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Reprinted from THE LANCET, Saturday 20 September 1997
Vol. 350 No. 9081 Pages 834-843

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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.

Lancet 1997; 350: 834-43

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 laws⁷ 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,¹⁰⁻¹² 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 homeop*, and the MeSH terms homeopathy, homoeopathy, and alternative medicine, and screening of all citations found; (3) contacts with homeopathic researchers, institutions reporting on homeopathic research, and homeopathic manufacturers, and follow-up on suggestions from these contacts; (4) searching several extensive homeopathic 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 homeopathic meetings, inquiring about research and searching the conference proceedings, abstract booklets, and indices from those, from other meetings, and from homeopathic 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 homeopathic "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.¹⁸ 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 homeopathy (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 homeopathy and into three levels of dilution. When a single homeopathic remedy was selected based on the total symptom picture of a patient, it was called "classical" homeopathy 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" homeopathy. When multiple remedies were mixed into a standard formula (Fertigarzneimittel) to "cover" a person's symptoms and diagnoses, it was called "complex" homeopathy. 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

Selection data	Number	Trials Included	Inadequate data
Controlled trials	186	Number	89
Clinical trials	171	Sample size	118
Placebo trials	133	Mean study quality	4.04
			3-46
Randomised and/or double-blind	119	Medline citation	25%
Prevention trials	7	Reported positive	67%
			10%
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		Homeopathic types	(out of 89)
"Low dilution" (10^{-1} to 10^{-10} mol/L)	33	Classical	13
"Medium dilution" (10^{-11} to 10^{-19} mol/L)	20	Clinical	49
"High dilution" ($\leq 10^{-20}$ mol/L)	31	Complex	20
Mixed dilution	5	Isopathy	7

*Number of studies meeting specific quality-criteria definitions.

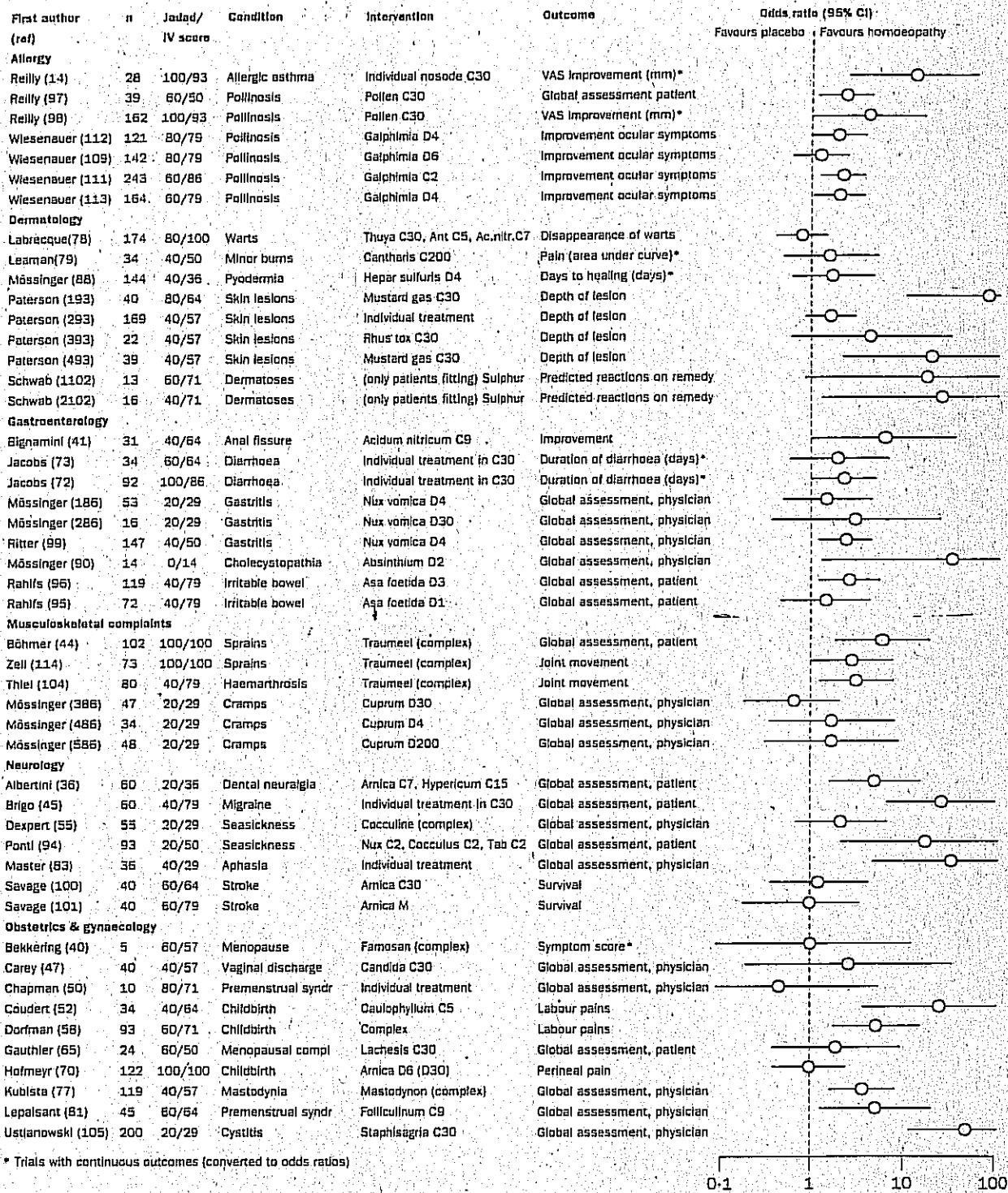
Table 1: Clinical trials of homeopathy

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^{-21} . "High potencies" were defined as those over D23 or C11, with estimated molar concentrations administered less than 10^{-21} .

We used a hierarchy of preser 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.^{22,23} 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



* 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 x 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),^{17,18} 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.²¹ 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 ($\alpha=0.10$) 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

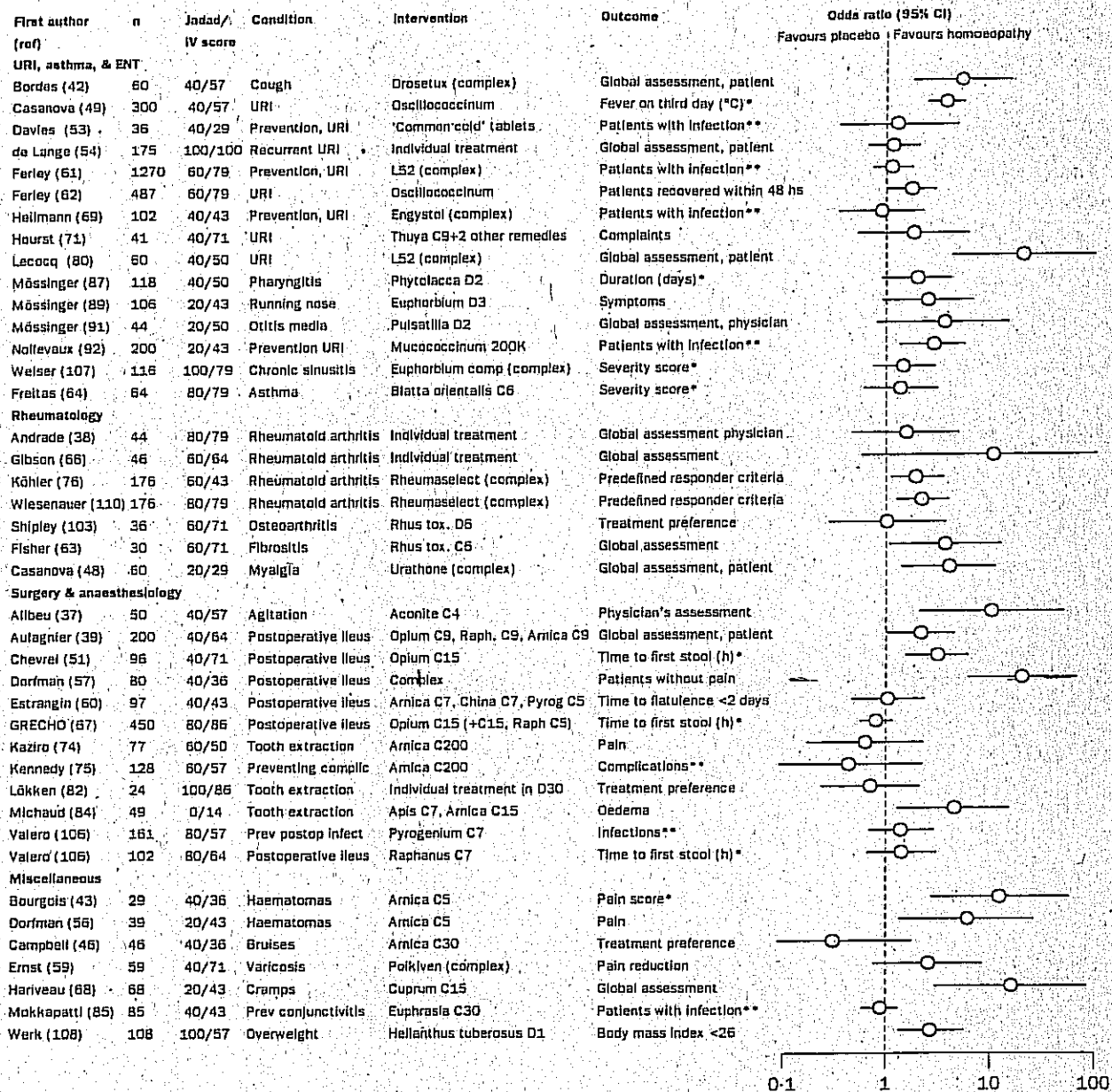


Table 2 - continued

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-effects²⁶ and the more conservative random-effects²⁷ 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

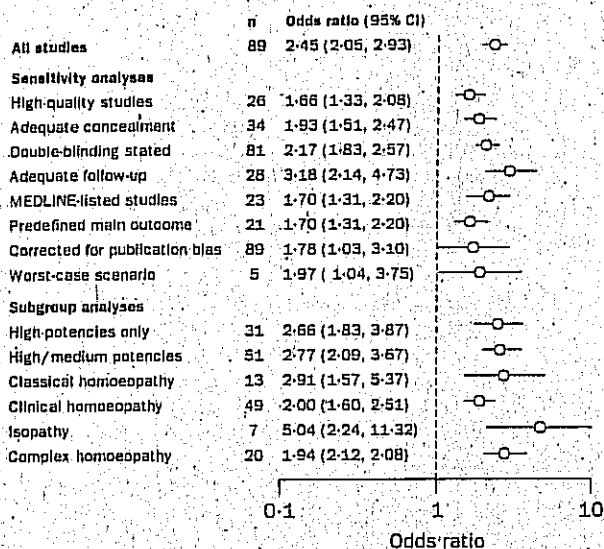


Table 3: Pooled odds ratios and 95% CI (random-effects model) when models for the selection process can be estimated. A general non-parametric selection model was applied to the entire collection of studies to estimate the extent and size of undetected reports.^{11,23} This analysis used a random-effects 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.²¹ 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.^{24,25}

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.^{14,16-114} 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 ($\kappa=0.76$) 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^{-11} 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.

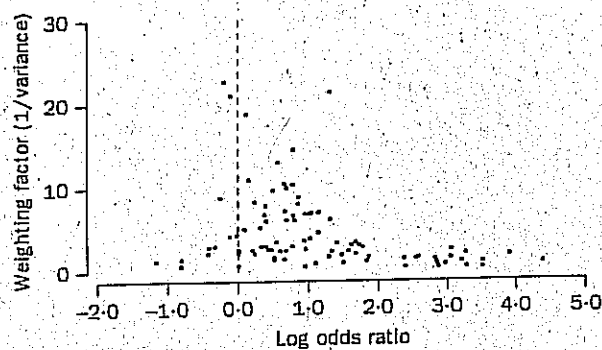
Quantitative data synthesis and sensitivity analyses

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)
Wiesenaue ¹¹²	D4	80/79	30/61	20/60	1.94 (0.93, 4.04)
Wiesenaue ¹¹⁶	D6	80/79	28/71	24/71	1.21 (0.65, 2.24)
Wiesenaue ¹¹¹	C2	60/86	75/121	52/122	2.19 (1.31, 3.67)
Wiesenaue 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 ($\chi^2=16.72$, 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.^{39,51,57,67,104} 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 ²⁴	100/100	Opium C9, Arnica C9, Raph. C9	40/64	-0.64 (-0.94, 0.36)	-0.55 (-0.84, 0.27)
Chevre ¹¹	50/46	Opium C15	40/71	-0.42 (-0.83, 0.02)	-0.63 (-1.04, 0.22)
Dorfman ²¹	40/40	Cincha C5, Arnica C9, Raph. C9	40/36	-0.59 (-1.04, 0.15)	Not measured
GRECHO ¹¹	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 ¹⁰⁴	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.¹⁰ 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 review¹³ and a meta-analysis¹³⁹ 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 studies¹⁴¹ 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,¹⁴ 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^{143,145} or attempt independent replication of the simpler clinical models that already exist, such as the studies by Reilly et al¹⁴ 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.

Acknowledgments

Part of this work was done for the MD thesis of NC and was partly supported by a grant from the Carl and Veronica Carstens Foundation (Essen, Germany). We thank, for their help and comments: A Oxman, J Chalmers, P Göttsche, C Mulrow, J Kleijnen, D Reilly, M Gooch, A Bol, A Vickers, F Worku, A Jadad, J Jacobs, R Brandmaier, and H Albrecht, and the documentation centres of the Laboratories of Boiron, Dolisos, and Heel.

References

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.

- Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States—prevalence, costs, and patterns of use. *N Engl J Med* 1993; 328: 246-52.
- Fisher P, Ward A. Complementary medicine in Europe. *BMJ* 1994; 309: 107-11.
- MacLennan AH, Wilson DH, Taylor AW. Prevalence and cost of alternative medicine in Australia. *Lancet* 1996; 347: 569-73.
- Ernst E, ed. Complementary medicine—an objective appraisal. Oxford: Butterworth Heinemann, 1996.
- Hahnemann S. Organon of medicine. Los Angeles: JP Tarcher, 1982.
- Endler PC, Schulte J. Ultra high dilution: physiology and physics. Dordrecht: Kluwer, 1994.
- Sampson A. Homoeopathy does not work. *Alt Ther* 1995; 1: 48-52.
- O'Keefe D. Is homoeopathy a placebo response? *Lancet* 1986; ii: 29: 1106-07.
- Göttsche P. Trials of homoeopathy. *Lancet* 1993; 341: 1533.
- Knipschild P, Kleijnen J, ter Riet G. Belief in the efficacy of alternative medicine among general practitioners in the Netherlands. *Soc Sci Med* 1990; 31: 625-26.
- Haltenhof H, Hesse B, Bühler KE. Beurteilung und Verbreitung komplementärmedizinischer Verfahren - eine Befragung von 793 Ärzten in Praxis und Klinik. *Gesundh-Wer* 1995; 57: 192-95.
- Schüppel R, Schlich T. Die Verbreitung der Homöopathie unter Ärzten in Deutschland. *Forsch Komplementärmed* 1994; 1: 177-83.
- Ernst E, Resch KL, White AR. Complementary medicine—what physicians think of it: a meta-analysis. *Arch Intern Med* 1995; 155: 2405-08.
- Reilly D, Taylor MA, Beattie N, et al. Is evidence for homoeopathy reproducible? *Lancet* 1994; 344: 1601-06.
- Kleijnen J, Knipschild P, ter Riet G. Clinical trials of homoeopathy. *BMJ* 1991; 302: 316-23.
- Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas* 1960; 20: 37-46.
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1-12.
- Khan KS, Daya S, Jadad AR. The importance of quality of primary studies in producing unbiased systematic reviews. *Arch Intern Med* 1996; 156: 661-66.
- Moher D, Fortin P, Jadad AR, et al. Completeness of reporting of trials published in languages other than English: implications for conduct and reporting of systematic reviews. *Lancet* 1996; 347: 363-66.
- Linde K, Worku F, Melchart D, et al. Randomized clinical trials of acupuncture for asthma—a systematic review. *Forsch Komplementärmed* 1996; 3: 148-55.
- Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. St John's wort for depression—an overview and meta-analysis of randomized clinical trials. *BMJ* 1996; 313: 253-58.
- Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979; 86: 420-28.
- Hasselblad V, Hedges LV. Meta-analysis of diagnostic and screening tests. *Psychol Bull* 1995; 117: 167-78.
- Hedges LV. Fixed effects models. In: Cooper H, Hedges LV, eds. The

- handbook of research synthesis. New York: Russell Sage Foundation, 1994: 286-98.
- 25 Fleiss JL. Measures of effect size for categorical data. In: Cooper H, Hedges LV, eds. The handbook of research synthesis. New York: Russell Sage Foundation, 1994: 245-60.
 - 26 Fleiss JL. Statistical methods for rates and proportions. New York: John Wiley, 1981.
 - 27 DerSimonian R, Laird NM. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177-88.
 - 28 Dickersin K. The existence of publication bias and risk factors for its occurrence. *JAMA* 1990; 263: 1385-89.
 - 29 Begg CB, Berlin JA. Publication bias: a problem in interpreting medical data. *J Roy Stat Soc* 1988; 151 (series A): 419-63.
 - 30 Light RJ, Pillemer DB. Summing up: The science of reviewing research. Cambridge: Harvard University Press, 1984.
 - 31 Hedges LV. Modelling publication selection effects in random effects models in meta-analysis. *Stat Sci* 1992; 7: 246-55.
 - 32 Vevea JL, Hedges LV. A general linear model for estimating effect size in the presence of publication bias. *Psychometrika* 1995; 60: 419-35.
 - 33 Hedges LV, Vevea JL. Estimating effect size under publication bias: small sample properties and robustness of a random effects selection model. *J Educ Behav Stat* 1996; 21: 299-333.
 - 34 Rosenthal R. The "file drawer problem" and tolerance for null results. *Psychol Bull* 1979; 86: 638-41.
 - 35 Orwin RG. A fail-safe-N for effect size in meta-analysis. *J Educ Stat* 1983; 8: 157-59.
 - 36 Albertini H, Goldberg W, Sangui, Toulza. Bilan de 60 observations randomisées—Arnica contre placebo dans les névralgies dentaires. *Homéopathie* 1984; 1: 47.
 - 37 Alibeu JP, Jobert J. Aconit en dilution homéopathique et agitation post-opératoire de l'enfant. *Pédiatrie* 1990; 45: 465-66.
 - 38 Andrade L, Ferraz MB, Ara E, Castro A, Silva MSM. A randomised controlled trial to evaluate the effectiveness of homeopathy in rheumatoid arthritis. *Scand J Rheumatol* 1991; 20: 304-08.
 - 39 Aulagnier G. Action d'un traitement homéopathique sur la reprise du transit post-opératoire. *Homéopathie*. 1985; 6: 42-45.
 - 40 Bekkering GM, van den Bosch W, van den Hoogen H. Bedrijft schone schijn? Een onderzoek om de gerapporteerde werking van een homeopathisch middel te objectiveren. *Huisarts Wetenschap* 1993; 36: 414-15.
 - 41 Biguomini M, Saruggia M, Sansonetti G. Homeopathic treatment of anal fissures using *Nitricum acidum*. *Berl J Res Hom* 1991; 1: 286-87.
 - 42 Bordes LR, Dorfman P. Evaluation de l'activité antidouleur du sirop Droserax: étude en double aveugle versus placebo. *Cahiers d'ORL* 1986; 21: 731-34.
 - 43 Bourgeois JC. Protection du capital veineux chez les perfusées au long cours dans le cancer du sein: Essai clinique en double aveugle. Université Paris Nord (thesis); 1984.
 - 44 Böhmer D, Ambrus P. Behandlung von Sportverletzungen mit Traumeel-Salbe - Kontrollierte Doppelblindstudie. *Biol Med* 1992; 21: 260-68.
 - 45 Brigo B, Serpelloni G. Homeopathic treatment of migraines: a randomized double-blind study of sixty cases (homeopathic remedy versus placebo). *Berl J Res Hom* 1991; 1: 98-106.
 - 46 Campbell A. Two pilot controlled trials of *Arnica montana*. *Br Hom J* 1976; 65: 154-58.
 - 47 Carey H. Double-blind clinical trial of borax and candida in the treatment of vaginal discharge. *Br Homeopath Res Group Comm* 1986; 15: 12-14.
 - 48 Casanova P. Essai clinique d'un produit appelé Urathone. Metz: Lab Lehnig; 1981 (unpublished).
 - 49 Casanova P, Gerard R. Bilan de 3 années d'études randomisées multicentriques oscillocoquinum/placebo. *Oscillocoquinum—rassegna della letteratura internazionale*. Milan: Laboratoires Boiron; 1992: 11-16.
 - 50 Chapman EH, Angelica J, Spitalny G, Strauss M. Results of a study of the homeopathic treatment of PMS. *J Am Inst Hom* 1994; 87: 14-21.
 - 51 Chevrel JP, Saglier J, Destable MD. Reprise du transit intestinal en chirurgie digestive. *Presse Med* 1984; 13: 883.
 - 52 Coudert M. Etude expérimentale de l'action du *Caulophyllum* dans le faux travail et de la dystocie de démarrage. Université de Limoges (thesis), 1981.
 - 53 Davies AE. Clinical investigations into the actions of potencies. *Br Hom J* 1971; 60: 36-41.
 - 54 de Lange de Klerk E, Blommers J, Kuik DJ, Bezemer PD, Feenstra L. Effects of homeopathic medicines on daily burden of symptoms in children with recurrent upper respiratory tract infections. *BMJ* 1994; 309: 1329-32.
 - 55 Dexpert M. Prévention des naupathies par Cocculine. *Homéopath française* 1987; 75: 353-55.
 - 56 Dorfman P, Amodeo G, Ricciotti F, Tétou M, Véroux G. Evaluation de l'activité d'*arnica* 3 CH sur les troubles veineux après perfusion prolongée. *Cahiers Biothérapie* 1988; 98 (suppl): 77-82.
 - 57 Dorfman P, Amodeo G, Ricciotti F, Tétou M, Véroux G. Iléus post-opératoire et homéopathie: bilan d'une évaluation clinique. *Cahiers Biothérapie* 1992; 114: 33-39.
 - 58 Dorfman P, Lasserre MN, Tétou M. Préparation à l'accouchement par homéopathie - expérimentation en double insu versus placebo. *Cahiers Biothérapie* 1987; 94: 77-81.
 - 59 Ernst E, Saradeth T, Resch KL. Complementary therapy of varicose veins—a randomized, placebo-controlled, double-blind trial. *Phlebology* 1990; 5: 157-63.
 - 60 Estrangin M. Essai d'approche expérimentale de la thérapeutique homéopathique. Université de Grenoble (thesis), 1983.
 - 61 Ferley JP, Poutignat N, Azzopardi Y, Charrel M, Zmirou D. Evaluation en médecine ambulatoire de l'activité d'un complexe homéopathique dans la prévention de la grippe et des syndromes grippaux. *Immunolog Méd* 1987; 20: 22-28.
 - 62 Ferley JP, Zmirou D, D'Adhemar D, Balducci F. A controlled evaluation of a homeopathic preparation in the treatment of influenza-like syndromes. *Br J Clin Pharmacol* 1989; 27: 329-35.
 - 63 Fisher P, Greenwood A, Huskisson EC, Turner P, Bejon P. Effect of homeopathic treatment on fibrositis (primary fibromyalgia). *BMJ* 1989; 299: 365-66.
 - 64 Freitas L, Goldenstein E, Sanna OM. A relação médico-paciente indireta e o tratamento homeopático na asma infantil. *Rev Homeopatia* 1995; 6: 26-31.
 - 65 Gauthier JE. Essai thérapeutique comparatif de l'action de la clonidine et du Lachesis mutus dans le traitement des bouffées et de la chaleur de la ménopause. Université de Bordeaux (thesis), 1983.
 - 66 Gibson RG, Gibson S, MacNeill AD, Watson Buchanan W. Homeopathic therapy in rheumatoid arthritis: evaluation by double-blind clinical therapeutic trial. *Br J Clin Pharmacol* 1980; 9: 453-59.
 - 67 GRECHO, ARC, GREPA. Protocole d'un essai de traitement homéopathique en chirurgie digestive. *Presse Med* 1987; 16: 192-93.
 - 68 Hariveau E. La recherche clinique à l'institut Boiron. *Homéopathie* 1987; 5: 55-58.
 - 69 Heilmann A. Ein injizierbares Kombinationspräparat (Engystol N) als Prophylaktikum des grippalen Infektes. *Biolog Med* 1992; 21: 225-29.
 - 70 Hofmeyer GJ, Piccioni V, Blauhof P. Postpartum homeopathic *Arnica montana*: a potency-finding pilot study. *Br J Clin Pract* 1990; 44: 619-21.
 - 71 Hourst P. Tentative d'appréciation de l'efficacité de l'homéopathie. Université Pierre et Marie Curie (thesis); 1981.
 - 72 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: 719-25.
 - 73 Jacobs J, Jimenez LM, Gloyds SS, Casares FE, Gaitan MP, Crothers D. Homeopathic treatment of acute childhood diarrhoea: a randomized clinical trial in Nicaragua. *Br Hom J* 1993; 82: 83-86.
 - 74 Kaziro G. Metronidazole (Flagyl) and *Arnica montana* in the prevention of post-surgical complications, a comparative placebo controlled clinical trial. *Br J Oral Maxillofacial Surg* 1984; 22: 42-49.
 - 75 Kennedy CO. A controlled trial. *Br Hom J* 1971; 60: 120-27.
 - 76 Köhler T. Wirksamkeitsnachweis eines Homöopathikums bei chronischer Polyarthritiden - eine randomisierte Doppelblindstudie bei niedergelassenen Ärzten. *Der Kassenarzt* 1991; 13: 48-52.
 - 77 Kubista E, Müller G, Spona J. Behandlung der Mastopathie mit zyklischer Mastodynie: klinische Ergebnisse und Hormonprofile. *Gynäkol Rundschau* 1986; 26: 65-79.
 - 78 Labrecque M, Auder D, Latulippe LG, Drouin J. Homeopathic treatment of plantar warts. *Can Med Assoc J* 1992; 146: 1749-53.
 - 79 Leaman AM, Gorman D. Cancharis in the early treatment of minor burns. *Arch Emergency Med* 1989; 6: 259-61.
 - 80 Lecoq P. L. 52. Les voies thérapeutiques des syndromes grippaux. *Cahiers Biothérapie* 1985; 87: 65-73.
 - 81 Lepaisant C. Essais thérapeutiques du syndrome prémenstruel—étude en double aveugle avec folliculinum. Université de Caen (thesis), 1994.
 - 82 Lökken P, Straumsheim PA, Tveiten D, Skjelbred P, Borchgrevink CF. Effect of homeopathy on pain and other events after acute trauma: placebo controlled trial with bilateral oral surgery. *BMJ* 1995; 310: 1439-42.
 - 83 Master EJ. Scope of homeopathic drugs in the treatment of Broca's aphasia. Proceedings of 42nd Congress LMHI, Arlington, Virginia, USA, 1987: 330-34.
 - 84 Michaud J. Action d'*Apis mellefica* et d'*Arnica montana* dans la prévention des œdèmes post-opératoires en chirurgie maxillo-faciale à propos d'une expérimentation clinique sur 60. Université de Nantes (thesis), 1981.
 - 85 Mokkapati R. An experimental double-blind study to evaluate the use of Euphrasia in preventing conjunctivitis. *Br Hom J* 1992; 81: 22-24.
 - 86 Mössinger P. Misslungene Wirksamkeitsnachweise. *Allg homöopath Ztg* 1976; 221: 26-31.
 - 87 Mössinger P. Untersuchung über die Behandlung der akuten

- Pharyngitis mit Phytolacca D2. *Allg homöopath Ztg* 1976; 221: 177-83.
- 88 Mössinger P. Zur therapeutischen Wirksamkeit von Hepar sulfuris calcareum D4 bei Pyodermien und Furunkeln. *Allg homöopath Ztg* 1980; 225: 22-28.
- 89 Mössinger P. Untersuchung zur Behandlung des akuten Fließschnupfens mit Euphorbium D3. *Allg homöopath Ztg* 1982; 227: 89-95.
- 90 Mössinger P. Homöopathie und naturwissenschaftliche Medizin—zur Überwindung der Gegensätze. Stuttgart: Hippokrates, 1984: 165-69.
- 91 Mössinger P. Zur Behandlung der Otitis media mit Pulsatilla. *Kinderarzt* 1985; 16: 581-82.
- 92 Nolleaux MA. Klinische Studie van Mucococcinum 200 K als preventieve behandeling van griepachtige aandoeningen: een dubbelblinde test tegenover placebo, 1994 (unpublished).
- 93 Paterson J. Report on the mustard gas experiments (Glasgow and London). *Br Hom J* 1943; 33: 1-12.
- 94 Pond M. Evaluation d'un traitement homéopathique du mal des transports bilan de 93 observations. In: Boiron J, Belon P, Hariveau E, eds. *Recherches en homéopathie*. Lyon: Fondation Française pour la Recherche en Homéopathie; 1986: 71-74.
- 95 Rahlfs VW, Mössinger P. Zur Behandlung des Colon irritabile. *Arzneimittelforschung* 1976; 26: 2230-34.
- 96 Rahlfs VW, Mössinger P. Asa foetida bei Colon irritabile—Doppelblindversuch. *Dtsch med Wschr* 1979; 104: 140-43.
- 97 Reilly DT, Taylor MA. Potent placebo or potency? *Br Hom J* 1985; 74: 65-75.
- 98 Reilly DT, Taylor MA, McSharry C, Aitchinson T. Is homoeopathy a placebo response? Controlled trial of homoeopathic potency, with pollen in hayfever as model. *Lancet* 1986; ii: 881-85.
- 99 Ritter H. Ein homöotherapeutischer doppelter Blindversuch und seine Problematik. *Hippokrates* 1966; 12: 472-76.
- 100 Savage RH, Roe FF. A double blind trial to assess the benefit of Arnica montana in acute stroke illness. *Br Hom J* 1977; 66: 207-20.
- 101 Savage RH, Roe FF. A further double-blind trial to assess the benefit of Arnica montana in acute stroke illness. *Br Hom J* 1978; 67: 210-22.
- 102 Schwab G. Lässt sich eine Wirkung homöopathischer Hochpotenzen nachweisen? Karlsruhe: Deutsche Homöopathische Union; 1990.
- 103 Shipley M, Berry H, Broster G, Jenkins M, Clover A, Williams I. Controlled trial of homoeopathic treatment of osteoarthritis. *Lancet* 1983; i: 97-98.
- 104 Thiel W, Boeho B. Die Therapie von frischen, traumatischen Blutergüssen der Kniegelenke (Hämarthros) mit Traumeel N Injektionslösung. *Biologische Medizin* 1991; 20: 506-15.
- 105 Usdanowski PA. A clinical trial of Staphysagria in postcoital cystitis. *Br Hom J* 1974; 63: 276-77.
- 106 Valero E. Etude de l'action préventive de: Raphanus sativus 7 CH, sur le temps de reprise du transit intestinal post-opératoire (à propos de 80 cas). Pyrogenium 7 CH sur les infections post-opératoires (à propos de 128 cas). Université Médicale de Grenoble (thesis), 1981.
- 107 Weiser M, Glasen B. Klinische Studie zur Untersuchung der Wirksamkeit und Verträglichkeit von Euphorbium compositum-Nasentropfen S bei chronischer Sinusitis. *Forsch Komplementärmed* 1994; 1: 251-59.
- 108 Werk W, Lehmann M, Galland F. Vergleichende, kontrollierte Untersuchung zur Wirkung der homöopathischen, pflanzlichen Arzneimittelzubereitung Helianthus tuberosus D1 zur adjuvanten Therapie bei Patienten mit behandlungsbedürftigem Übergewicht. *Therapiewoche* 1994; 44: 34-39.
- 109 Wiesenauer M, Gaus W. Double-blind trial comparing the effectiveness of the homoeopathic preparation Galphimia potentissima D6, galphimia dilution 10⁶ and placebo on pollinosis. *Arzneimittelforschung* 1985; 35: 1745-47.
- 110 Wiesenauer M, Gaus W. Wirksamkeitsnachweis eines Homöopathikums bei chronischer Polyarthrit. Eine randomisierte Doppelblindstudie bei niedergelassenen Ärzten. *Akt Rheumatol* 1991; 16: 1-9.
- 111 Wiesenauer M, Gaus W, Häussler S. Behandlung der Pollinosis mit Galphimia glauca. Eine Doppelblindstudie unter Praxisbedingungen. *Allergologie* 1990; 13: 359-63.
- 112 Wiesenauer M, Häussler S, Gaus W. Pollinosis-Therapie mit Galphimia glauca. *Forsch Med* 1983; 101: 811-14.
- 113 Wiesenauer M, Lüdtker R. The treatment of pollinosis with Galphimia glauca D4—a randomized placebo-controlled double-blind clinical trial. *Phytomedicine* 1995; 2: 3-6.
- 114 Zell J, Connert WD, Mau J, Feuerstake G. Behandlung von akuten Sprunggelenksdistorsionen. *Fortschr Med* 1988; 106: 96-100.
- 115 Benzécri JP, Maiti GD, Belon P, Questel R. Comparaison entre quatre méthodes de sevrage après une thérapeutique anxiolytique. *Cahiers Anal Domnés* 1991; 16: 389-402.
- 116 Bignamini M, Bertoli A, Consolandi AM. Controlled double-blind trial with Baryta carbonica 15 CH versus placebo in a group of hypertensive subjects confined to bed in two old people's homes. *Br Hom J* 1987; 76: 114-19.
- 117 Carlini EA, Braz S, Lanfranco RP, et al. Efeito hipnótico de medicação homeopática e do placebo. Avaliação pela técnica de "duplo-cego" e "cruzamento". *Rev Ass Med Brasil* 1987; 33: 83-88.
- 118 Davies AE. A pilot study to measure aluminium levels in hair samples of patients with dementia and the influence of aluminium 30c compared with placebo. *Br Hom Res Group Comm* 1988; 18: 42-46.
- 119 Delaunay M. Homéopathie à la maternelle. *Méd douce* 1985; 44: 34-37.
- 120 Fisher P. An experimental double-blind trial method in homoeopathy: use of a limited range of remedies to treat fibrositis. *Br Hom J* 1986; 75: 142-47.
- 121 Gaucher C, Jeulin D, Peyru P, Amengual C. A double-blind randomized placebo controlled study of cholera treatment with highly diluted and succussed solutions. *Br Hom J* 1994; 83: 132-34.
- 122 Gibson J, Haslam Y, Laurensen L, et al. Double blind trial of Arnica in acute trauma patients. *Br Hom Res Group Comm* 1991; 21: 34-41.
- 123 Hardy J. A double blind, placebo controlled trial of house dust potencies in the treatment of house dust allergy. *Br Hom Res Group Comm* 1984; 11: 75-76.
- 124 Hariveau E. Comparaison de Cocculine au placebo et à un produit de référence dans le traitement de la naupathie. *Homéopath française* 1992; 80; 17-22.
- 125 Hildebrandt G, Eltze C. Über die Wirksamkeit einer Behandlung des Muskelkaters mit Rhus toxicodendron D4. Zwei Beiträge zur Pharmakologie adaptiver Prozesse. Heidelberg: Haug Verlag, 1983.
- 126 Hill N, Hanselen R. Clinical trial of a homoeopathic insect after-bite treatment. *Hom Int R&D News* 1993; 3/4: 4-5.
- 127 Janssen G, Veer A, Hagenars J, Kuy A. Lessons learnt from an unsuccessful clinical trial of homoeopathy: results of a small-scale, double-blind trial in proctocolitis. *Br Hom J* 1992; 81: 132-38.
- 128 Kurz C, Nagele F, Zorzi M, Karras H, Enzelsberger H. Bewirkt Homöopathie eine Verbesserung der Reizblasensymptomatik? *Gynäkol Geburtshilfliche Rundsch* 1993; 33 (suppl 1): 330-31.
- 129 Lewis D. Double-blind controlled trial in the treatment of whooping cough using drosera. *Midlands Hom Res Group* 1984; 11: 49-58.
- 130 Matusiewicz R. Wirksamkeit von Engystrol N bei Bronchialasthma unter kortikoidabhängiger Therapie. *Biolog Med* 1995; 24: 242-46.
- 131 Pinsent R, Baker G, Ives G, Davey RW, Jonas S. Does Arnica reduce pain and bleeding after dental extraction? *Br Hom Res Group Comm* 1986; 15: 3-11.
- 132 Saruggia M, Corghi E. Effects of homoeopathic dilutions of china rubra on intradialytic symptomatology in patients treated with chronic haemodialysis. *Br Hom J* 1992; 81: 86-88.
- 133 Sommer RG. Doppelblind-Design mit Arnica bei Muskelkater. *Therapeutikon* 1987; 1: 16.
- 134 Tveiten D, Bruseth S, Borchgrevink CF, Lohne K. Effect of Arnica D30 on hard physical exercise. *Tidsskr Nor Lægeforen* 1991; 111: 3630-31.
- 135 Whitmarsh TE, Coleston DM, Steiner TJ. Homoeopathic prophylaxis of migraine. *Cephalgia* 1993; 13: 254 (abstr).
- 136 Wiesenauer M, Gaus W, Bohnacker U, Häussler S. Wirksamkeitsprüfung von homöopathischen Kombinationspräparaten bei Sinusitis. *Arzneimittelforschung* 1989; 39: 620-25.
- 137 Wiesenauer M. Naturheilverfahren in der Allgemeinmedizin. In: Albrecht H, ed. 10 Jahre Karl und Veronica Carstens-Stiftung, Essen: Karl und Veronica Carstens-Stiftung, 1992: 142-47.
- 138 Yakir M, Kreider S, Oberbaum M, Bzizinsky A, Vithoulkas G, Benwich Z. Homoeopathic treatment of premenstrual syndrome—a pilot study. Proceedings of 8th GIRI Meeting, Jerusalem, 1994: 49-50 (abstr).
- 139 Boissel JP, Cucherat M, Haugh M, Gauthier E. Critical literature review on the effectiveness of homoeopathy: overview of data from homoeopathic medicine trials. Homoeopathic Medicine Research Group. Report to the European Commission. Brussels 1996, 195-210.
- 140 Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodologic quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; 273: 408-12.
- 141 Wiesenauer M, Lüdtker R. A meta-analysis of the homoeopathic treatment of pollinosis with Galphimia glauca. *Forsch Komplementärmed* 1996; 3: 230-34.
- 142 Wulach H, Häussler W, Löwes T, et al. Classical homoeopathic treatment of thronic headaches. *Cephalgia* 1997; 17: 119-26.
- 143 Whitmarsh TE, Coleston-Shields SM, Steiner TJ. Double-blind randomized placebo-controlled study of homoeopathic prophylaxis of migraine. *Cephalgia* 1997; 17: 600-04.
- 144 Sainte-Laudy J, Belon P. Application of flow cytometry to the analysis of the immunosuppressive effect of histamine dilutions on human basophil activation: Effect of cimetidine. *Inflamm Res* 1997; 46: S27-28.
- 145 Enderl PC, Pongratz W, Kastberger G, Wiegant FAC, Schulte J. The effect of highly diluted thyroxine on the climbing activity of frogs. *Vet Hum Toxicol* 1994; 36: 56-59.