebo-controlled randomised multicentre trials of Galphimia glauca for pollinosis**



Funnel plot

overall or subcomponent quality ratings) did not eliminate the statistical significance of the results. For example, studies in the "worst-case" scenario (MEDLINE only, high-quality studies with predefined outcome measures, medium and high dilutions only, n=5) had an odds ratio of 1·97 (1·04 to 3·75).

Adjustment for publication bias

The figure is a funnel plot of the odds ratio by the inverse of the variance for each of the 89 studies. Under the assumption that all effects of homoeopathy are homogeneous, the asymmetry indicates missing negative trials. The general non-parametric selection model applied to the 89 studies confirmed that there was statistically significant publication bias (χ^2=16·72, 8 degrees of freedom, p=0·033) and suggested the bias was primarily due to under-reporting of studies with statistically insignificant effects (p>0·30) and with negative effects (p>0·5). The overall estimate of the odds ratio corrected for publication bias was 1·78 (1·03 to 3·10, z=2·09). Thus correction for publication bias decreases the odds ratio by about 27%; however, it remained substantial and statistically significant. If the missing trials had an average odds ratio of 1 (that is, if these trials showed null results on average), it would require 923 missing trials of average size (ie, 118) to reduce the pooled-effect size to insignificance at the 0.05 level with the random-effects test and 4511 missing trials with the fixed-effects test.

Tests for reproducibility

No series of studies completely met our predefined criteria for reproducibility, which required at least three independent replications (different investigators) on the same clinical condition, with the same model of homoeopathy, remedy, outcome measurement, and a similar population. Four studies on the effects of a single remedy on seasonal allergies did meet the above criteria except that they were by the same principal investigator.[109,111-113] Outcome data, however, was collected by various physicians at multiple practice-sites. These studies involved a 4-week treatment with the remedy Galphimia glauca. The outcome measure was a four-level severity scale of both nasal and ocular symptoms. These studies were homogeneous and so an odds ratio for a fixed-effects model was calculated. The pooled odds ratio for ocular symptoms at 4 weeks was 2·03 (1·51 to 2·74) with a similar result for nasal symptoms (table 4). Five other studies were independently conducted by different investigators with a "clinical" or "complex" homoeopathy model for postoperative ileus.[39,51,57,67,106] Each of these studies evaluated the effect of up to four remedies (Opium, Arnica, Raphanus, and Cinchona) in different combinations on the time from the end of abdominal surgery to the passing of flatus and stool. The results of these studies were not statistically homogeneous. The pooled mean effect-size-difference between the remedy combinations and placebo was -0·22 (95%CI -0·36 to -0·09) for flatus, and -0·18 (-0·33 to -0·03) for stool (table 5). Although the pooled effect-size-difference in this series was in favour of homoeopathy, the largest and best performed trial had a negative outcome, which was the opposite of the effect reported in the other four trials.

Discussion

The results of our meta-analysis are not compatible with the hypothesis that the clinical effects of homoeopathy are completely due to placebo. But there is insufficient evidence from these studies that any single type of homoeopathic treatment is clearly effective in any one clinical condition. The evidence in our overall analysis would be more compelling if there were independently replicated, large-scale rigorous trials of defined homoeopathic approaches in at least a few specific disorders. In addition, we cannot completely rule out bias as an explanation for these results. Although we have attempted to address all the major explanations for our findings, two issues still complicate their interpretation.

Publication bias

It is difficult to estimate the influence of publication bias on our results. We attempted to address this problem in several ways. We used an extensive search strategy for finding published and unpublished trials. None of the unpublished reports had an odds ratio smaller than 1. In addition, a recently formed review group on homoeopathy, sponsored by the European Commission, did an extensive independent search and came up with a similar number of trials.[139] After extensive inquiry with manufacturers, researchers, and practitioners in this field, we estimate that the number of unpublished trials that we could not obtain and are unlikely to be published is

First author	Treatment/placebo	Treatment	Scores method (Jadad/ internal-validity)	*d* (95% CI)	
				Time to first flatulence	Time to first stool
Aulagnier[39]	100/100	Opium C9, Arnica C9, Raph. C9	40/64	–0·64 (–0·94, 0·36)	–0·55 (–0·84, 0·27)
Chevrel[51]	50/46	Opium C15	40/71	–0·42 (–0·83, 0·02)	–0·63 (–1·04, 0·22)
Dorfman[57]	40/40	Cnina C5, Arnica C9, Raph. C9	40/36	–0·59 (–1·04, 0·15)	Not measured
GRECHO[67]	300*/150	1) Opium C15 2) Opium C15, Raphanus C5	80/86	+0·09 (–0·10, 0·29)	+0·11 (–0·09, 0·30)
Valero[106]	37/43	Raphanus C7	80/64	–0·22 (–0·66, 0·22)	Not measured
Pooled	527/379			–0·22 (–0·36, 0·09)	–0·18 (–0·33, 0·03)

Effect sizes were estimated by Cohen's *d* (mean treatment group minus mean placebo group divided by pooled standard deviation).
*3-armed trial with two different homoeopathic intervention groups. n=150; for this analysis, values for less favourable group were taken.

Table 5: **Results of randomised trials of various homoeopathic remedies for postoperative ileus after abdominal surgery**

around 15–30. Our selection model indicated evidence for publication bias against small negative trials. Correction and adjustment of the overall results for these missing trials reduced, but did not eliminate, the effect in favour of homoeopathy (odds ratio 1·78). If the odds ratio of the missing trials were around the null result, the number of trials required to reduce the result to insignificance would need to be several hundred.

Interpretation of the funnel plot is difficult. If homoeopathy has an effect at all, one would expect that the effect is not homogeneous for all clinical conditions. In that case the funnel plot would represent multiple overlapping funnel plots. Since trials of more effective treatments need smaller samples sizes, the pattern of such a plot would mimic publication bias even when there was none. Thus, from both our analysis and experience searching this field, it seems highly unlikely that publication bias alone can explain the results. Only preregistration of trials, perhaps with the recently established Complementary Medicine Field Group in the Cochrane Collaboration, could solve this problem.

Quality of evidence

A second major problem is the quality of the studies we included. Our quality-assessment scores suggest that the homoeopathy trials have at least similar quality (52% of the maximum on the Jadad scale) to those published in the leading medical journals (51% of maximum), but this is clearly not the case.[19] Our trial set included only placebo-controlled trials. Homoeopathic remedies can be perfectly matched with placebos, making double-blinding and allocation concealment easy. Such trials are more likely to score higher on scales emphasising these criteria than studies from general medical journals where perfect blinding may not always be possible. Our impression from detailed examination of these trials, however, is that about two-thirds were methodologically poor, a third reasonable, and a tenth very good. Much of this research reflects the lack of infrastructure needed to conduct good studies and develop appropriate research strategies in this area. Many trials were "low-budget" and done by advocates with high enthusiasm. This risks incomplete and selective reporting. In addition, major shortcomings of these trials were evident on the clinical level (definition of the condition, clear and reliable outcome measures, &c). However, an analysis restricted to only the very best subset of these trials reduced, but again did not eliminate, the effect found (odds ratio of high-quality trials, 1·66).

Overall, inferior methodological quality of this research alone, therefore, is not an adequate explanation for the results. Overall quality-assessments of trials, however, can mix and therefore obscure confounding that might occur from specific methodological flaws. For example, unequal distribution of prognostic factors between comparison groups might explain positive results reported in one group; knowledge and expectations about receiving "active" treatment can bias judgments during reporting or measurement of outcomes; dropouts, withdrawals, or otherwise inadequate follow-up can result in unequal distribution of results between groups not due to treatment effects; and multiple outcome-measures or post-hoc selection of outcomes can lead to reporting false-positive results. In addition, inadequate peer-review without bias for or against homoeopathy might not allow for other "fatal flaws" to go undetected. Whilst no-one can guarantee that these items are strictly followed in any trial, we independently checked the adequacy of how each of these components was reported and analysed the top subgroups. Eliminating trials with insufficient methods in reporting of concealment (odds ratio 1·93), double-blinding (2·17), follow-up (3·18), predefined outcome-measures (1·70), or critical peer-review (1·70) did not remove statistical significance from the overall findings.

Finally, we tested a worst-case scenario in which only high-quality studies, of high or medium dilutions, published in MEDLINE-listed journals, and with predefined measures of primary outcome were analysed (odds ratio 1·97). Overall dropout-rates were equivalent in the homoeopathic and placebo groups (13·2 and 13·4%, respectively). All odds ratios were calculated by intention-to-treat analyses in which the ratios are calculated on the number of participants randomised. This approach should reduce the impact of dropouts on bias in the results. However, there were some trials in which the exact number randomised had to be estimated, making this technique for controlling dropout bias less certain in these studies. Whilst correction for concealment and blinding decreased the combined odds ratio, studies with adequate reporting and minimum dropouts (<5%), or proper handling of dropouts in the analysis, had an increased odds ratio (3·18) in favour of the treatment groups, a finding reported in other study sets.[140] With the more conservative random-effects model for combining results, in all cases, our selection process, quality assessments, choice of statistical methods, and sensitivity analyses imposed increasingly stringent criteria on the hypothesis. None of these factors could account for the overall results or completely eliminate the increased effect-sizes reported for homoeopathy over placebo (table 3). Although neither publication bias nor poor-quality trials alone seem to explain our findings, we cannot be sure that combinations of these factors or others still unaccounted for might have led to an erroneous result. These results are, however, consistent with another comprehensive systematic review[15] and a meta-analysis[139] of homoeopathic clinical trials.

Since our meta-analysis, several relevant new trials have been published. Wiesenauer and Lüdtke published a meta-analysis of their studies on Galphimia glauca for pollinosis which included data from three studies[141] which had been available only in summary without data for meta-analysis.[137] Two of the trials confirmed the previous positive results whilst in one study, the placebo group did better than the homoeopathically treated group. In 1997, two rigorous trials of placebo-controlled classical homoeopathic treatment of chronic headache became available.[142,143] One had been available as an abstract.[135] Both trials found no effect of homoeopathy over placebo. These results contradict a trial by Brigo and Serpelloni,[45] which reported positive effects in favour of homoeopathy.

Implications

Our study has no major implications for clinical practice because we found little evidence of effectiveness of any single homoeopathic approach on any single clinical condition. Our study does, however, have major implications for future research on homoeopathy. We believe that a serious effort to research homoeopathy is clearly warranted despite its implausibility. Deciding to conduct research on homoeopathy recognises that this approach is a relevant social and medical phenomenon.

Patients, physicians, and purchasers need valid and reliable information (unencumbered by opinion) on which to make decisions, whether or not one believes the approach is scientifically reasonable. This research must not only be high quality but also use a systematic strategy that reflects clear and relevant goals. Whilst randomised placebo-controlled trials hold an important place in such decisions, simply doing more, bigger, and better trials of this type in homoeopathy is more likely to perpetuate than resolve the debate. It is likely that higher quality trials in homoeopathy will show less significant results than those we found. This would be expected, even if homoeopathy has a true clinical effect. What then is a reasonable strategy for approaching this area?

One approach is to develop laboratory models that explore possible mechanisms[144,145] or attempt independent replication of the simpler clinical models that already exist, such as the studies by Reilly et al[14] or Wiesenauer et al[109,111-113] on seasonal allergies. If the results of these attempts are positive, one might conclude that homoeopathy is not always placebo and that it might have some clinical relevance. However, such models rarely reflect actual clinical practice and could be difficult to replicate consistently, as illustrated by the studies on postoperative ileus (table 5). In that trial set, a large, rigorous confirmatory trial produced negative results that were contrary to the other trials and the meta-analysis. In addition, the approach tested in these trials does not accurately reflect how homoeopathy is usually used. Even if positive findings from similar trial sets were found in the future, pharmacologists and other scientists are likely to remain doubtful unless plausible mechanisms are discovered.

Another approach would be to separate research addressing whether homoeopathy is placebo (the academic question currently dominating the debate) more clearly from research exploring whether or not it provides a useful tool in health care (the question of more relevance to patients and health-care providers). To do this, much more detailed information is needed on who is treated with homoeopathy (population characteristics), the reliability of homoeopathic classifications (clinical accuracy), how homoeopathy is applied (standards and decision models of practice), and response rates (effect sizes) of these approaches on specific conditions. This type of detailed clinical information is obtainable from prospective observational studies and would allow for rational planning of randomised trials that truly reflect homoeopathic practice and have clinical and scientific implications.

The resources needed for such a systematic research strategy would be considerable with the risk that in the end homoeopathy may be found to have no value. We wonder, however, if society can afford to ignore this problem and continue to allow it to be approached in an unsystematic and inefficient way. No matter what the end result is for homoeopathy, an investment in such a systematic research strategy could provide us with a model for the evaluation of other emerging fields of medicine, both complementary and conventional.

Contributors

Nicola Clausius participated in protocol development, literature searching, data extraction and assessment, descriptive analysis of study characteristics. Gilbert Ramirez planned and performed most of the statistical analyses, programmed the meta-analysis software, and provided the respective parts for the methods section. Larry Hedges planned and performed all analyses on publication bias, assisted and supervised the planning and performing of the other statistical analyses, and provided the respective parts for the manuscript. Florian Eitel and Dieter Melchart supervised and assisted NC and KL in protocol development, data extraction and assessment, and analyses of study characteristics. DM provided general funding for the Münchener Modell from the Bavarian Parliament and so indirectly made the work possible. FE supervised NC, who did her work for the MD thesis. Wayne Jonas assisted in protocol development, checked some of the scoring and extraction, participated in the statistical analysis, and wrote the final manuscript. Klaus Linde participated in protocol development, literature searching, data extraction and assessment, descriptive analysis of study characteristics and the statistical analysis, and coordinated the study.

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Note for readers: references 48 and 92 are unpublished and hence should not form part of a Vancouver-style reference list. However, they are included below for ease of reading.

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