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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

**Citizen Petition to Require All OTC Homeopathic Drugs to be
Tested for Effectiveness and Labeled Accurately**

The undersigned submit this petition on behalf of the Center for Inquiry (“CFI”) and its affiliate, the Committee for Skeptical Inquiry (“CSI”), pursuant to Federal Food and Drug Administration (“FDA” or “Agency”) laws and regulations that require all commercially available drugs to be proven effective and be adequately labeled for their intended uses.

CSI is a nonprofit organization dedicated to promoting scientific inquiry and critical investigation, including critical investigation of claims relating to unconventional healthcare practices, such as homeopathic medicine. CSI’s advisors include a number of leading scientists, many of whom are medical specialists. See http://www.csicop.org/about/csi_fellows_and_staff/. CFI is a nonprofit organization supporting the activities of CSI, among other organizations.

A. Action requested

The undersigned hereby request the Commissioner of Food and Drugs to initiate a rulemaking procedure with a proposed rule: 1. requiring all over-the-counter (“OTC”) homeopathic drugs to meet the standards of effectiveness applicable to non-homeopathic OTC drugs; and 2. requiring OTC homeopathic drugs not tested for effectiveness, and all advertisements for such drugs, to carry a warning label stating: “WARNING: The FDA has not determined that this product is safe, effective, and not misbranded for its intended use.”

B. Statement of grounds

1. The Agency is authorized by law to take the action requested.

Although the Agency has not yet done so, the Federal Food, Drug, and Cosmetic Act (the “Act”) permits the Agency to require OTC homeopathic drugs to meet the same effectiveness standards that apply to other OTC drugs.

Section 505(d) of the Act requires “substantial evidence” of effectiveness before a drug can be placed on the market and sold to consumers. In most instances, the Agency has interpreted this to mean that a drug manufacturer must provide adequate and well-controlled clinical studies distinguishing a drug’s effectiveness “from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.” 21 C.F.R. § 314.126.

The Act’s language makes clear that homeopathic drugs fall under the definition of the term “drug” as used broadly in the Act. Section 201(g)(1) of the Act defines the term “drug” as used in the Act to include “articles recognized in the official United States Pharmacopeia [“USP”], the official Homeopathic Pharmacopeia of the United States [“HPUS”], or official National Formulary [“NF”], or any supplement to them; and articles intended for use in the diagnosis, cure, mitigation, treatment, or the prevention of disease in man or other animals; articles (other than food) intended to affect the structure or any function of the body of man or other animals; and articles intended for use as a component of any articles” so specified. Whether or not they are official homeopathic remedies, those products offered for the cure, mitigation, prevention, or treatment of disease conditions are regarded as drugs within the meaning of Section 201(g)(1) of the Act.

Section 400.400 of the FDA Compliance Policy Guidelines, “Conditions Under Which Homeopathic Drugs May be Marketed,” states that a product’s “compliance with requirements of the HPUS, USP, or NF does not establish that it has been shown by appropriate means to be safe, effective, and not misbranded for its intended use.”

The plain meaning of the Act therefore permits the Agency to subject OTC homeopathic drugs to the same effectiveness standards that apply to other OTC drugs.

The Agency has broad authority over the labeling of drugs. *See* Section 502 of the Act and 21 C.F.R. Part 201. Through its rulemaking authority, the Agency has required both testing for effectiveness and appropriate labeling of certain classes of drugs. *E.g.*, Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use, 76 Fed. Reg. 35620 (June 17, 2011).

2. The collective weight of the scientific evidence establishes that homeopathic drugs are no more effective than placebos.

Homeopathic drugs are ineffective for at least two independent reasons, either of which is sufficient to establish homeopathic drugs’ inefficacy in light of basic, well-established principles of biochemistry and pharmacology.

First, there is no reliable scientific evidence that the alleged active ingredients in homeopathic drugs cure the diseases and conditions for which they are indicated. Indeed, as discussed further below, homeopathic “theory” is premised on the magical notion that very small doses of substances that cause disease symptoms can alleviate those same symptoms.

Second, producers of homeopathic drugs typically dilute the drugs’ alleged active ingredients in solution to the point that the solution contains, on average, not a single molecule of the alleged

active ingredient.¹ In other words, what the producers and retailers of homeopathic drugs market as “medications” are nothing more than solutions that are devoid of active ingredients (often the solutions are simply water), which then have been combined with various inactive ingredients, such as balls of ordinary sugar.

Homeopathy, which was developed and popularized in the late 18th century by the German physician Samuel Hahnemann, purports to stimulate the body’s ability to heal itself by administering vanishingly small doses of highly diluted substances.² Homeopathy is based on two principles, both of which contradict basic, well-established laws of modern chemistry and pharmacology: the “principle of similars,” which holds that a disease can be cured by a substance that produces similar symptoms in healthy people; and the “principle of dilutions,” which holds that the lower the dose of the medication, the greater its effectiveness.³ Pursuant to Hahnemann’s teachings, most homeopathic remedies sold today have been diluted repeatedly to the extent that not a single molecule of the alleged healing substance remains.⁴

As one would expect, the scientific evidence establishes that any apparent benefits from homeopathic drugs are mere placebo effects.

The medical journal *The Lancet* published a comprehensive review of homeopathic treatments in 2005.⁵ The authors analyzed every clinical investigation then published on the effects of homeopathy. Their analysis identified 110 well-designed investigations into its effects. The results of those trials were then compared to 110 well-designed investigations of conventional medical therapies for the same ailments. The authors concluded:

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

¹ Homeopaths denote a 1-to-100 dilution by the letter “C,” and a 1-to-10 dilution by the letter “X.” For example, a “6X” homeopathic preparation is a 1-to-10 dilution repeated six times, leaving the alleged active ingredient as one part per million. Homeopathic drugs designated as 24X, 12C or higher contain, on average, no molecules of the original substance from which they were prepared. *See generally* Stehlin, Isadora. “Homeopathy: real medicine or empty promises?” *FDA Consumer*, Dec. 1996. Available online at http://findarticles.com/p/articles/mi_m1370/is_n10_v30/ai_18979004/.

² National Institutes of Health (“NIH”) National Center for Complimentary and Alternative Medicine Backgrounder: Homeopathy, An Introduction (July 2009). Available online at <http://nccam.nih.gov/health/homeopathy/>.

³ *Id.*

⁴ *Id.*

⁵ Shang A, Huwiler-Müntener K, Nartey L, et al. “Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy.” *Lancet* 2005; 366: 726-732. Available online at [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(05\)67177-2/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(05)67177-2/fulltext). (Attached hereto as Exhibit A.)

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.⁶

The highly esteemed Cochrane Collaboration has published reviews of homeopathic treatments for the treatment of a number of diseases and medical conditions, including, among others, dementia, chronic asthma, attention deficit hyperactivity disorder (ADHD), and influenza. In each instance the reviews concluded that evidence for homeopathic drugs' efficacy is nonexistent, unreliable, or too scarce to warrant recommendations regarding homeopathic treatment.⁷

Although most analyses have concluded that there is little evidence to support homeopathy as an effective treatment for any specific condition, some studies have reported positive findings.⁸ Studies reporting positive findings, however, are generally poorly controlled and/or have not been replicated.⁹

⁶ *Id.*

⁷ See, e.g., McCarney, R.W., et al., "Homeopathy for chronic asthma," Cochrane Database of Systematic Reviews 1999, Issue 1. Art. No.: CD000353. DOI: 10.1002/14651858.CD000353.pub2 (available online at <http://www2.cochrane.org/reviews/en/ab000353.html>); Heirs, M. and Dean, M.E., "Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder," Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD005648. DOI: 10.1002/14651858.CD005648.pub2 (available online at <http://www2.cochrane.org/reviews/en/ab005648.html>); McCarney, R.W., et al., "Homeopathy for dementia," Cochrane Database of Systematic Reviews 2003, Issue 1. Art. No.: CD003803. DOI: 10.1002/14651858.CD003803 (available online at <http://www2.cochrane.org/reviews/en/ab003803.html>); Vickers, A. and Smith, C., "Homoeopathic Oscilloccinum for preventing and treating influenza and influenza-like syndromes," Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD001957. DOI: 10.1002/14651858.CD001957.pub4 (available online at <http://www2.cochrane.org/reviews/en/ab001957.html>).

⁸ NIH National Center for Complimentary and Alternative Medicine Backgrounder: Homeopathy, An Introduction (July 2009). Available online at <http://nccam.nih.gov/health/homeopathy/>.

⁹ For example, a 1997 meta-analysis of placebo-controlled trials of homeopathic drugs concluded that patients receiving homeopathic drugs were more likely than patients receiving placebos to show signs of improvement. Linde, K., et al., "Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials." *Lancet*, 1997; 350 (9081): 834-43. Available online at <http://www.ncbi.nlm.nih.gov/pubmed/9310601>. The authors of the report later re-examined their meta-analysis. In a follow-up paper that accounted for new, high-quality trials showing negative results, the authors concluded that "in the study set investigated, there was clear evidence that studies with better methodological quality tended to yield less positive results . . . It seems likely, therefore, that our [1997] meta-analysis at least over-estimated the

The collective weight of scientific evidence demonstrates that homeopathic drugs yield no benefit beyond the placebo effect. In addition, the premise upon which the effectiveness of “homeopathic medicine” is founded—that highly diluted preparations of substances that cause symptoms in healthy individuals will reduce similar symptoms in patients—has no basis in reality and has been disproved repeatedly.¹⁰ Accordingly, major health and medical organizations, including the American Medical Association, have concluded that there is no convincing scientific evidence to support the use of homeopathic treatments in medicine.¹¹

3. The Agency’s failure to regulate homeopathic products has enabled a multi-million dollar industry to market ineffective products to unsuspecting, ill consumers.

Although the Agency has the authority to require homeopathic products to undergo the effectiveness testing that applies to prescription and new OTC drugs, it has to date declined to exercise that authority. The Agency’s permissive regulatory policy has enabled the growth of a multi-million dollar market for products for which there is no credible scientific evidence of effectiveness beyond what is expected from the placebo effect.

Consumer sales of homeopathic treatments in the U.S. reached \$870 million in 2009.¹² According to a 2007 study conducted by the Center for Disease Control and Prevention (“CDC”), an estimated 3.9 million U.S. adults and approximately 900,000 children used homeopathic products in the previous year.¹³ Ill consumers who desire effective medical treatment turn, unwittingly, to homeopathic drugs, using them for a broad range of health concerns, including the treatment of diseases and conditions such as allergies, asthma, chronic fatigue syndrome, depression, digestive disorders, ear infections, headaches, and skin rashes.¹⁴

effects of homeopathic treatments.” Linde, K., et al. “Impact of Study Quality on Outcome in Placebo-Controlled Trials of Homeopathy,” *Journal of Clinical Epidemiology* 1999:52 (7): 631–6. Available online at <http://www.ncbi.nlm.nih.gov/pubmed/10391656> (Attached hereto as Exhibit B.)

¹⁰ See, e.g., Ernst, E. “A systematic review of systematic reviews of homeopathy,” *Br. J. Clin. Pharmacol.* V.54(6): 577-582 (Dec. 2002). Available online at <http://www.ncbi.nlm.nih.gov/pubmed/12492603>. (Attached hereto as Exhibit C.)

¹¹ AMA Council on Scientific Affairs. “Alternative Medicine: Report 12 of the Council on Scientific Affairs (A-97)” page 8. American Medical Association (1997).

¹² “Homeopathy prospers even as controversy rages.” J. Deardorff, *Chicago Tribune*, March 6, 2011. Available online at http://articles.chicagotribune.com/2011-03-06/news/ct-met-0306-homeopathy-20110306_1_homeopathy-oscillocochinum-products.

¹³ NIH National Center for Complimentary and Alternative Medicine Backgrounder: Homeopathy, An Introduction (July 2009). Available online at <http://nccam.nih.gov/health/homeopathy/>.

¹⁴ *Id.*

Homeopathic drugs are typically marketed in ways that lead consumers to believe that they are effective for preventing and treating illnesses and symptoms, some of which can lead to severe complications, hospitalization, or death if improperly treated.

By way of example, the retail giant Wal-Mart Stores, Inc. (“Wal-Mart”) promotes the sale of the homeopathic drug Boiron Oscillococcinum, a homeopathic drug produced by Boiron USA (“Boiron”), through Wal-Mart’s website, www.walmart.com. The website indicates that Boiron Oscillococcinum is indicated for the treatment of “flu-like symptoms.”¹⁵ The website¹⁶ also features an image of the product’s package, which indicates that the product “Reduces [the] Duration and Severity of Flu Symptoms,” including “Fever, Chills, Body Aches and Pains.”

Boiron itself is even bolder, engaging in advertising that is highly misleading as it seeks to suggest this Agency has approved its product. Boiron’s website for Oscillococcinum, <http://www.oscillo.com/about/facts-about-oscillo>, maintains that four clinical studies show the effectiveness of its product, and this claim is then immediately followed by the assertion that “Oscillo complies with a well-established framework of guidelines, regulations, and quality standards established by the FDA.”

Consumers undoubtedly purchase the product based on Wal-Mart’s and Boiron’s assurances that Boiron Oscillococcinum is, in fact, effective for preventing and treating the flu—especially as Boiron implies its product has been tested by this Agency.

Yet there is no credible scientific evidence to support the effectiveness of Boiron Oscillococcinum beyond what is expected from the placebo effect.¹⁷ This is hardly surprising, as Boiron Oscillococcinum’s alleged ingredient—liquefied duck liver and heart—was mistakenly identified in the early 20th century as a possible homeopathic agent on the basis of the false

¹⁵ See <http://www.walmart.com/ip/Boiron-Oscillococcinum-Homeopathic-Flu-Medicine-6ct/10316942#ProductDetail>.

¹⁶ Wal-Mart’s misleading promotion of this homeopathic drug as a treatment for flu is not limited to the webpage on which the product is displayed. Consumers will reach this page only after visiting Wal-Mart’s “Medicine Cabinet” page, <http://www.walmart.com/cp/Medicine-Cabinet/976798>, which assures customers that the products Wal-Mart carries will “fight colds and the flu.” From there, website visitors will navigate to the “Cough, Colds & Flu Wellness Shop” page, <http://health.walmart.com/health-tips/cough-cold-flu/20>, which promises to help the customer “Stay on top of cold and flu season by learning about products that can help you and your family stay well, relieve symptoms and recover fast.” In its “Cough, Cold, and Flu Buying Guide,” <http://health.walmart.com/health-advice/cough-cold-flu-buying-guide/689/>, Wal-Mart asserts that its products will provide the customer “with everything you and your family need for battling a cold or the flu.”

¹⁷ Guo, R., et al., “Complementary Medicine for Treating or Preventing Influenza or Influenza-like Illness,” *Am. J. Med.*, Vol. 120 Issue 11, 923-929 (2007). Available online at <http://www.amjmed.com/article/S0002-9343%2807%2900876-5/abstract>.

belief that it contained “oscillococci,” microscopic bacteria that proved to be imaginary.¹⁸ Moreover, like most producers of homeopathic drugs, Boiron dilutes its alleged active ingredient to the point that the likelihood that even a single molecule of the substance remains is vanishingly small.¹⁹

The homeopathic industry’s marketing of homeopathic drugs, aided by major retailers such as Wal-Mart, is a profound disservice to the public. Beyond leading consumers to squander hundreds of millions of dollars annually on ineffective remedies, homeopathic drug producers and retailers place the public health at risk by displacing proven, effective medical treatments. Influenza, for example, is a serious illness that can lead to complications resulting in hospitalization or even death, especially among the elderly, the very young, and individuals with certain health conditions.²⁰ Yet U.S. sales of the wholly ineffective homeopathic flu remedy Oscillococcinum reached \$15 million in 2008 alone.²¹

The Agency should act to ensure that consumers are not led to believe that effective preventive and therapeutic measures can be ignored in favor of products that amount to mere placebos, at best.

4. As the Agency recognizes, accurate labeling is critical if consumers are to make an informed choice.

As demonstrated by the Agency’s recently issued rule on labeling of sunscreen products, Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use, 76 Fed. Reg. 35620 (June 17, 2011), this Agency recognizes its responsibility to ensure that consumers are provided with all material information regarding a product so they can make an informed choice. The choice of a sunscreen can be very important. At least equally important, however, are choices relating to the treatment of serious diseases such as influenza. Homeopathic drug producers and retailers are misleading consumers into believing that their products are effective. As indicated by Boiron’s promotion of Oscillococcinum, manufacturers of homeopathic products are not averse to implying that this Agency has approved their product.

¹⁸ Nienhuys, J. “The True Story of Oscillococcinum” (2003). Available online at <http://www.homeowatch.org/history/oscillo.html>.

¹⁹ Boiron Oscillococcinum uses a “200C” homeopathic preparation, indicating a 1-to-100 dilution repeated two hundred times. By way of comparison, a mere “30C” preparation is so dilute that a single molecule of the original substance dissolved would occupy a volume of solution that is more than 30 billion times the size of the earth. See Barret, S. “Homeopathy: The Ultimate Fake.” Available online at <http://www.quackwatch.org/01QuackeryRelatedTopics/homeo.html>.

²⁰ See, e.g., Centers for Disease Control and Prevention, “Seasonal Influenza: The Disease.” Available online at <http://www.cdc.gov/flu/about/disease/>.

²¹ Park, Robert L. “Superstition: Belief in the Age of Science,” Princeton University Press. ed., pp. 146 (2008).

Homeopathic manufacturers and distributors know that (as of now) their products are not tested for effectiveness by this Agency; this Agency obviously knows this as well; most consumers, however, are not aware of this fact. Given this Agency's well-deserved reputation for vigorous protection of American consumers, undoubtedly most consumers believe that this Agency requires homeopathic drugs to meet the same effectiveness standards as conventional, allopathic medication.

To ensure that consumers are properly informed, until such time as a homeopathic drug has been adequately tested for effectiveness, this Agency should require packages and advertisements for homeopathic drugs to bear a warning label stating: "WARNING: The FDA has not determined that this product is safe, effective, and not misbranded for its intended use."

C. Environmental impact

Nothing requested in this petition will have an impact on the environment.

D. Economic impact

The only potential loss of income that might result from the requested action is to the manufacturers and distributors of OTC homeopathic drugs. There would be savings of up to \$870 million to consumers if Agency testing of homeopathic drugs established they were ineffective and such drugs were to be removed from the marketplace. In addition, an indeterminate amount of economic benefit would accrue, to individual patients and the economy as a whole, from sick persons ceasing to rely on ineffective drugs.

E. Certification

The undersigned certify that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the undersigned which are unfavorable to the petition.



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EXHIBIT A

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.^{1–4} 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 Homoeopathic Library, the Homeopathy Abstract page, HomInform Homoeopathic library, NCCAM, and

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SIGLE. The search terms in MEDLINE were (homeop* OR homeop* 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 homeopathic 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 homeopathy 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 homeopathic "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 homeopathy 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

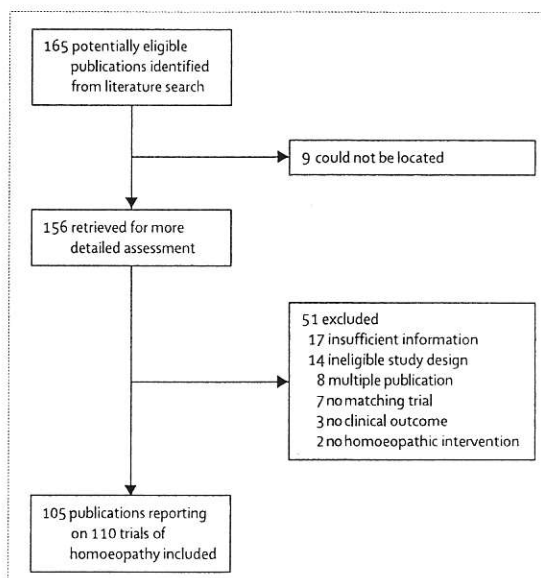


Figure 1: Identification of 110 eligible placebo-controlled trials of homeopathy that could be matched to an equal number of placebo-controlled trials of conventional medicine

population, intervention, outcome measures, and trial quality. Data were extracted independently by two observers, and discrepancies were resolved by consensus.

Homeopathic interventions were defined as classical, clinical, or complex homeopathy, or as isopathy. Classical homeopathy was defined as comprehensive homeopathic 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 homeopathic history was taken and all patients received a single, identical remedy, interventions were classified as clinical homeopathy. Complex homeopathy 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 Hedges¹⁵ 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).

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 $\chi^2=309$, df 109, $p<0.0001$) than for conventional medicine (heterogeneity $\chi^2=481$, 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

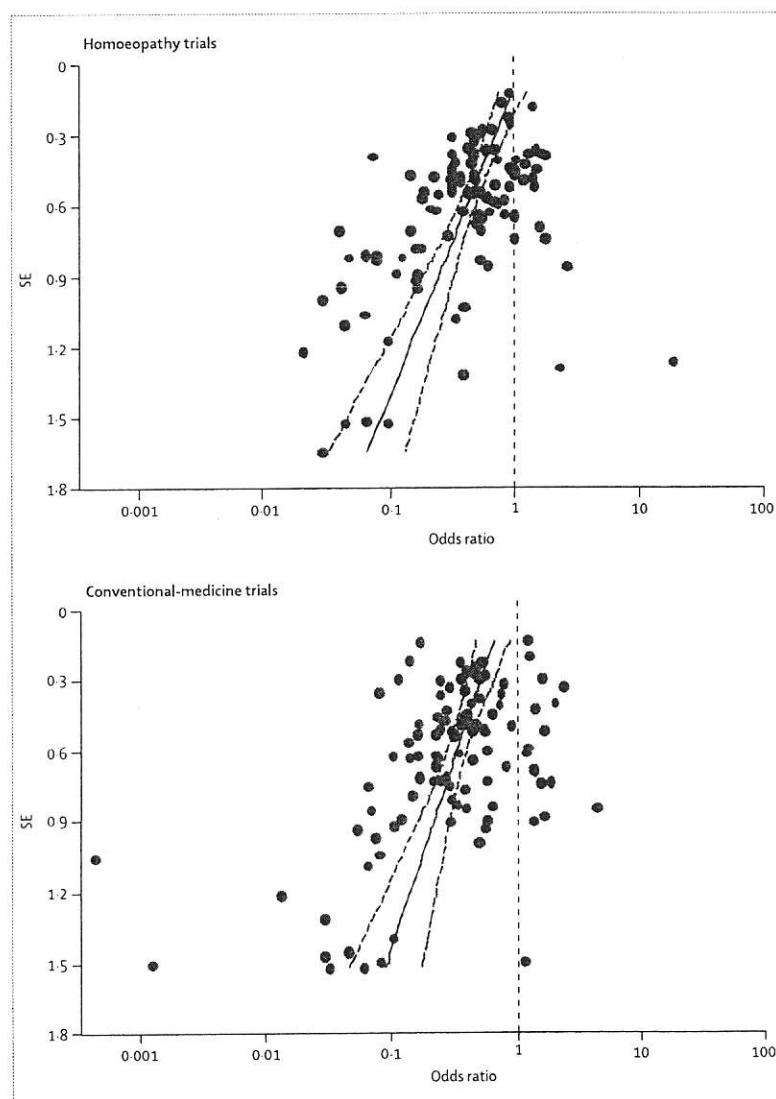


Figure 2: Funnel plot of 110 homoeopathy trials and 110 matched conventional-medicine trials. Solid lines indicate predicted treatment effects from meta-regression, with dotted lines representing the 95% CI.

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 colleagues²⁰ 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.²¹ 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-workers¹² 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-analysis¹² 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.²⁷ 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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EXHIBIT B



Impact of Study Quality on Outcome in Placebo-Controlled Trials of Homeopathy

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ABSTRACT. We investigated the influence of indicators of methodological quality on study outcome in a set of 89 placebo-controlled clinical trials of homeopathy in three different ways: (1) The results of studies meeting single criteria (explicit statement of random allocation, allocation concealment, double-blinding, completeness of follow-up) of methodological quality were compared with those of studies not meeting the criteria in univariate and multivariate analyses; (2) The results of studies scoring above and below predefined scores in two quality assessment scales were compared; (3) Primary studies were consecutively entered into a cumulative meta-analysis according to the summary scores derived from the quality assessment scales. All analyses were performed using meta-regression methods. Studies that were explicitly randomized and were double-blind as well as studies scoring above the cut-points yielded significantly less positive results than studies not meeting the criteria. In the cumulative meta-analyses, there was a trend for increasing effect sizes when more studies with lower-quality scores were added. However, there was no linear relationship between quality scores and study outcome. We conclude that in the study set investigated, there was clear evidence that studies with better methodological quality tended to yield less positive results. Because summarizing disparate study features into a single score is problematic, meta-regression methods simultaneously investigating the influence of single study features seem the best method for investigating the impact of study quality on outcome. J CLIN EPIDEMIOL 52:7:631–636, 1999. © 1999 Elsevier Science Inc.

KEY WORDS. Study quality, meta-analysis, homeopathy, randomized controlled trials, bias

INTRODUCTION

There is increasing evidence that more rigorous trials tend to yield less optimistic results than trials with less precautions against bias [1–3]. In a controversial area like complementary and alternative medicine, in which many trials are performed by proponents with little research experience and published in non-peer-reviewed journals, one might expect that this problem could be even more pronounced. Quality assessment, therefore, should be a mandatory element of systematic reviews of such therapies.

However, the assessment of clinical trial quality is problematic. Although a number of instruments designed for this purpose have been used (see [4] for an overview), there

is no widely accepted single method. There is not even a uniform definition of quality. Most assessment methods focus on criteria dealing with the likelihood of bias such as randomization, blinding, completeness of follow-up, and intent-to-treat analysis. The “dimension” assessed with such criteria is that of “methodological quality” or “internal validity.” There is also substantial controversy over whether quality can be assessed with scoring systems that combine, weight, and sum a catalogue of criteria, or whether the influence of single-quality components should be investigated separately [5,6].

We compared three different approaches to investigate the impact of quality aspects on outcome in a published meta-analysis of placebo-controlled trials of homeopathy [7]: (1) investigating the influence of single-quality components on the outcome, (2) using cut-off points in quality scores as inclusion criterion, and (3) entering trials into meta-analysis consecutively according to quality scores (cumulative meta-analysis).

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METHODS

The general methods of our review have been described in detail elsewhere [7] and are reported here only in a cursory manner. In this article, we focus on the specific methods regarding study quality and outcome.

Selection Criteria and Literature Search

We included all available double-blind and/or randomized clinical trials in which a homeopathic intervention and a placebo had been compared for preventive or therapeutic purposes. Eligible trials were identified through multiple sources including MEDLINE, Embase, complementary medicine databases, contacts with researchers, and checking bibliographies of identified articles. A total of 119 studies meeting the inclusion criteria were identified, and 89 presented sufficient data to be included in the quantitative meta-analysis. Study characteristics and results were extracted by two independent reviewers using a pretested form.

Assessment of Methodological Quality

For assessing the methodological quality, the scale by Jadad *et al.* [8] and a system developed by one of us (KL) were used. The Jadad scale is a scoring system that has three items adding up to a maximum score of five points. Zero, 1, or 2 points can be given for randomization (explicit statement that allocation was randomized and description of an adequate generation of the random sequence), 0, 1, or 2 points for double-blinding (explicit statement that patients and evaluators were blinded and that treatments were indistinguishable), 0 or 1 point for the description of drop-outs and withdrawals (numbers and reasons in all compared groups given separately).

The second scale (Internal Validity Scale = IVS; detailed description submitted for publication), which has

been used in a slightly modified version in other reviews on complementary medicine also [9,10], has seven items scoring 0, 0.5, or 1 point each. Item 1 is a statement of random allocation; item 2 assesses the adequacy of randomization concealment; item 3, baseline comparability; item 4, blinding of patients; item 5, blinding of evaluators; item 6, the likelihood of selection bias after allocation; and item 7, the adequacy of the statistical analysis. Both scales were operationalized with detailed instructions (available from the authors). All trials were assessed by at least two independent reviewers. Each reviewer used both quality scales.

Statistical Analyses

Odds ratios (OR) and their respective 95% confidence intervals (95% CI) were calculated for each trial, with values > 1 indicating that the homeopathic intervention was more effective than placebo. For this analysis, the data from the original meta-analysis [7] were reanalyzed by using meta-regression methods allowing among-trial heterogeneity. First, ORs were natural log-transformed before analysis. This results in a treatment effect $y_i = \ln(OR_i)$ of study i , $i = 1, \dots, n$. We assumed the meta-regression model [11,12]

$$y_i = x_i\beta + b_i + \varepsilon_i, \quad (1)$$

where x_i denotes a vector of known covariates for study i , $b_i \sim N(0, \tau^2)$ is a study-specific random effect reflecting the residual among-trial heterogeneity and $\varepsilon_i \sim N(0, \sigma_i^2)$ with the individual within-trial variance σ_i^2 . The variance σ_i^2 was estimated by the known sample variance s_i^2 of the i th trial. For b_i , ε_i independent $\text{var}(y_i)$ equals $\tau^2 + s_i^2$. Under this model assumption, the estimated linear predictor $x_i\hat{\beta}$ represents the mean effect of all trials having covariate vector x_i , and \hat{b}_i is the i th trial's deviation from this mean. Parameter estimates were obtained via a likelihood-based method (restricted maximum likelihood, REML [13]) im-

TABLE 1. Component and minimum score analysis

	Met		Not met		ROR (95%CI)	Heterogeneity
	n	OR (95%CI)	n	OR (95%CI)		
Component analysis (univariate)						
Explicitly randomized	64	2.23 (1.81–2.75)	25	3.40 (2.32–4.97)	0.66 (0.43–1.01)	0.41 (0.23–0.87)
Adequate concealment	34	2.00 (1.50–2.65)	55	2.83 (2.23–3.58)	0.71 (0.49–1.02)	0.39 (0.22–0.87)
Double-blinding	81	2.18 (1.83–2.60)	8	9.14 (4.81–17.4)	0.24 (0.12–0.46)	0.31 (0.18–0.71)
Complete follow-up	28	3.03 (2.12–4.33)	61	2.29 (1.84–2.86)	1.31 (0.88–2.00)	0.44 (0.26–0.91)
Component analysis (multivariate)						
Explicitly randomized		2.15 (1.78–2.59)		3.36 (2.37–4.78)	0.64 (0.43–0.94)	0.28 (0.15–0.69)
Adequate concealment		2.11 (1.62–2.74)		2.50 (2.00–3.11)	0.84 (0.60–1.18)	
Double-blinding		2.08 (1.75–2.47)		7.85 (4.10–15.0)	0.26 (0.14–0.51)	
Complete follow-up		2.70 (1.97–3.72)		2.21 (1.81–2.69)	1.23 (0.85–1.77)	
Minimum score analysis (univariate)						
Jadad score > 2	40	1.81 (1.41–2.32)	49	3.23 (2.53–4.13)	0.56 (0.40–0.79)	0.34 (0.19–0.78)
IV scale > 4.5	34	1.95 (1.50–2.59)	55	2.92 (2.29–3.73)	0.67 (0.47–0.97)	0.40 (0.23–0.86)
Both	26	1.72 (1.28–2.31)	63	2.95 (2.37–3.67)	0.58 (0.40–0.79)	0.36 (0.20–0.82)

TABLE 2. Pooled odds ratios of studies with the same quality scores and cumulative meta-analysis according to quality

IV Score (n studies)	OR (95%CI)	IV score (n studies)	Cumulative OR (95%CI)	
7.0 (5)	1.55 (0.77–3.10)	= 7.0 (5)	1.55 (0.77–3.10)	
6.5 (2)	4.61 (0.91–23.4)	≥ 6.5 (7)	2.02 (1.06–3.85)	
6.0 (4)	1.35 (0.74–2.45)	≥ 6.0 (11)	1.67 (1.10–2.54)	
5.5 (13)	1.74 (1.38–2.19)	≥ 5.5 (24)	1.71 (1.36–2.15)	
5.0 (10)	2.95 (2.00–4.34)	≥ 5.0 (34)	1.89 (1.53–2.35)	
4.5 (9)	4.33 (1.86–10.1)	≥ 4.5 (43)	2.09 (1.69–2.59)	
4.0 (13)	3.16 (2.00–4.98)	≥ 4.0 (56)	2.29 (1.88–2.80)	
3.5 (9)	2.82 (1.57–5.05)	≥ 3.5 (65)	2.35 (1.94–2.83)	
3.0 (8)	1.97 (1.14–3.40)	≥ 3.0 (73)	2.29 (1.92–2.74)	
2.5 (5)	3.91 (0.97–15.8)	≥ 2.5 (78)	2.42 (2.00–2.91)	
2.0 (9)	2.47 (1.11–5.52)	≥ 2.0 (87)	2.44 (2.02–2.93)	
1.0 (2)	6.92 (1.53–31.4)	all (89)	2.47 (2.06–2.97)	
Jadad score		Jadad score		
5 (10)	2.00 (1.37–2.91)	= 5 (10)	2.00 (1.37–2.91)	
4 (11)	1.42 (1.02–1.99)	≥ 4 (21)	1.68 (1.29–2.18)	
3 (19)	1.83 (1.44–2.34)	≥ 3 (40)	1.73 (1.44–2.08)	
2 (32)	3.24 (2.27–4.63)	≥ 2 (72)	2.26 (1.87–2.73)	
1 (15)	3.58 (2.11–6.08)	≥ 1 (87)	2.44 (2.02–2.93)	
0 (2)	6.92 (1.53–31.4)	all (89)	2.47 (2.06–2.97)	

plemented in PROC MIXED of the SAS stem release 6.12 (SAS Institute, Cary, NC).

A likelihood ratio test was used to examine the null hypothesis of no residual among trial heterogeneity ($\tau^2 = 0$) by comparing the likelihood of this restricted model with that of a model where τ^2 is estimated. If the restriction holds, model (1) reduces to the fixed-effects model. The results are given either on the original OR-scale or in terms of ratios of odds ratios (ROR). A ROR of 1.0 for a dichotomous quality criterion indicates no difference between the two ORs. In our coding scheme, a ROR < 1.0 always reflects that trials meeting the quality criterion had a smaller OR compared with the trial not fulfilling this quality standard.

Approaches to Test the Impact of Quality on Outcome

The relationship between study quality indicators and outcome was tested by three different approaches:

1. Component analysis: Comparison of pooled effect sizes of studies meeting a criterion and of studies not meeting a criterion (explicit statement that allocation to groups was randomized, adequate concealment of randomization, double-blinding, complete follow-up, or intent-to-treat analysis). Both univariate and multivariate analyses were performed.

2. Minimum score analysis: Comparison of pooled effect sizes of studies scoring above or below predefined cut-off-points (≥ 3 in the Jadad score, ≥ 5 in the IVS score, separately and combined).
3. Cumulative meta-analysis: Primary studies were entered consecutively into meta-analysis according to the quality scores received (Jadad and IV scale).

RESULTS

The mean quality score of the 89 trials was 2.58 (SD 1.29) from a maximum of five on the Jadad scale and 4.20 (1.46) from a maximum of seven on the IV scale. Forty (45%) of the trials scored over the predefined quality cut-off (three or higher) on the Jadad scale, and 34 (38%, five or higher) on the IV scale. Twenty-six (29%) trials scored above the cut-off in both scales. Sixty-four (72%) trials explicitly stated that allocation to groups was randomized; 21 (24%) made no clear statement (only double-blinding mentioned); and 4 (4%) trials had used quasi-random methods. For 34 (38%) trials, an adequate method of allocation concealment (mostly consecutively numbered drug containers) was reported; 50 (56%) did not describe the method; and in 5 (6%) concealment was inadequate. Eighty-one (91%) studies were double-blind; 3 (3%), single-blind; and in 5 (6%) there was no statement about blinding. Twenty-eight

(37%) trials either appeared to have included all patients randomized into the analysis or did an intent-to-treat analysis; in 20 studies (22%), major bias seemed unlikely; in 19 (21%) trials major bias seemed possible or likely; and in 22 (25%), the item could not be rated owing to insufficient information.

The pooled mean random effects OR all 89 studies included was 2.45 (95% CI 2.05–2.93). Because there was strong heterogeneity ($\tau^2 = 0.43$; 95%CI 0.25–0.90; $P = 2.4 \times 10^{-13}$), only random effects analyses are reported here. If the analysis was restricted to trials that were explicitly randomized, adequately concealed, or double-blinded, the resulting mean ORs were 2.23 (a decrease of 9% compared with when all 89 trials were pooled), 2.00 (18% decrease), and 2.18 (11% decrease) respectively (see Table 1). The 11% reduction of the overall OR by excluding eight non-double-blind trials indicates that these studies had yielded greatly inflated effect sizes and their removal considerably decreased heterogeneity (see Table 1, last column). Trials with complete follow-up yielded a slightly larger mean OR than did trials not meeting this criterion.

Double-blinding had the strongest impact on outcome in both the univariate and the multivariate analysis. The ratio of odds ratios (ROR) were 0.24 (95%CI 0.12–0.46; $P < 0.0001$) and 0.26 (95%CI 0.14–0.51; $P = 0.0002$), respectively. In the multivariate analysis also the explicit statement of randomization reached significance (ROR 0.64; 95%CI 0.43–0.94; $P = 0.03$). The influence of allocation

concealment and complete follow-up was not statistically significant.

If the analysis was restricted to trials that scored three or higher on the Jadad scale, five or higher on the IV scale, or both, the mean OR was decreased to 1.81 (1.41–2.32, 28% decrease), 1.97 (1.50–2.59, 22% decrease), and 1.72 (1.28–2.31, 30% decrease), respectively. The heterogeneity was reduced most (35%) in the multivariate component analysis.

When the primary studies were entered into the cumulative meta-analysis in descending order of IVS scores, there was a trend for increasing effect sizes when studies with lower quality were added (see Table 2, upper part). If only the five studies scoring highest (seven points) were pooled, the resulting OR was 1.55 (0.79–3.01), and for the studies scoring more than two thirds of the items (≥ 5 points) 1.89 (1.53–2.35). When using the Jadad scale, the mean OR of the highest scoring trials was more positive (2.00; 1.37–2.91) than if trials scoring four or three of the possible five points were added (see Table 2, lower part).

When the OR of primary studies are plotted against quality scores, it becomes obvious that there is no clear linear relationship between these two parameters (Fig. 1 and 2).

DISCUSSION

Our analyses provide clear evidence that in the study set investigated more rigorous trials tended to yield smaller effect sizes. The most plausible explanation of this finding is bias.

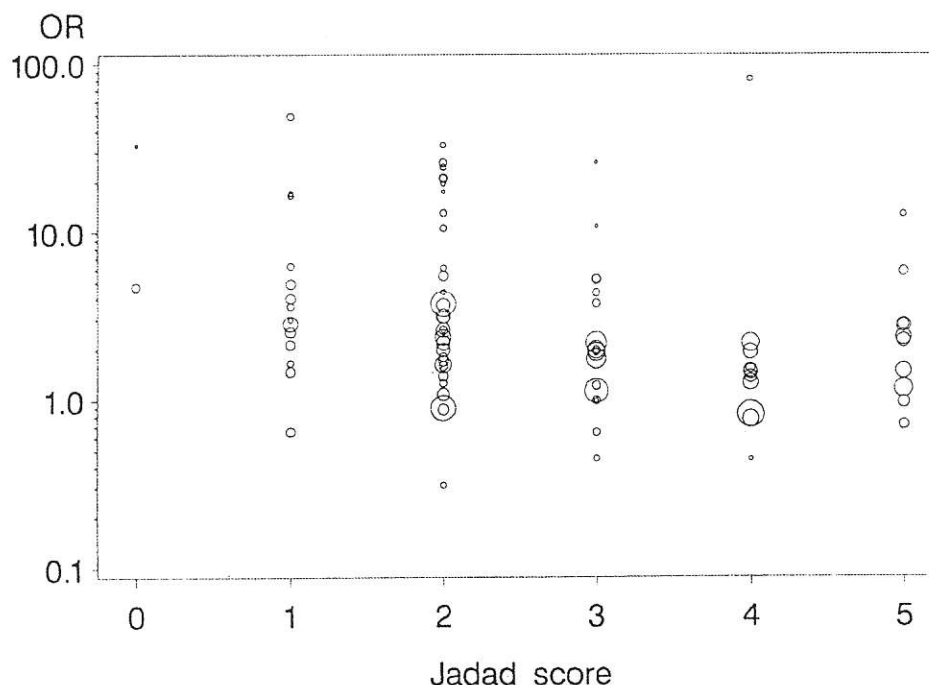


FIGURE 1. Scatterplot of odds ratios of 89 trials of homeopathy plotted against Jadad score (circle areas are scaled proportional to the variance of the trials odds ratio).

The results are comparable to those from similar analyses in conventional medicine. However, the influence of different quality factors depends on the context. Schulz *et al.* [1] found in their analysis covering 250 trials from 33 meta-analyses from the Cochrane Pregnancy and Childbirth database that allocation concealment was the most relevant quality factor. Double-blinded trials also yielded significantly smaller effect sizes; however, the method of sequence generation for the allocation had no influence, and trials with complete follow-up had slightly more positive outcomes. In an analysis of 127 trials from 11 meta-analyses on a variety of conditions by Moher *et al.* [3], the findings were similar to those of Schulz *et al.* for allocation concealment and sequence generation, whereas double-blinding had no effect. In the homeopathy studies evaluated here, double-blinding proved to be the most relevant influence factor. A possible explanation is that bias from this factor might be particularly important, as in these trials homeopathy was mainly used for mild and chronic conditions for which there are few objective outcome measures.

The evidence of bias weakens the findings of our original meta-analysis [7]. Since we completed our literature search in 1995, a considerable number of new homeopathy trials have been published. The fact that a number of the new high-quality trials (e.g. [14,15]) have negative results, and a recent update of our review for the most "original" subtype of homeopathy (classical or individualized homeopathy [16]), seem to confirm the finding that more rigorous trials

have less-promising results. It seems, therefore, likely that our meta-analysis [7] at least overestimated the effects of homeopathic treatments.

The use of the predefined cut-off points to separate higher- and lower-quality trials of homeopathy produced more conservative effect estimates than the use of single components in the univariate analysis. Also, in the cumulative meta-analyses, pooled effect sizes tended to increase when studies with lower scores were entered. However, the scatterplots reveal that a convincing linear relationship does not exist. There are several possible explanations for this result. (1) If the overall hypothesis that all homeopathy is placebo is incorrect, our study set is clinically extremely heterogeneous and the "true" effect sizes might vary strongly between treatment and conditions. This heterogeneity might obscure the slight correlation suggested by the cumulative meta analysis. Other explanations are (2) that the relationship between quality and outcome is rather weak or (3) that the scores used are not suitable to detect an existing relationship. In a set of seven (clinically more homogeneous) meta-analyses applying the widely used scale by Chalmers *et al.* [17], Emerson and coworkers [18] also failed to find a clear relationship between quality and outcome. This would support the explanations (2) and (3).

Quality scores have been criticized for mixing disparate study features into a nontransparent quantitative estimate and introducing an arbitrary element into the analysis [19]. Empirical research providing sound evidence on the valid-

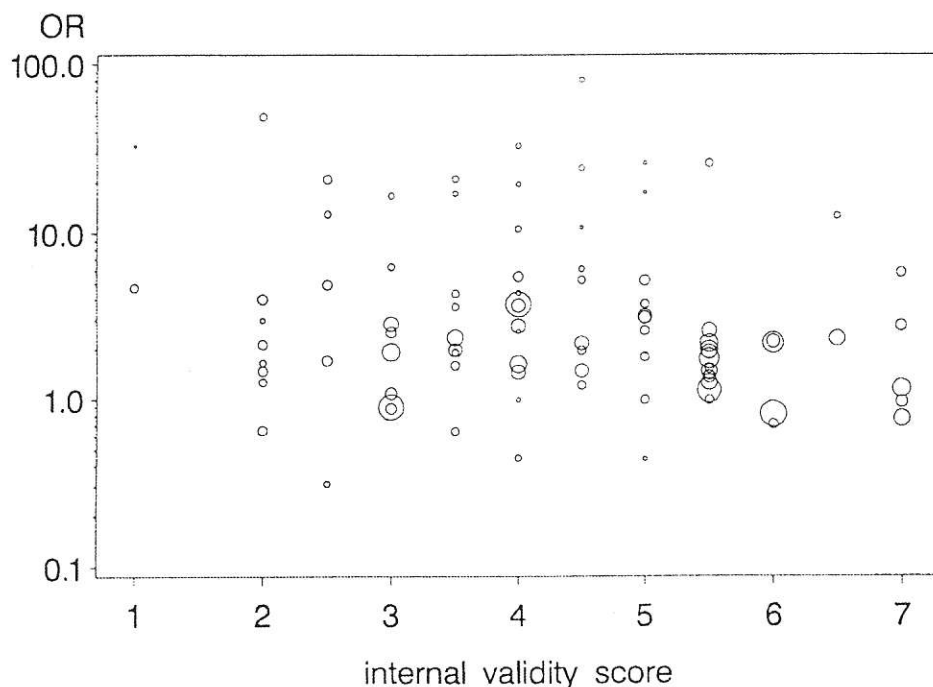


FIGURE 2. Scatterplot of odds ratios of 89 trials of homeopathy plotted against internal validity (IV) score (circle areas are scaled proportional to the variance of the trials odds ratio).

ity and comparability of the various instruments is almost nonexistent [20]. Our results indicate that quality scores might be useful and can lead to similar results as component analysis. Nevertheless, if feasible, meta-regression with multivariate modeling of the influence of single components seems to us the first choice to test the influence of quality on outcome, as this approach is transparent and has a straightforward rationale.

The small number of primary studies in most meta-analyses strongly limits the power of meta-regression. It seems reasonable to use minimum scores in such situations to investigate whether high-quality studies yield results that are different from lower-quality studies. This approach has been used in the literature (e.g. [2,21]). A look on our scatter plot and the results by Emerson *et al.* [18] suggest that in small study sets this might be hazardous. Also, using quality scores to weight primary studies [3] in meta-analysis seems problematic based on such results.

Whether using summary scores or components, readers should be aware that all quality assessments based on published reports are very crude. For example, a single phrase (which even might have been included by the authors but deleted after editorial review because of lack of space) might be used to decide whether a trial is assessed as adequately concealed or not. Even if we assume that allocation concealment is a relevant indicator, the presence or lack of a statement on it does not necessarily mean that a trial is high or low quality. Guidelines such as the CONSORT statement [22] should improve the reporting of key methodological issues in future years.

There is a clear need to investigate the influence of study design factors and aspects of methodological quality on study outcomes in more detail. The available tools for quality assessment are far from being perfect. In our opinion, there is no reason why single-quality criteria and summary scores should not be used in parallel. However, in the present situation we recommend that investigators should not rely on quality scoring methods alone when performing sensitivity analyses. Such analyses should be interpreted with great caution, as their accuracy and relevance may be greatly influenced by context and reporting factors.

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EXHIBIT C

A systematic review of systematic reviews of homeopathy

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Homeopathy remains one of the most controversial subjects in therapeutics. This article is an attempt to clarify its effectiveness based on recent systematic reviews. Electronic databases were searched for systematic reviews/meta-analysis on the subject. Seventeen articles fulfilled the inclusion/exclusion criteria. Six of them related to re-analyses of one landmark meta-analysis. Collectively they implied that the overall positive result of this meta-analysis is not supported by a critical analysis of the data. Eleven independent systematic reviews were located. Collectively they failed to provide strong evidence in favour of homeopathy. In particular, there was no condition which responds convincingly better to homeopathic treatment than to placebo or other control interventions. Similarly, there was no homeopathic remedy that was demonstrated to yield clinical effects that are convincingly different from placebo. It is concluded that the best clinical evidence for homeopathy available to date does not warrant positive recommendations for its use in clinical practice.

Keywords: alternative medicine, clinical trials, homeopathy, meta-analysis, systematic review

Introduction

Homeopathy is a therapeutic method using preparations of substances whose effects when administered to healthy subjects correspond to the manifestations of the disorder (symptoms, clinical signs, pathological states) in the individual patient. The method was developed by Samuel Hahnemann (1755–1843) and is now practised throughout the world [1]. Homeopathy is based on two main principals [1–3]. According to the ‘like cures like’ principle, patients with particular signs and symptoms can be helped by a homeopathic remedy that produces these signs and symptoms in healthy individuals. According to the second principle, homeopathic remedies retain biological activity after repeated dilution and succussion even when diluted beyond Avogadro’s number.

Few therapies have attracted more debate and controversy than homeopathy. Throughout its 200-year history, critics have pointed out that its very principles fly in the face of science, while proponents have maintained that it is narrow minded to reject an overtly helpful approach to healing only because one cannot explain how it might work [2]. Similarly, proponents have quoted seemingly

rigorous trials that suggest efficacy, while critics had little trouble citing equally rigorous studies that implied the opposite.

The existence of contradicting evidence is not unusual in therapeutics. One solution to resolve such contradictions is to conduct systematic reviews and meta-analyses of rigorous studies. In 1997, Linde *et al.* [3] did just that. The conclusions of this technically superb meta-analysis expressed the notion that homeopathic medicines are more than mere placebos. The authors also stated that no indication was identified in which homeopathy is clearly superior to placebo. Despite this and other caveats, homeopaths worldwide celebrated this publication as the ultimate proof of their treatment. Since then, a flurry of interest in homeopathy has emerged, and several further systematic reviews have been published. This article is an attempt to critically evaluate all such papers published since 1997 with a view to defining the clinical effectiveness of homeopathic medicines.

Methods

Literature searches were carried out in the following databases: Medline (via Pubmed), Embase, Amed, CISCOR (from inception to October 2001). The search terms used were homeopath..., homoeopath..., clinical trial, meta-analysis, systematic review, efficacy, effectiveness. In addition, other experts in the field

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($n = 5$) were consulted and my own, extensive files were studied. The bibliographies of all articles thus located were scanned for further relevant references. No language restrictions were applied.

Only systematic reviews (including meta-analyses) of controlled clinical trials of homeopathy with human patients or volunteers were included. Non-systematic reviews, overviews, clinical trials and reviews of non-clinical investigations were excluded. All articles were evaluated by the present author. The following information was extracted from the original articles: inclusion/exclusion criteria, total sample size, assessment of methodological quality, results of meta-analyses, overall conclusion of the authors.

Results

Six re-analyses of Linde *et al.*'s original meta-analysis [3] were located [4–9]. Table 1 summarizes key data from these publications. The results of these re-analyses demonstrate that the more rigorous trials are associated with smaller effect sizes which, in turn, render the overall effect insignificant [5, 6, 8]. One re-analysis suggests that the initial positive meta-analytic result [3] was largely due to publication bias [9], a notion that had been considered by the original authors but was rejected by them. Most notably, perhaps, the authors of the original meta-analysis [3] concluded that their re-analysis 'weakened the findings of their original meta-analysis' [6]. Collectively these re-analyses imply that the initial conclusions of Linde *et al.* [3] was not supported by critical evaluation of their data.

In addition, 11 independent systematic reviews were located [10–20]. Table 2 summarizes key data from these publications. Collectively the findings do not provide strong evidence in favour of homeopathy. With the exception of postoperative ileus [10] and influenza [17] (see below) there is no condition for which homeopathy is convincingly effective [10, 11, 13, 18–20]. Arnica, the most frequently tested homeopathic remedy, is not demonstrably different from placebo [12, 15]. One homeopathic remedy (*oscillococcinum*) was found to be superior to placebo as a treatment and prevention of influenza but the effect size was small and therefore of debatable clinical relevance [17]. Moreover, the volume of the evidence for *oscillococcinum* is small and therefore not fully conclusive. Our systematic review of various homeopathic medicines for postoperative ileus produced an overall positive result [10]. Yet several caveats need to be taken into account, most importantly the fact that the definitive study designed as a multicentre trial to replicate several of smaller studies failed to demonstrate a positive effect [10]. One independent review of all homeopathic RCTs regardless of indication or type of remedy yielded a positive result [16]. Yet the statistical approach to gen-

erate this result was of debatable validity and the authors are keen to point out that their overall result is weak and not sufficient for definitive recommendations.

Discussion

Collectively these data do not provide sound evidence that homeopathic remedies are clinically different from placebos. However, the present analysis has several limitations that should be kept in mind when interpreting its conclusions. Even though a thorough search strategy was adopted, there is no absolute guarantee that all relevant articles were located. Many of the included reviews are from the present author's team, and this could have introduced bias. Finally the validity of conducting a systematic review of systematic reviews has its limitations; most importantly it does not create any information that was not available before.

The clinical evidence summarized above is not dissimilar from the preclinical data. Vickers recently conducted a systematic review of preclinical investigations of homeopathy [21]. Even though 120 papers could be included in the evaluation, this author found that lack of independent replications, serious methodological flaws, and contradictory results precluded any firm conclusion. This systematic review therefore casts considerable doubt on one of the main assumptions of homeopathy, namely that homeopathic remedies retain biological activity even when diluted beyond Avogadro's number (see above).

Perhaps the most recent trial evidence, not yet included in systematic reviews, helps clarify the question whether homeopathic remedies are more than placebos. Since the publication of the systematic reviews, both positive, e.g. [22–24], as well as negative clinical trials e.g. [25–27] have emerged. It seems therefore unlikely that these new findings would substantially change the results of any of the systematic reviews were they to be up-dated.

The recent observation of solute clusters in highly diluted water has been interpreted by several homeopaths as increasing the plausibility of homeopathy [28]. This novel finding requires independent replication. Furthermore, this observation (if confirmed) does not lend itself to explaining how solute clusters could have any effects on human health. Thus both the clinical evidence and the basic research underpinning homeopathy remain unconvincing.

If one accepts this conclusion, one might ask what its implications for future research may be. Two opposing views exist. One holds that the definitive trial of homeopathy should be conducted to once and for all settle the question [29]. The other states that 'new trials ... are no longer a research priority' and advocates 'outcome studies to evaluate the individual treatment decisions ... and

Table 1 The systematic review by Linde *et al.* [3] and its subsequent re-analyses.

Reference	Included trials (number)	Total patient number	Assessment of methodological quality	Meta-analysis	Overall conclusion*	Comment
Linde (1997) [3]	All double-blind and/or randomized placebo-controlled trials of any clinical condition ($n = 186$)	2588	Yes	Of 89 trials which could be submitted to meta-analysis: OR = 2.45; of 26 'good quality trials': OR = 1.66 (both in favour of homeopathy)	Clinical effects of homeopathy are not completely due to placebo	Review was criticised for 1) including different remedies 2) including different conditions 3) including nonrandomized trials
Ernst (1998) [4]	All studies from Linde <i>et al.</i> [3] which received 90 (of 100) points in at least 1 of the 2 quality ratings, using highly dilute remedies, following the principles of 'classical' homeopathy ($n = 5$)	587	Yes	OR = 1.0 (no evidence in favour of homeopathy)	Homeopathic remedies are associated with the same clinical effects as placebo	This analysis specifically tested the efficacy of highly diluted remedies (other remedies could still work via conventional pharmaceutical effects)
Linde (1998) [5]	All trials from Linde <i>et al.</i> [3] which tested 'classical' homeopathic remedies against placebo, no treatment or another treatment ($n = 32$)	1778	Yes	19 placebo-controlled trials were submitted to meta-analysis; OR = 1.62; however, when this analysis was restricted to the methodologically best trials the effect was no longer significant	Individualized homeopathy has an effect over placebo; the evidence, however, is not convincing	Not all of the included trials were randomized and many had other serious methodological weaknesses
Linde (1999) [6]	All trials from Linde <i>et al.</i> [3] which could be submitted to meta-analysis ($n = 89$)	n.d.p.	Yes	The mean OR of the best studies was not in favour of homeopathy	There was clear evidence that studies with better methodological quality tended to yield less positive results	The authors felt that these results 'weaken the findings of [their] original meta-analysis'
Morrison (2000) [7]	26 trials classified by Linde <i>et al.</i> [3] as high quality ($n = 26$)	n.d.p.	Yes	None	No significant trend was seen when correlating security of randomization and trial result	Large multicentre trials were recommended
Ernst (2000) [8]	All trials from Linde <i>et al.</i> [3] that received quality ratings between 1 and 4 on the Jadad score ($n = 77$)	n.d.p.	Yes	None	There is a ... strong linear correlation between OR and Jadad score ($n = 0.97$, $P < 0.05$); homeopathic remedies are, in fact, placebos	Extrapolation from this correlation implies that the most rigorous studies yield an effect size of zero
Sterne (2001) [9]	89 trials of Linde <i>et al.</i> [3] review compared with 89 trials of allopathic medicines	n.d.p.	Yes	Strong evidence for publication bias causing a false positive result in favour of homeopathy	When adjusting high quality trials [of homeopathy] for publication bias, the OR changed from 0.52 to 1.19 but remained unchanged for allopathy	Paper probably not peer-reviewed, adjusting for bias nullified the effect of homeopathy but not for allopathy

RCT = randomized clinical trial, OR = odds ratio, * = verbatim quotes, n.d.p. = no details provided. °Classical homeopathy = approach where remedies are individualized according to patient characteristics deemed important by homeopaths.

Table 2 Independent systematic reviews of homeopathy.

Reference	Included trials (number)	Total patient number	Assessment of methodological quality	Meta-analysis	Overall conclusion*	Comment
Barnes (1997) [10]	All placebo-controlled trials of homeopathy for postoperative ileus ($n = 6$)	776	Yes	Weighted mean difference to time until first sign of peristalsis was in favour of homeopathy (-7.4 h)	Homeopathic treatment can reduce the duration of postoperative ileus, however, several caveats preclude a definitive judgement	The methodologically best trial was convincingly negative
Ernst (1998) [11]	All placebo-controlled trials of homeopathy for delayed onset muscle soreness (DOMS) ($n = 8$)	311	Yes	No meta-analysis possible, all randomized trials were negative	The evidence does not support the hypothesis that homeopathic remedies are more efficacious than placebo for DOMS	DOMS was chosen because it was submitted to clinical trials more often than any other condition
Ernst (1998) [12]	All placebo-controlled trials of homeopathic arnica ($n = 8$)	338	Yes	No meta-analysis possible, no clear trend in favour of homeopathy	The claim that homeopathic arnica is efficacious beyond a placebo effect is not supported by rigorous clinical trials	This analysis set out to test the remedy that had been most frequently submitted to clinical trials, i.e. arnica (see also Lüdtkke below)
Ernst (1999) [13]	All RCTs of homeopathy for migraine prophylaxis ($n = 4$)	284	Yes	No meta-analysis possible; 3 of 4 trials were negative (including the methodologically best)	The trial data ... do not suggest that homeopathy is effective in the prophylaxis of migraine or headache beyond a placebo effect	This analysis tested the efficacy for a condition that homeopaths often treat in clinical practice
Ernst (1999) [14]	All controlled clinical trials of 'classical' homeopathy vs conventional treatments ($n = 6$)	605	No	No meta-analysis possible	No clear trend in favour of homeopathy	Nonrandomized studies were also included
Lüdtkke (1999) [15]	All controlled clinical trials of homeopathic arnica ($n = 37$)	n.d.p.	Yes	No meta-analysis possible	No clear evidence in favour of homeopathic arnica was found	Paper probably not peer-reviewed, trials that used arnica in combination with other remedies and those which were not placebo controlled were also included
Cucherat (2000) [16]	All RCTs of homeopathy vs placebo with clinical or surrogate endpoints ($n = 16$)	2617	Yes	Combined 2-tailed P value was highly significant ($P = 0.000056$) in favour of homeopathy	There is some evidence that homeopathic treatments are more effective than placebo	Strength of evidence was estimated to be low by the authors
Vickers (2000) [17]	All RCTs of homeopathic osillococcinum vs placebo for influenza ($n = 7$)	3459	Yes	RR = 0.64 for influenza prevention RR = 0.28 for influenza treatment	Treatment reduced length of illness significantly by 0.28 days	The authors stated that 'the data are not strong enough to make a general recommendation'
Linde (2000) [18]	All RCTs of homeopathy vs placebo for chronic asthma ($n = 3$)	154	Yes	No meta-analysis possible	No clear trend in favour of homeopathy	Not enough evidence for reliable assessment
Jonas (2000) [19]	All controlled clinical trials of homeopathy for rheumatic conditions ($n = 6$)	392	Yes	Combined OR = 2.19	Homeopathic remedies work better than placebo	Not enough trials for any specific condition to allow reliable assessment
Long (2001) [20]	All RCTs of homeopathy for osteoarthritis ($n = 4$)	406	Yes	No meta-analysis possible	No clear trend in favour of homeopathy	Not enough evidence for reliable assessment

RCT = randomized clinical trial, OR = odds ratio, RR = relative risk. *Classical homeopathy = approach where remedies are individualized according to patient characteristics deemed important by homeopaths.

compare outcomes to orthodox treatment' [30]. Such outcome studies exist. They are burdened with a myriad of methodological weaknesses, most importantly a proneness to selection bias, and usually report findings which are convincingly in favour of the homeopathic approach [31]. This could imply that the individualized, empathetic and time-intensive approach most homeopaths adopt to healthcare yields good clinical results. This emphasizes the importance of the therapeutic encounter and is in accordance with a wealth of information in this area [32]. It does not, however, answer the 'placebo question'. I insist that this question does require an answer – for the sake of scientific honesty and possibly in the name of clinical progress.

In conclusion, the hypothesis that any given homeopathic remedy leads to clinical effects that are relevantly different from placebo or superior to other control interventions for any medical condition, is not supported by evidence from systematic reviews. Until more compelling results are available, homeopathy cannot be viewed as an evidence-based form of therapy.

Conflict of interest: The author is a trained homeopath; he has no financial interests in this area.

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