The end of homoeopathy

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That homoeopathy fares poorly when compared with allopathy in Aijing Shang and colleagues' systematic evaluation is unsurprising. Of greater interest is the fact that this debate continues, despite 150 years of unfavourable findings. The more dilute the evidence for homoeopathy becomes, the greater seems its popularity.

For too long, a politically correct laissez-faire attitude has existed towards homoeopathy, but there are now signs of enlightenment from unlikely sources. The UK Parliamentary Select Committee on Science and Technology issued a report about complementary and alternative medicine in 2000. It recommended "any therapy that makes specific claims for being able to treat specific conditions should have evidence of being able to do this above and beyond the placebo effect". Going one step further, the Swiss Government, after a 5-year trial, has now withdrawn insurance coverage for homoeopathy and four other complementary treatments because they did not meet efficacy and cost-effectiveness criteria.

In a Comment, Jan Vandenbroucke gives a philosophical interpretation of Shang's study. One other philosopher he might have included is Kant, who reminds us that we see things not as they are, but as we are. This observation is also true of health-care consumers, who may see homoeopathy as a holistic alternative to a disease-focused, technology-driven medical model. It is the attitudes of patients and providers that engender alternative-therapy seeking behaviours which create a greater threat to conventional care—and patients' welfare—than do spurious arguments of putative benefits from absurd dilutions.

Surely the time has passed for selective analyses, biased reports, or further investment in research to perpetuate the homoeopathy versus allopathy debate. Now doctors need to be bold and honest with their patients about homoeopathy's lack of benefit, and with themselves about the failings of modern medicine to address patients' needs for personalised care. ■ *The Lancet*

Would you trust an "intelligent" antipersonnel mine?

AP

http://hrw.org/backgrounder/arms/arms0805/arms0805.pdf

The terrible plight of landmine victims, often children in developing countries, and concerted international efforts to clear and destroy antipersonnel mines are never far from the public eye. As of Aug 17, 153 countries have signed the 1997 Ottawa Mine Ban Treaty. After some cautious optimism at the Nairobi conference at the end of last year, some worrying developments concerning new antipersonnel landmines, banned under the Ottawa treaty, have been brought to the world's attention by a new Human Rights Watch briefing paper *Back in Business? US Landmine Production and Exports*, published this month.

As one of the non-signatories, the US Government under President Clinton had planned to join by 2006. However, on Feb 27, 2004, President George W Bush announced a new landmine policy that abandoned the goal of joining the treaty because "its terms would have required us to give up a needed military capability". The US policy shifted towards the goal of elimination and a global ban of exporting all persistent landmines but allowing those that self-destruct. According to the Human Rights Watch report, the US Government has spent more than US$300 million as part of a research and development plan of so-called smart or intelligent antipersonnel landmines in the past years. One of these, called Spider, is detonated by remote control, which can be overridden. A decision on whether to produce Spider is expected in December this year. Another programme as an alternative to conventional landmines is the Intelligent Munitions System: "an integrated system of effects (lethal, non-lethal, anti-vehicle, anti-personnel, demolitions) software, sensors/seekers, and communications that may be emplaced by multiple means and is capable of unattended employment." A total of $1·3 billion has been requested for development and production of this system.

Weapons can never and will never be "intelligent". As long as governments spend more energy and resources on devising so-called smart landmines than on harnessing and joining the international effort for a landmine-free world, the future of the Mine Ban Treaty looks bleak. ■ *The Lancet*

Homoeopathy and "the growth of truth"

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The comparison between homoeopathy and conventional medicine (allopathy) by Aijing Shang and colleagues[1] in today's *Lancet* goes to the root of the acquisition of knowledge in medicine. In 1846, John Forbes compared homoeopathy and allopathy, mostly informally, but also with a few shrewd experiments.[2] He found the results of homoeopathy for certain ailments as good as those of his own treatments. Because he considered the theory of increased potency by greater dilutions "an outrage to human reason", and therefore any effect of homoeopathy impossible, he proposed that his findings should lead to introspection about the effectiveness of the allopathic medicine of his time.[2] Now, 160 years later, Shang and colleagues compare homoeopathy and allopathy in a meta-analysis of two sets of 110 placebo-controlled trials.[1] At first sight, both homoeopathy and allopathy seem effective. However, a meta-regression and a subgroup of trials of higher quality showed higher sensitivity to potential bias for homoeopathic than for allopathic trials. This difference might be even larger than estimated because one cannot always reliably assess study quality from a publication. Thus Shang and colleagues arrive at a class judgment about homoeopathy that will be gladly accepted by many who always thought homoeopathic evidence was contaminated.[3] Others will claim that this analysis amounts to "data dredging".

Can a sophisticated application of statistics in meta-analysis in itself solve the problem that randomised trials might have provided a wrong answer? Evidence does not exist in isolation. The philosopher Susan Haack coined the crossword analogy wherein the clues are the analogue of experimental evidence, and the entries already completed are the analogue of background information (figure).[4] How reasonable an entry is depends on how well it is supported by the clue and by the background knowledge. We question the results of a randomised trial of homoeopathy because we know that pharmacological action of infinite dilutions is highly implausible.[5] This reasoning is also the explicit starting point of Shang and colleagues and their analyses only gain meaning because of that background. (Lest one concludes that basic science is always the ultimate arbiter: all work to identify carcinogens in tobacco smoke and specific mutations caused by smoking is only undertaken and can only be meaningfully interpreted because we know the epidemiology of smoking and lung cancer.[6])

Shang and colleagues present a subgroup of eight trials of homoeopathy in acute respiratory tract infections that withstands meta-analytical techniques for detecting bias. They are not prepared to accept these results either, because they declare the group of trials is too small, and they prefer to stick to their overall judgment about homoeopathy on the basis of all 110 trials. It seems unscientific to use the argument of "bias" against all investigations in a field. Nevertheless, the logician Douglas Walton proposed that a consistent track record of bias might lead to the conclusion that the bearer of the argument, and therefore the argument, has lesser credibility.[7] This comes close to Shang's proposal to apply judgment to a whole field.

Suppose that the respiratory trials were about a chemical investigated by an allopathic pharmaceutical company, with a meaningful mechanism and a record of effects in laboratory mice and early studies in volunteers. We might be equally mistaken in accepting the results: the trials will be sponsored by the industry, and industry trials have a strong record of coming out in favour of their product.[8] Various mechanisms account for this favouritism, and which might be responsible is usually impossible to judge from the publication.[9] But, should not we have been on safe ground already—the laboratory science is in complete concordance with the

Getty Images

Figure: **Science progresses like solving a crossword puzzle**

trial findings? Safer yes, but not infallibly so.[5,6] The construct might prove to be a "house of cards", as with cyclo-oxygenase 2 antagonists[10]—in which all evidence, from laboratory experiments to randomised trials, seems to have been selectively analysed and published.

Science is an intrinsically human affair. When new theories are created and new evidence sought, judgment will retain a subjective element. This does not mean that it is impossible to sift out which interpretation is more valuable: stimulated by debates and steered by opinions of protagonists, new insights and new data will emerge. These new insights and data will in turn be scrutinised and perhaps accused of bias. In 1906, William Osler delivered an oration on "The growth of truth" and stated: "Truth may suffer all the hazards incident to generation and gestation . . . [and] . . . all scientific truth is conditioned by the state of knowledge at the time of its announcement."[11] Stephen Gould echoed this sentiment at the brink of the 21st century: even if science progresses in a "fitful and meandering way", it achieves progressively more adequate understanding of an objective outside world.[12] The ultimate proof is that science makes progress in changing reality: in allopathic medicine by preventing, alleviating, and curing disease ever more effectively.

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T-cell depletion to prevent GVHD after unrelated-donor marrow transplantation

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Over the past three decades, allogeneic haemopoietic stem cell transplantation (allo-HSCT) has been increasingly used as the treatment of choice for patients affected by several haematological malignancies. With this procedure, the survival prospects of such patients have profoundly changed.[1]

Despite the successes achieved by allo-HSCT, the treatment is still associated with a remarkable incidence of failures, mainly attributable to the development of immune complications (ie, graft-versus-host disease [GVHD] and graft failure),[2] to relapse of malignancy,[3] or to the profound state of immune deficiency that characterises patients given an allograft and favours the occurrence of fatal infections.[4] GVHD is caused by donor-derived alloreactive T-cells contained in the graft attacking non-shared recipient antigens on target tissues. A two-step vicious circle generates the clinical syndrome: conditioning-induced tissue damage activates antigen-presenting cells (mainly of recipient origin) which present recipient alloantigens to donor T-cells transferred with the graft, and in response to recipient antigens, activated donor CD4+ cells expand and generate inflammatory cytokines that cause tissue damage and promote differentiation of cytotoxic CD8+ T-cells, which, in turn, kill recipient cells and further disrupt tissues.[5] In its most severe forms, GVHD may be largely refractory to immunosuppressive therapy, leading directly or indirectly, mainly because of infections, to the patient's death. On the other hand, GVHD has been reported to be associated with a graft-versus-leukaemia (GVL) effect, because of widely distributed histocompatibility antigens of the recipient

Critics slam draft WHO report on homoeopathy

A WHO group that caused controversy with a 2003 report on acupuncture has now turned its attention to homoeopathy. But if the allegations of bias levelled at a draft version of the report are anything to go by, the group has once again put itself in the firing line. Michael McCarthy reports.

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Sceptics of alternative medicine are calling for WHO to extensively revise a draft report on homoeopathy that they claim is little more than pro-homoeopathy propaganda.

The report, says Cees Renckens, a gynaecologist and chairman of the Dutch Union Against Quackery, plays up research that supports homoeopathy while ignoring studies that cast doubt on its effectiveness. "I think it is pathetic that WHO is publishing this kind of paper", he told *The Lancet*. Renckens and others obtained a copy of the confidential draft after it was sent out for comments.

WHO officials call the criticism unfair: "It's preliminary and only a draft", says Xiaorui Zhang, who is acting team coordinator for traditional medicine with the WHO's Department of Essential Drugs and Medicine Policy, which is preparing the report.

But critics are sceptical. The report's tone and approach are identical to a controversial 2003 report on acupuncture prepared by the same group, says Willem Betz, chair of the department for training in family practice at the University of Brussels and chair of SKEPP (Studie Kring voor Kritische Evaluatie van Pseudowetenschap en het Paranormale, the Study Circle for the Critical Evaluation of Pseudoscience and the Paranormal).

The acupuncture report stated that acupuncture had been shown to be effective in controlled clinical trials for more than a score of conditions, including bacillary dysentery and leucopenia. The evidence does not support such claims, said Betz. The acupuncture report and now the homoeopathy report are evidence that "WHO has been infiltrated by missionaries for alternative medicine", Betz said.

The 40-page draft on homoeopathy, entitled *Homoeopathy: review and analysis of reports on controlled clinical trials*, states that the "majority" of peer-reviewed scientific papers published over the past 40 years "have demonstrated that homoeopathy is superior to placebo in placebo-controlled trials and is equivalent to conventional medicines in the treatment of illnesses, in both humans and animals."

The report describes the findings of a selected group of systematic reviews, meta-analysis, controlled trials, cost-effectiveness and outcome studies, observational studies. Almost all of the studies cited support the practice of homoeopathy.

Edzard Ernst, professor of complementary medicine at the Peninsula Medical School (Exeter, UK), said the draft "seems overtly biased, ie, it is based on data that are positive while 'forgetting' the negative studies and systematic reviews."

The randomised clinical trials cited, he said, "all happen to be positive; they are not the most rigorous ones, not the most recent. This does not inspire the reader to think the WHO report was even intended to be objective."

"I find it terribly worrying", he added, "because WHO shouldn't be promoting homoeopathy as it did acupuncture."

Homoeopathy was developed in the late 1700s by Samuel Hahnemann (1755–1843), a German physician and chemist. Hahnemann argued that it was possible to restore health by stimulating the body to regain its balance. This could be done, he said, by administering substances that provoked the same signs and symptoms as the disease. He called this the "similia principle" or "like cures like". The term homoeopathy is derived from the Greek words homoios (similar) and pathos (suffering).

In addition to the signs and symptoms of disease, homoeopathic practitioners say they must also take into account such things as the patient's emotional response to their illness, their personality and temperament before deciding on which homoeopathic regimen to prescribe. Therefore, different patients will receive different treatments for the same disease, making it difficult to conduct randomized controlled trials, homoeopathic practitioners argue.

Hahnemann also believed that it was possible to make homoeopathic preparations, typically herbal or mineral solutions, more powerful by

Still Pictures

Wellcome Library, London

making the solutions more dilute, a principle he called "potentisation". For potentisation to be effective it was necessary that the solution be shaken in a specific manner with each dilution, a process he called "succussion."

Homoeopathic preparations can be so dilute that they do not contain a single molecule of the original herb. Supporters of homoeopathy contend that such preparations retain their effectiveness because the water retains a "memory" of the "vital essence" of the herb or mineral.

Critics of homoeopathy argue that there is no scientific foundation for such claims and no convincing evidence from efficacy from clinical trials. Nevertheless, homoeopathy is extremely popular and its use on the upswing worldwide.

In recent years, however, a number of reviews and clinical trials have called the effectiveness of homoeopathy into question. On its website the National Center for Complementary and Alternative Medicine at the US National Institutes of Health says that "the results of individual, controlled clinical trials of homoeopathy have been contradictory . . . Systematic reviews have not found homoeopathy to be a definitively proven treatment of any medical condition."

According to its 2002 strategy plan, WHO's traditional medicines programme was set up to help countries to develop national policies for the evaluation and regulation of traditional and complementary and alternative medical practices, create a stronger evidence base on the safety and efficacy of TM/CAM (traditional medicine/complementary and alternative medicine) products and practices, promote therapeutically sound use of TM/CAM and document traditional medicines and remedies.

Zhang started out as a "bare foot doctor" in China and went on to train at Beijing University of Traditional Medicine. She became Medical Officer in charge of WHO's traditional Medicine programme in 1992. In 2002, she became Team Coordinator for Traditional Medicine in the Department of Essential Drugs and Medicines Policy.

Zhang says given the widespread use of traditional medicine it is important for WHO to provide these reports. Many alternative and traditional medicine practitioners are not familiar with current scientific research techniques, she said, and that her group found the quality of many of acupuncture, homoeopathy, and other TM/CAM studies to be "very poor".

"Our purpose is to improve the research approaches and appropriate clinical studies", she said.

The reports should be used only as references and should not be taken to be recommendations, she said. "If you carefully read the introduction (to the acupuncture report) you will understand what the objectives are and how to read and use these documents", she said.

In that introduction, Zhang wrote that the report was intended to facilitate research on and the evaluation and application of acupuncture. "Only national health authorities can determine the diseases and conditions for which acupuncture treatment can be recommended", she writes.

"Perhaps I should move that into the text" of the new homoeopathy report, Zhang said in a telephone interview.

But critics say such disclaimers have little effect. Supporters of acupuncture routinely cite the WHO report as an endorsement of the practice, critics say. "Any report WHO puts out will have an impact", says Ernst, who says in debates supporters of acupuncture will counter his evidence by simply citing the claims backed in the WHO report. "Who am I against the WHO?", he asks. "What better name could you think of but WHO?"

Ernst says the WHO homoeopathy report should be extensively revised. Among the changes he would like to see is a methodology section that explains what criteria were used to select papers for review and full disclosure of the names—and any conflicts of interest—of those who drew up the report. "It would be good to see that the panel consists of people who are all well informed and that it covers the entire spectrum from opponents to proponents of homoeopathy."

According to a letter that went out with the homoeopathy draft, the document was prepared based on the discussions at WHO working group meetings held in 2003 and 2004. Zhang declined to reveal the names of the workshop participants, though she said their names would be revealed when the final report was released.

Renckens argues that it is wrong that such reports should not be prepared in secret behind closed doors: "They should send it to some real experts in pharmacology. Homoeopathy is a kind of drug so they should have an open appraisal when they published these kinds of papers and reports", he said. "Of course, when these claims are scrutinised, they will disappear and there would be no report."

Zhang said that she has received many helpful comments from peer reviewers and expected that considerable revision would be done. She said she could not say when the report might now be released.

Michael McCarthy

Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy

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Summary

Background **Homoeopathy is widely used, but specific effects of homoeopathic remedies seem implausible. Bias in the conduct and reporting of trials is a possible explanation for positive findings of trials of both homoeopathy and conventional medicine. We analysed trials of homoeopathy and conventional medicine and estimated treatment effects in trials least likely to be affected by bias.**

Methods **Placebo-controlled trials of homoeopathy were identified by a comprehensive literature search, which covered 19 electronic databases, reference lists of relevant papers, and contacts with experts. Trials in conventional medicine matched to homoeopathy trials for disorder and type of outcome were randomly selected from the Cochrane Controlled Trials Register (issue 1, 2003). Data were extracted in duplicate and outcomes coded so that odds ratios below 1 indicated benefit. Trials described as double-blind, with adequate randomisation, were assumed to be of higher methodological quality. Bias effects were examined in funnel plots and meta-regression models.**

Findings **110 homoeopathy trials and 110 matched conventional-medicine trials were analysed. The median study size was 65 participants (range ten to 1573). 21 homoeopathy trials (19%) and nine (8%) conventional-medicine trials were of higher quality. In both groups, smaller trials and those of lower quality showed more beneficial treatment effects than larger and higher-quality trials. When the analysis was restricted to large trials of higher quality, the odds ratio was 0·88 (95% CI 0·65–1·19) for homoeopathy (eight trials) and 0·58 (0·39–0·85) for conventional medicine (six trials).**

Interpretation **Biases are present in placebo-controlled trials of both homoeopathy and conventional medicine. When account was taken for these biases in the analysis, there was weak evidence for a specific effect of homoeopathic remedies, but strong evidence for specific effects of conventional interventions. This finding is compatible with the notion that the clinical effects of homoeopathy are placebo effects.**

Introduction

Homoeopathy is a widely used but controversial complementary or alternative therapy.[1–3] The basic premise is that like is cured by like (*similia similibus curentur*)—diseases can be treated by substances that produce the same signs and symptoms in a healthy individual.[4,5] The preparation of remedies involves serial dilution, commonly to the extent that no molecules of the original substance remain, and vigorous shaking between dilutions (potentisation). During this process information is thought to be transferred from the diluted substance to the solvent,[6] which in the light of current knowledge seems implausible. Many people therefore assume that any effects of homoeopathy must be non-specific placebo effects.[7]

Bias in the conduct and reporting of trials is a possible explanation for positive findings of placebo-controlled trials of both homoeopathy and allopathy (conventional medicine).[8,9] Publication bias is defined as the preferential and more rapid publication of trials with statistically significant and beneficial results than of trials without significant results.[10] The low methodological quality of many trials is another important source of bias.[11] These biases are more likely to affect small than large studies; the smaller a study, the larger the treatment effect necessary for the results to be statistically significant, whereas large studies are more likely to be of high methodological quality and published even if their results are negative. We examined the effects of homoeopathy and conventional medicine observed in matched pairs of placebo-controlled trials, assessed trial quality and the probability of publication and related biases, and estimated results of large trials least affected by such biases.

Methods

Literature search and data sources

We updated a previous comprehensive search for placebo-controlled trials of homoeopathy, which covered publications up to August, 1995.[12] We searched 19 electronic databases, including specialised homoeopathic and complementary-medicine registries, covering the period from 1995 to January, 2003: MEDLINE, Pre-MEDLINE, EMBASE, DARE, CCTR, CDSR, CINAHL, AMED, MANTIS, Toxline, PASCAL, BIOL, Science Citation Index, CISCOM, British Homeopathic Library, the Homeopathy Abstract page, HomInform Homoeopathic library, NCCAM, and

SIGLE. The search terms in MEDLINE were (homeop* OR homoeop* OR homeopathy (MeSH)) AND (placebo* OR placebos (MeSH) OR placebo effect (MeSH) OR sham). Search terms for the other databases were much the same. We also checked the reference lists of relevant papers, including reviews and meta-analyses of homoeopathic interventions, and contacted experts in the specialty. There were no language restrictions.

We searched the Cochrane Controlled Trials Register to identify placebo-controlled trials of conventional medicine. This bibliographic database of controlled trials is maintained by the Cochrane Collaboration. As part of an international effort to search systematically health-care journals worldwide and other sources of information, the collaboration has combined results of electronic searches and searches by hand to create a comprehensive database of trials.[13] We searched issue 1, 2003, of the Cochrane Controlled Trials Register, which included 353 809 bibliographic references.

Study selection

We defined inclusion and exclusion criteria a priori and applied the same criteria to trials of homoeopathy and of conventional medicine. Inclusion criteria were: that the trial was controlled and of treatments or preventive measures with clinical outcomes; that it had a parallel-group design with placebo control; that there was random or quasi-random assignment to treatment and placebo groups; and that a written report (eg, journal publication, abstract, thesis, conference proceeding, unpublished report, book chapter, monograph) was available with sufficient data to allow the calculation of odds ratios. We excluded trials of homoeopathic "provings" in which remedies are given to healthy individuals to assess their effects, cross-over trials, and N-of-1 trials.

Procedures

We used prespecified criteria to identify outcomes for inclusion in the analyses. The first choice was the main outcome measure, defined as the outcome used for sample-size calculations. If no main outcome was specified, we selected other outcomes, in the order: patients' overall assessment of improvement; physicians' overall assessment of improvement; and the clinically most relevant other outcome measure (for example, the occurrence or duration of an illness). Outcomes were selected randomly if several were judged equally relevant. For each homoeopathy trial, we identified matching trials of conventional medicine that enrolled patients with similar disorders and assessed similar outcomes. We used computer-generated random numbers to select one from several eligible trials of conventional medicine. Outcomes were selected and trials matched without knowledge of trial results.

We used a piloted data-extraction sheet, which covered descriptive information on the trial and study population, intervention, outcome measures, and trial quality. Data were extracted independently by two observers, and discrepancies were resolved by consensus.

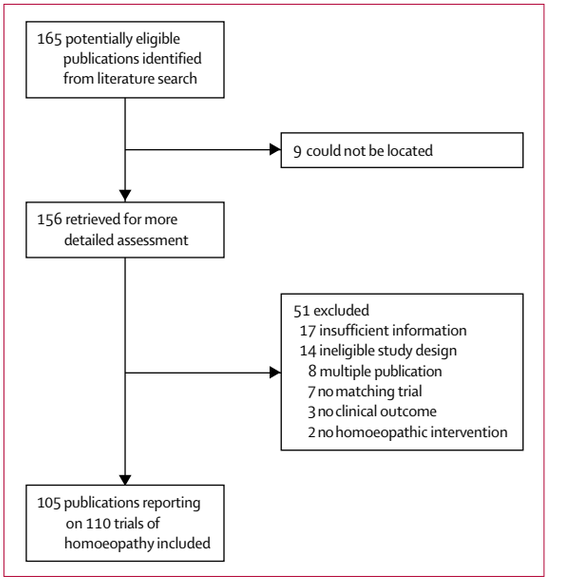

Figure 1: **Identification of 110 eligible placebo-controlled trials of homoeopathy that could be matched to an equal number of placebo-controlled trials of conventional medicine**

Homoeopathic interventions were defined as classical, clinical, or complex homoeopathy, or as isopathy. Classical homoeopathy was defined as comprehensive homoeopathic history-taking, followed by the prescription of a single individualised remedy, possibly with subsequent change of remedy in response to changing symptoms. If no comprehensive homoeopathic history was taken and all patients received a single, identical remedy, interventions were classified as clinical homoeopathy. Complex homoeopathy was defined as the prescription of a mixture of several different remedies. Interventions were classified as isopathy if the agent that was judged to be the cause of the disorder was used (for example, pollen in pollinosis). Indications for treatment were classified as acute or chronic or primary prevention or prophylaxis (interventions with the intention of

Clinical topic	Number of trial pairs
Respiratory-tract infections	21 (19%)
Pollinosis and asthma	16 (15%)
Gynaecology and obstetrics	14 (13%)
Surgery and anaesthetics	12 (11%)
Gastroenterology	12 (11%)
Musculoskeletal disorders	11 (10%)
Neurology	10 (9%)
Other	14 (13%)

Table 1: **Distribution of pairs of placebo-controlled trials by clinical topic**

	Homoeopathy trials (n=110)	Conventional-medicine trials (n=110)
Sample size		
Median (range)	65·5 (10–1573)	65 (12–1367)
Mean (SD)	117 (211)	133 (226)
Median year of publication (range)	1992 (1966–2003)	1994 (1974–2002)
Type of publication		
In English	58 (53%)	94 (85%)
Journal article	94 (85%)	110 (100%)
MEDLINE-indexed journal	45 (41%)	95 (86%)
Type of outcome		
Overall assessment of response	54 (49%)	49 (45%)
Occurrence or duration of disorder	26 (24%)	26 (24%)
Assessment of symptoms	21 (19%)	26 (24%)
Measurement of function or state	6 (5%)	6 (5%)
Assessment of clinical signs	3 (3%)	3 (3%)
Trial quality		
Described as double-blind	101 (92%)	96 (87%)
Adequate generation of allocation sequence	27 (25%)	30 (27%)
Adequate concealment of allocation	49 (45%)	21 (19%)
Analysis by intention to treat	33 (30%)	40 (36%)
Higher quality*	21 (19%)	9 (8%)

*Trials described as double-blind, with adequate generation of allocation sequence and adequate concealment of allocation.

Table 2: **Characteristics of placebo-controlled trials of homoeopathy and conventional medicine**

preventing the occurrence of a disorder or complication). The duration of follow-up was measured in weeks from the start of the treatment to the assessment of outcomes.

Assessment of study quality focused on three key domains of internal validity:[11,14] randomisation (generation of allocation sequence and concealment of allocation), masking (of patients, therapists, and outcome assessors), and data analysis (by intention to treat or other). Random-number tables, computer-generated random numbers, minimisation, coin-tossing, card-shuffling, and lot-drawing were classified as adequate methods for the generation of the allocation sequence. Sealed, opaque, sequentially numbered assignment envelopes, central randomisation, independently prepared and coded drug packs of identical appearance, and on-site computerised randomisation systems were classified as adequate methods of allocation concealment. Analysis by intention to treat was assumed if the reported number of participants randomised and the number analysed were identical. Descriptions of other methods were coded either as inadequate or unclear, depending on the amount of detail provided. Trials described as double-blind, with adequate methods for the generation of allocation sequence and adequate concealment of allocation, were classified as of higher methodological quality.

Graphical and statistical analysis

We expressed results on the odds ratio scale and used the method described by Hasselblad and Hedges[15] to convert differences in continuous outcomes to odds ratios. We recoded outcomes if necessary, so that odds ratios below 1·0 indicated a beneficial effect of treatment in all cases. We used descriptive analyses to compare characteristics of homoeopathy and conventional-medicine trials. We examined heterogeneity between trials with standard χ^2 tests and calculated I^2 statistics, which measure the proportion of variation in treatment effect estimates due to between-study heterogeneity.[16] We investigated the association between study size and trial results in funnel plots, by plotting odds ratios on the horizontal axis (on a logarithmic scale) against their SE on the vertical axis.[17] The extent to which study-level variables were associated with log odds ratios was examined by fitting of univariable and multivariable meta-regression models.[18] The following variables were considered: SE of log odds ratio, language of publication, indexing of the publication in MEDLINE, trial quality (masking, generation of allocation sequence, concealment of allocation, intention-to-treat analysis), duration of follow-up, and clinical topic. For homoeopathy trials, we also examined whether effects varied between types of homoeopathy and types of indications (acute, chronic, primary prevention, or prophylaxis).

We combined treatment effects from larger trials of higher quality by use of standard random-effects meta-analysis and used meta-regression analysis to predict treatment effects in trials as large as the largest trials included in the study. Trials with SE in the lowest quartile were defined as larger trials. Results are given as odds ratios, ratios of odds ratios, or asymmetry coefficients with 95% CI. Ratios of odds ratios of less than 1·0 correspond to a smaller odds ratio for trials with the characteristic and hence a larger apparent benefit of the intervention. Funnel-plot asymmetry was measured by the asymmetry coefficient: the ratio of odds ratios per unit increase in SE of log odds ratio.[19] All analyses were done in Stata version 8.2.

Role of the funding source

The funding sources had no role in the study design; collection, analysis, or interpretation of data; or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the paper for publication.

Results

We identified 165 potentially eligible reports of placebo-controlled trials of homoeopathy and excluded 60 reports. The commonest reasons for exclusion were insufficient information (precluding the calculation of odds ratios), ineligible study design, multiple publication, and inability to identify a matching trial of conventional medicine (figure 1). We included 105 publications that reported on a total of 110 independent trials of homoeopathy (webappendix 1) and 110 publications of 110 matched trials of conventional medicine (webappendix 2).

See Lancet Online for webappendices 1 and 2

The clinical topics studied in pairs of trials ranged from respiratory infections to surgery and anaesthesiology (table 1). The outcomes studied were closely matched; overall assessments of response were analysed in 49% of homoeopathy trials and 45% of trials of conventional medicine (table 2). More detailed information on outcomes is given in the webtable. The average study size was similar for the two groups, with a median of around 65 participants. Overall, study size ranged from ten to 1573 participants. Among homoeopathy trials 48 (44%) concerned clinical homoeopathy, 35 (32%) complex homoeopathy, 18 (16%) classical homoeopathy, and eight (7%) isopathy. For the remaining trial, the nature of the homoeopathic intervention was unclear. 101 (92%) of the conventional-medicine trials investigated drugs, eight (7%) immunotherapy, and one a vaccine. The drugs most frequently tested were non-steroidal anti-inflammatory agents (11 trials), anti-allergy drugs (11 trials), virostatic drugs (11 trials), and antibiotics (seven trials).

53% of homoeopathy trials were published in English compared with 85% of trials in conventional medicine. 50 homoeopathy trials were published in German or French. The two groups of trials also differed in the proportion published in MEDLINE-indexed journals. The two groups had similar methodological quality in terms of masking, generation of allocation sequence, and analysis according to intention to treat, but a higher proportion of homoeopathy trials reported adequate concealment of patients' allocation. 21 (19%) homoeopathy trials and nine (8%) conventional-medicine trials were of higher quality (table 2).

Most odds ratios indicated a beneficial effect of the intervention (figure 2). SE ranged from 0·12 to 1·65 for homoeopathy trials and 0·13 to 1·52 for conventional-medicine trials. Heterogeneity of trial results was less pronounced for homoeopathy (heterogeneity χ^2=309, df 109, p<0·0001) than for conventional medicine (heterogeneity χ^2=481, df 109, p<0·0001). This difference is unlikely to be due to chance (p=0·011 by *F* test). The proportion of total variation in the estimates of treatment effects due to between-study heterogeneity (I^2)[16] was 65% for homoeopathy and 77% for conventional medicine.

Funnel plots were asymmetrical, with smaller trials (larger SE) in the lower part of the plot showing more beneficial treatment effects than larger trials (smaller SE, figure 2). In meta-regression models, the association between SE and treatment effects was similar for trials of homoeopathy and conventional medicine: the respective asymmetry coefficients were 0·17 (95% CI 0·10–0·32) and 0·21 (0·11–0·40). Therefore, with each unit increase in the SE, the odds ratio decreased by a factor of 0·17 for homoeopathy and 0·21 for conventional medicine (table 3).

Other sources of heterogeneity between homoeopathy trials included the language of publication (more beneficial effects in trials published in languages other than English), indexing in MEDLINE (more beneficial effects in trials not indexed in MEDLINE), and indicators of trial quality (more beneficial effects in trials of lower quality). The effects of these variables were generally similar for conventional-medicine trials but did not reach statistical significance (table 3). There was little evidence that treatment effects varied according to duration of follow-up (p=0·862 for homoeopathy, p=0·594 for conventional medicine) or clinical topic (p=0·660 for homoeopathy, p=0·360 for conventional medicine) or that effects differed between different types of homoeopathy (p=0·636) or type of indication (p=0·487). In multivariable analyses, the SE of the log odds ratio (asymmetry coefficient) was the dominant variable in both groups. Coefficients of other

See Lancet Online for webtable

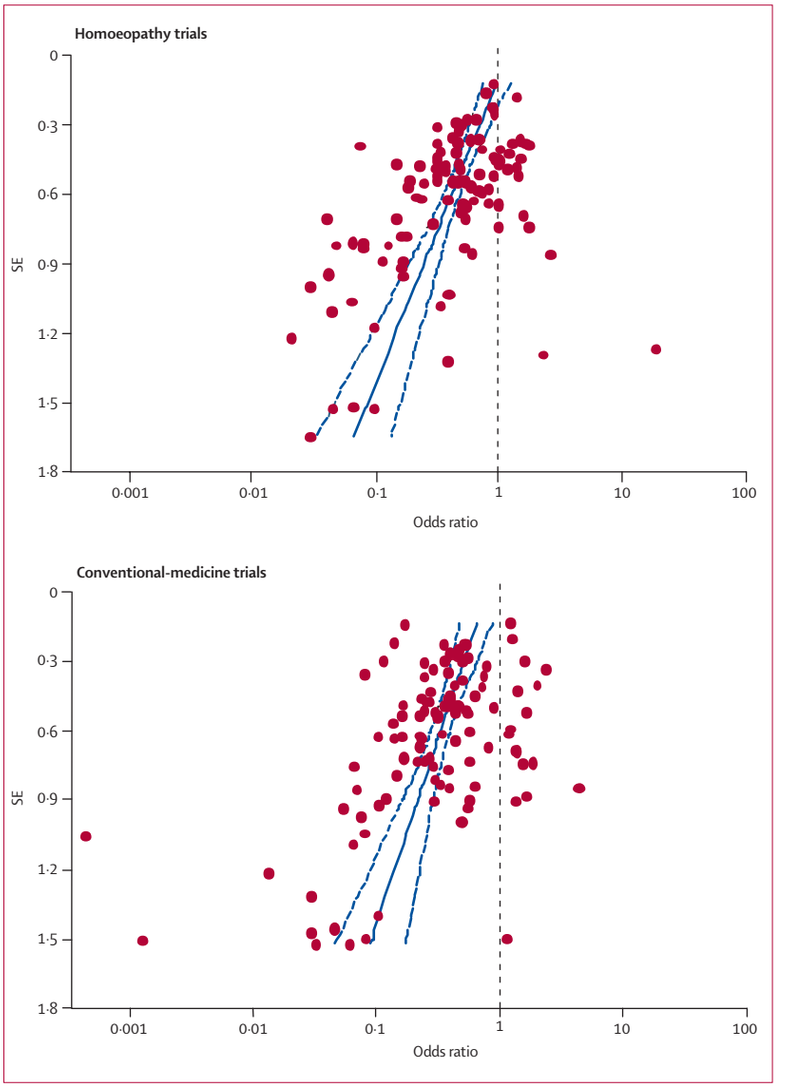

Figure 2: **Funnel plot of 110 homoeopathy trials and 110 matched conventional-medicine trials**
Solid lines indicate predicted treatment effects from meta-regression, with dotted lines representing the 95% CI.

Study characteristic	Homoeopathy		Conventional medicine	
	Ratio of odds ratios* (95% CI)	p	Ratio of odds ratios* (95% CI)	p
Asymmetry coefficient†	0·17 (0·10–0·32)	<0·0001	0·21 (0·11–0·40)	<0·0001
Publication type				
Non-English *vs* English	0·73 (0·53–1·00)	0·05	0·67 (0·40–1·14)	0·144
Not MEDLINE-indexed *vs* MEDLINE-indexed	0·69 (0·50–0·94)	0·019	1·03 (0·61–1·75)	0·906
Study quality				
Not double-blind *vs* double-blind	0·44 (0·22–0·87)	0·017	0·63 (0·36–1·11)	0·107
Generation of allocation sequence not adequate or unclear *vs* adequate	0·67 (0·48–0·95)	0·024	0·98 (0·65–1·46)	0·913
Concealment of allocation sequence not adequate or unclear *vs* adequate	0·78 (0·57–1·07)	0·117	0·76 (0·48–1·16)	0·193
Analysis not by intention to treat or unclear *vs* by intention to treat	1·25 (0·87–1·80)	0·225	1·14 (0·78–1·66)	0·506
Not higher quality or unclear *vs* higher quality	0·62 (0·43–0·90)	0·011	0·61 (0·34–1·09)	0·095

*Odds ratio with characteristic divided by odds ratio without characteristic. Ratios below 1·0 correspond to a smaller odds ratio for trials with characteristic and hence a larger apparent benefit of interventions. Trials published in languages other than English show a more beneficial treatment effect than those published in English, for example. †Ratio of odds ratio per unit increase in SE of log odds ratio.

Table 3: **Univariable meta-regression analysis of treatment effects in 110 placebo-controlled trials of homoeopathy and 110 matched trials of conventional medicine**

variables, including study quality, were attenuated and became non-significant.

When the analysis was restricted to the larger trials of higher reported methodological quality, the odds ratio from random-effects meta-analysis was 0·88 (0·65–1·19) based on eight trials of homoeopathy and 0·58 (0·39–0·85) based on six trials of conventional medicine. Similarly, for prediction of treatment effects in trials as large as the largest trials, the odds ratio was 0·96 (0·73–1·25) for homoeopathy and 0·67 (0·48–0·91) for conventional medicine.

Discussion

We compared the effects of homoeopathy and conventional medicine that are seen in placebo-controlled trials, examined the presence of bias resulting from inadequate methods and selective publication, and estimated results in trials least affected by these biases. We assumed that the effects observed in placebo-controlled trials of homoeopathy could be explained by a combination of methodological deficiencies and biased reporting. Conversely, we postulated that the same biases could not explain the effects observed in comparable placebo-controlled trials of conventional medicine. Our results confirm these hypotheses: when analyses were restricted to large trials of higher quality there was no convincing evidence that homoeopathy was superior to placebo, whereas for conventional medicine an important effect remained. Our results thus provide support for the hypothesis that the clinical effects of homoeopathy, but not those of conventional medicine, are unspecific placebo or context effects.

In 1991, Kleijnen and colleagues[20] argued that there is no reason to believe that compared with homoeopathy "the influence of publication bias, data massage, bad methodology, and so on is much less in conventional medicine". Indeed, we found that trials of homoeopathy tended to be of higher methodological quality than conventional-medicine trials, although most trials of either type of medicine were of low or uncertain quality. In both groups, smaller trials and those of lower quality showed more beneficial treatment effects than larger trials and those of higher quality. Between-trial heterogeneity was less pronounced among homoeopathy trials. This finding might be expected if heterogeneity between homoeopathy trials is essentially due to biased reporting and conduct of trials, whereas in the conventional-medicine sample treatment effects represented an additional relevant source of heterogeneity. When we discussed results with practitioners of homoeopathy, they contended that classical homoeopathy and homoeopathic treatment of chronic disorders, in trials with longer follow-up, would yield specific effects. We addressed these points in additional analyses but found no strong evidence in support of these hypotheses.

This study directly compared the presence of biases and their influence on effect estimates in homoeopathy and conventional-medicine trials. Identical definitions were used, and data were abstracted independently by two observers. The search of homoeopathic publications was comprehensive, and we are confident that we identified a near-complete set of published placebo-controlled trials of homoeopathy. The identification of unpublished studies is notoriously difficult, and we probably missed some of these trials. Conventional-medicine trials were randomly selected from the largest existing database of clinical trials (the Cochrane Controlled Trials Register) and were carefully matched to homoeopathy trials for clinical subject and type of outcome.

Different sources of bias are difficult to disentangle. The methodological quality of randomised trials cannot be reliably assessed from published articles because reporting on important features of the methods is incomplete in many cases.[21] Indeed, deficiencies in methods of smaller trials that were either not reported or not assessed by us could also have contributed to the asymmetrical shape of the funnel plot. We have argued elsewhere that the funnel plot should be seen not only as a means of detecting publication bias, but also as a generic tool for examination of small-study effects—the tendency for the smaller studies to show larger treatment effects.[22] If reporting is inadequate, study size can be a more precise measure of trial quality than formal assessments of trial quality. We addressed this possibility by modelling the effects expected in trials as

large as the largest trial included in our study; again, we found little evidence for an effect of homoeopathy but stronger evidence for conventional medicine. Another limitation of our study is the exclusive focus on the beneficial effects of homoeopathy and conventional medicine, rather than on both benefits and risks. However, the trials included in the study were small and lacked the power to reveal infrequent but important adverse effects. Furthermore, reporting on adverse effects is inadequate even in larger trials.[23] A comprehensive and valid assessment of adverse effects would probably not have been possible within the framework of this study.

A previous review, which did not include a meta-analysis, also found that many trials of homoeopathy show beneficial effects but are of low methodological quality.[20] A meta-analysis by Linde and co-workers[12] was based on an extensive literature search, which we updated for our study, but it did not include trials of conventional medicine. These researchers concluded that their results were "not compatible with the hypothesis that the clinical effects of homoeopathy are completely due to placebo". However, in a subsequent, more detailed analysis of the same data,[24] they observed that more rigorous trials yielded smaller effect sizes and that their meta-analysis[12] probably "at least overestimated the effects of homoeopathic treatments". In a separate study, the same group observed that many trials in complementary medicine have important methodological weaknesses.[25] Finally, a study of 23 trials of homoeopathy that were considered to be of high methodological quality found that the few trials that used objective endpoints were all negative.[26]

Our study has implications beyond the question of whether homoeopathic remedies have specific effects. First, an important point to keep in mind is that most systematic reviews and meta-analyses are based on relatively few trials. Simulation studies have shown that detection of bias is difficult when meta-analyses are based on a small number of trials.[22] For example, for the eight trials of homoeopathic remedies in acute infections of the upper respiratory tract that were included in our sample, the pooled effect indicated a substantial beneficial effect (odds ratio 0·36 [95% CI 0·26–0·50]) and there was neither convincing evidence of funnel-plot asymmetry nor evidence that the effect differed between the trial classified as of higher reported quality and the remaining trials. Such sensitivity analyses might suggest that there is robust evidence that the treatment under investigation works. However, the biases that are prevalent in these publications, as shown by our study, might promote the conclusion that the results cannot be trusted. We submit that similar studies should be done in other types of both complementary and conventional medicine. Such studies would "borrow strength" from a large number of trials and provide empirical information to assist reviewers and readers in the interpretation of findings from small meta-analyses that focus on a specific intervention and disorder. Second, although important progress has been made lately,[11,27] further research is needed to identify the dimensions of methodological quality that are important in different clinical contexts, different outcomes, and different types of trials. Finally, the relation between the probability of publication of a study and its methodological quality should be examined in more detail.

We emphasise that our study, and the trials we examined, exclusively addressed the narrow question of whether homoeopathic remedies have specific effects. Context effects can influence the effects of interventions, and the relationship between patient and carer might be an important pathway mediating such effects.[28,29] Practitioners of homoeopathy can form powerful alliances with their patients, because patients and carers commonly share strong beliefs about the treatment's effectiveness, and other cultural beliefs, which might be both empowering and restorative.[30] For some people, therefore, homoeopathy could be another tool that complements conventional medicine, whereas others might see it as purposeful and antiscientific deception of patients, which has no place in modern health care. Clearly, rather than doing further placebo-controlled trials of homoeopathy,[3] future research efforts should focus on the nature of context effects and on the place of homoeopathy in health-care systems.

Our study powerfully illustrates the interplay and cumulative effect of different sources of bias. We acknowledge that to prove a negative is impossible,[31] but we have shown that the effects seen in placebo-controlled trials of homoeopathy are compatible with the placebo hypothesis. By contrast, with identical methods, we found that the benefits of conventional medicine are unlikely to be explained by unspecific effects.

Contributors

M Egger conceived the study and wrote the first draft of the report. All the authors contributed to the final draft. A Shang, K Huwiler-Müntener, L Nartey, S Dörig, and P Jüni did the literature searches, identified eligible studies, and extracted data. P Jüni advised on data extraction and quality assessment. D Pewsner helped with data extraction and classification of homoeopathy trials. A Shang, J A C Sterne, P Jüni, and M Egger did the statistical analyses and contributed to data interpretation.

Conflict of interest statement

We declare that we have no conflict of interest.

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