Are the clinical effects of homoeopathy placebo effects?

Aijing Shang and colleagues (Aug 27, p 726)[1] show that small-study bias pervades all clinical research. They suggest that, for homoeopathy, this observation is a mortal blow because the combined odds ratios of the largest homoeopathy trials converge to zero. We believe that there are some flaws in this argument.

First, the argument hinges on the fact that the studies chosen are representative of homoeopathy in practice and therefore externally valid. As far as we are aware, none of the studies assesses individualised classic homoeopathy, as commonly practised in the UK and Europe. However, Shang and colleagues have not disclosed the details of the eight largest homoeopathic studies.

Second, the six studies of conventional interventions are, by comparison, highly selected. The substances assessed within them have gone through the four clinical pharmacological stages of drug testing. Most newly developed pharmaceuticals do not make it to the last stage of large, multicentre phase IV trials. Therefore the allopathy trials chosen by Shang and colleagues tested medications that had already been largely proven to be efficacious, whereas most homoeopathy trials start from a far less systematic and rigorous evidence base. There have, after all, been very few placebo-controlled randomised trials in homoeopathy, which is why there is an absence of evidence. We are only just beginning to understand how to research homoeopathy and complementary medicine in general. This seems to be an argument for more research, not less.

Third, the argument of "no differential benefit over placebo" presupposes that the standard against which effects are compared—ie, non-specific effects in the placebo groups—is comparable across trials, diseases, and therapeutic modalities. This is not true for such a variety of conditions. We know from many studies that complementary medicine produces large non-specific effects.[2,3] Hence the therapeutic effect seen in placebo groups receiving complementary medicines such as homoeopathy may be stronger than the specific effects of conventional medications in the therapeutic groups of conventional trials. This has been called the "efficacy paradox",[4] and it could confound the conclusions from placebo-controlled trials. To presuppose that the effects across control groups of different studies are roughly the same is probably incorrect, particularly since we have shown that the non-specific effects of treatments in conventional medicine have the largest effect size and that this effect size can vary substantially.[5]

The challenge is not to be better than placebo, but to produce the largest clinical effect, safely and ethically. We believe that homoeopathy has been inadequately tested in this context.

We declare that we have no conflict of interest.

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1 Shang A, Huwiler-Münteler 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:** 726–32.
2 Lewith GT, Watkins AD, Hyland ME, et al. Use of ultramolecular potencies of allergen to treat asthmatic people allergic to house dust mite: double blind randomised controlled clinical trial. *BMJ* 2002; **324:** 520–23.
3 White P, Lewith G, Prescott P, Conway J. Acupuncture versus placebo for the treatment of chronic mechanical neck pain. *Ann Intern Med* 2004; **141:** 911–19.
4 Walach H. Das Wirksamkeitsparadox in der Komplementärmedizin. *Forschende Komplementärmedizin und Klassische Naturheilkunde* 2001; **8:** 193–95.
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We congratulate Aijing Shang and colleagues[1] on their meta-analysis examining the clinical effects of homoeopathy. Their methods largely reproduce those of our meta-analysis on the same topic published in *The Lancet* 8 years ago.[2] We agree that homoeopathy is highly implausible and that the evidence from placebo-controlled trials is not robust. However, there are major problems with the way Shang and colleagues present and discuss their results, as well as how *The Lancet* reviewed and interpreted this study. We will point out two.

First, Shang and colleagues do not follow accepted and published guidelines for reporting meta-analyses. In 1999, *The Lancet* published the QUOROM statement for improving the quality of reports of meta-analyses[3] and the Cochrane Collaboration guidelines are listed in the instructions for authors. Shang and colleagues did not follow either of these guidelines, nor did *The Lancet* intervene. The QUOROM statement clearly requires that meta-analyses present "descriptive data for each trial" and "data needed to calculate effect sizes and confidence intervals". Shang and colleagues do not report the trials excluded from the review, the quality assessments and odds ratios of all trials included in the review, nor which eight trials were included in the final meta-analysis. This lack of detail is unacceptable in a paper drawing a strong clinical conclusion.

Second, problems with pooling are not discussed. Pooling of data from clinical trials makes sense only if all the trials measure the same effect. In our 1997 meta-analysis, we justified the pooling of different interventions, conditions, and outcomes on the basis that, if homoeopathy is always a placebo, all trials measure, in principle, the same thing. There are major limitations associated with this assumption. If homoeopathy (or allopathy) works for some conditions and not for others (a statement for which there is some evidence[4]), then interpretation of

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funnel plots and meta-regressions based on sample size is severely hampered. Since sample size is not independent of the disease, intervention, and outcome, it is impossible to separate the influence of bias from the true effect size by this method. Therefore, restricting an analysis to the largest studies risks producing a false-negative result. Furthermore, since the main analysis is based on only eight and six (probably unmatched) studies, the outcome could easily be due to chance, as is suggested by the large confidence intervals. Given these limitations, Shang and colleagues' conclusion that their findings "provide support to the notion that the clinical effects of homoeopathy are placebo effects" is a significant overstatement.

The Lancet should be embarrassed by the Editorial[5] that accompanied the study. The conclusion that physicians should tell their patients that "homoeopathy has no benefit" and that "the time has passed for. . . further investment in research" is not backed at all by the data. Our 1997 meta-analysis has unfortunately been misused by homoeopaths as evidence that their therapy is proven. We now find it extremely disappointing that a major medical journal misuses a similar study in a totally uncritical and polemical manner. A subversive philosophy serves neither science nor patients.

We declare that we have no conflict of interest.

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1 Shang A, Huwiler-Müntener K, Nartey L, et al. Are the effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. *Lancet* 2005; **366:** 726–32.
2 Linde K, Clausius N, Ramirez G, et al. Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 1997; **350:** 834–43.
3 Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF, for the QUORUM Group. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUORUM statement. *Lancet* 1999; **354:** 1896–900.
4 Jonas WB, Kaptchuk TJ, Linde K. A critical overview of homeopathy. *Ann Intern Med* 2003; **138:** 393–99.
5 The Lancet. The end of homoeopathy. *Lancet* 2005; **366:** 690.

We wish to raise concerns about the meta-analysis of homoeopathy by Aijing Shang and colleagues.[1] It is based on 110 trials of homoeopathy and 110 of conventional medicine, which are said to be matched, although the criteria are not clearly stated. They were not well matched for at least one crucial parameter—trial quality—which was higher for the homoeopathy studies.

The conclusion that "the clinical effects of homoeopathy are placebo effects" is based on only eight, anonymous, clinical trials. These studies are not referenced and no information about them is given. The quality criteria are standard measures of internal validity, but before reaching their conclusion, Shang and colleagues added a further criterion—study size. We wonder how sensitive their analysis would be to changes in the cut-off points for this criterion. For instance, what would the result be if the 21 "higher quality" homoeopathy trials were used? The opacity of this paper means that it fails a key test of a good scientific report: that a reader should, in principle, be able to reproduce it.

We also have concerns about the literature review: some studies seem to have been inappropriately included and excluded, although the lack of clarity in the paper makes it impossible to be certain.

This paper also highlights the dangers of relying exclusively on measures of internal validity. Some studies of homoeopathy have been criticised for having inappropriate outcome measures. For instance, a study of the treatment of childhood asthma,[2] which would have scored as high quality under these criteria, reported negative findings, but as the subsequent correspondence showed, it was flawed by a "ceiling effect". A study which might have been included in the final eight looked at the use of a homoeopathic medicine for prophylaxis of influenza.[3] However, homoeopathy is not recommended for such an indication, and the report obscured the identity of the homoeopathic medication. Several other instances could be cited, but since we do not know which studies are under discussion, there is little point.

Shang and colleagues state that "eight trials of homoeopathic remedies in acute infections of the upper respiratory tract . . . indicated a substantial beneficial effect . . . [and] 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". Here Shang and colleagues suggest that eight studies is too few to question their conclusion about the whole set of publications. Their conclusion about the whole set, however, was also based on eight studies. Is eight enough or not? Shang and colleagues simply refuse to believe the results of positive clinical trials of homoeopathy.

They also fail to quote emerging basic science evidence for the activity of ultramolecular dilutions,[4] data that have implications for the implausibility of the claims made for homoeopathy.

The accompanying Editorial proclaims the end of homoeopathy.[5] We agree that the time has passed for "selective analyses and biased reports", but find it ironic that this Editorial rides on the back of just such a report.

Other signatories of this letter are: Iris R Bell, Philippe Belon, Fabio Bolognani, Martien Brands, Trish Connolly, Flávio Dantas, P Christian Endler, Francisco De Freitas, Michael Emmans Dean, Francisco Eizayaga, Jose Eizayaga, Jean Pierre Jansen, Kim Jobst, Dick Koster, George Lewith, Robert Mathie, Stewart Mercer, Ton Nicolai, Menachem Oberbaum, David Peters, Bernard Poitevin, David Riley, Lex Rutten, Gary Schwartz, David Spence, Aslak Steinsbekk, Elizabeth Thompson, Harald Walach, and Peter J Whitehouse.