

ORIGINAL PAPER

The research evidence base for homeopathy: a fresh assessment of the literature

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Background. The claims made for the clinical effects of homeopathy are controversial. The results of several meta-analyses of clinical trials are positive, but they fail in general to highlight specific medical conditions that respond well to homeopathy.

Aims. This review examines the cumulative research from randomised and/or double-blind clinical trials (RCTs) in homeopathy for individual medical conditions reported since 1975, and asks the question: What is the weight of the original evidence from published RCTs that homeopathy has an effect that is statistically significantly different from that in a comparative group?

Method. Analysis of the 93 substantive RCTs that compare homeopathy either with placebo or another treatment.

Results. 50 papers report a significant benefit of homeopathy in at least one clinical outcome measure, 41 that fail to discern any inter-group differences, and two that describe an inferior response with homeopathy. Considering the relative number of research articles on the 35 different medical conditions in which such research has been carried out, the weight of evidence currently favours a positive treatment effect in eight: childhood diarrhoea, fibrositis, hayfever, influenza, pain (miscellaneous), side-effects of radio- or chemotherapy, sprains and upper respiratory tract infection. Based on published research to date, it seems unlikely that homeopathy is efficacious for headache, stroke or warts. Insufficient research prevents conclusions from being drawn about any other medical conditions.

Conclusions. The available research evidence emphasises the need for much more and better-directed research in homeopathy. A fresh agenda of enquiry should consider beyond (but include) the placebo-controlled trial. Each study should adopt research methods and outcome measurements linked to a question addressing the *clinical significance of homeopathy's effects*. *Homeopathy* (2003) 92, 84–91

Keywords: homeopathy; research design; evidence-based medicine; clinical trials

Introduction

To sceptics, homeopathy is an archaic and ineffective method of treatment that proclaims an implausible mode of action. In contrast, the individual and collective experience of homeopathic practitioners

presents a convincing picture of its clinical effectiveness. Homeopathy's possible mechanisms of action remain intangible theories, and it will be important ultimately to substantiate these. The principal issues for the present and immediate future, however, are whether there is compelling research evidence that homeopathy actually does exert a remedial effect, and whether such an effect is remedy-specific.

What comprises 'compelling evidence'? Many homeopaths are cheerfully sustained by their own successful clinical experience: 'We know it works, so why do research to prove it?' However, if homeopathy truly enables people attain better health, then it is

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Received 19 November 2002; revised 19 December 2002; accepted 6 January 2003

vitaly important that it achieves much wider respect within medicine at large. To do this, homeopathy must convince sceptics 'by rigorous research evidence' of its *clinical effectiveness*. It must also face up to the challenge of demonstrating the specific *efficacy* of at least some of its medicines. These challenges are best met by data obtained from randomised controlled clinical trials (RCTs), where homeopathy is compared to another intervention or with placebo. Some homeopaths throw up their hands in horror at such a proposition, but new research programmes can grow from observational (cohort) studies,¹ for example, which can inform later RCTs.

A key to success of any study design is that clinical outcome measures must properly reflect the whole-person approach to healthcare that typifies homeopathy. Quality of life assessment and other patient-centred measures, for example, may be at least as important as the measurement of biochemical markers or other physical determinants of health status. After all, in an holistic therapy like homeopathy, the individual symptom- (and thus remedy-) picture often does not equate to a named disease, and so it is inappropriate to measure only disease-specific outcomes in such studies.

Another vital concern is that any statistically significant difference/s between treatment groups in trials should not automatically be equated to clinical importance. It is only the latter that truly matters, and this must be properly accommodated in the power calculations (and thus statistical conclusions) connected with clinical trials. The existing homeopathic research literature has not reflected this issue well—emphasis has been placed on statistical significance with incomplete regard to the clinical value of any inter-group differences observed.

What is the current evidence from which new research in homeopathy can develop? Given the limitations of past research in homeopathy, the optimum question that can be asked of the available evidence base is limited to: *What is the weight of the original evidence from published RCTs that homeopathy has an effect that is statistically significantly different from that in a comparative group?*

Only since 1975 have rigorous research methods been applied to homeopathy. Prior literature comprised only four minor trials or brief communications.^{2–5} The work reported up to 1997 is captured in the comprehensive meta-analysis of placebo-controlled trials of homeopathy published by Linde *et al* in *The Lancet*.⁶ Nearly half the trials cited in that paper showed a homeopathic treatment effect statistically significantly greater than that of placebo; none of the trials found placebo more effective than homeopathy. The authors concluded that homeopathy's clinical effects are not attributable solely to placebo, though they could not single out any medical condition for which homeopathy seemed clearly efficacious.⁶

Since 1997, some 50 new clinical trials or meta-analyses in homeopathy have been published. Many of these newer trials have essentially the same Null hypothesis: '*Homeopathy has an effect which is not statistically significantly different from that of placebo*'; in effect, the Null hypothesis that was rejected by Linde's meta-analysis. In 2002, the NHS Centre for Reviews and Dissemination based at the University of York, UK, published an overview of all the published systematic reviews and meta-analyses in homeopathic research.⁷ The authors conclude: 'There are currently insufficient data ... to recommend homeopathy as a treatment for any specific condition'. This statement is hardly distinguishable from one of Linde's conclusions 5 years earlier.

There has been a recent increase in the number of research papers that carry the more original Null hypothesis: '*Homeopathy has an effect which is not statistically significantly different from that of another active treatment*'. Such comparative trials of clinical effectiveness are included in the focus of the present review.

The present paper reports the total currently available statistical evidence from the published research literature for and against the specific efficacy or clinical effectiveness of homeopathy, based on the frequency with which the above two Null hypotheses have been rejected or not rejected in clinical trials. This is neither a meta-analysis nor a formal systematic review—the paucity and heterogeneity of published research in homeopathy limits the value of such formalised approaches. The originality of the present approach lies mainly in the following: (a) it considers the number of individual trials in homeopathy that report outcome statistics, and by type of medical condition studied; (b) it reports only full, published, research papers; (c) it includes comparative as well as placebo-controlled trials. The coverage reflects the entire range of medical conditions in which the effects of homeopathy have been the subject of research and, like Linde *et al*,⁶ it only includes trials that are randomised and/or double-blinded. Based on my review, I conclude by recommending some opportunities for future research development in homeopathy.

Literature search methods

This review examines all published clinical trials on human subjects that appeared in the literature from 1975 until December 2002, and which compared homeopathic treatment with placebo or with another medication, where a randomised and/or double-blind study design has been used. The analysis includes only full papers reporting original research, and excludes conference proceedings, brief communications, book chapters and theses. Reports of case series, clinical outcomes (cohort) studies and other non-controlled investigations are also excluded. All forms of homeopathic intervention are included, from

classical to single-remedy and isopathy. Principal information sources were: The National Library of Medicine (Medline); The Cochrane Library; The Centralised Information Service for Complementary Medicine (CISCOM); The British Homoeopathic Library (Hom-Inform); cross-referencing between published papers.

Two principal outcomes are identified: 'Null hypothesis rejected' and 'Null hypothesis *not* rejected'. For papers in the category *Null hypothesis rejected*, the findings are classed as either 'positive' (ie *for* homeopathy) or 'negative' (ie *against* homeopathy), based on a two-tailed test. A *positive* trial is one where at least one outcome measure was statistically significantly improved by homeopathy compared with placebo or alternative treatment ($P \leq 0.05$). A *negative* study is one where homeopathic treatment was statistically significantly inferior to the compared treatment (placebo, in the two actual cases cited below) in at least one outcome measure ($P \leq 0.05$). *Null hypothesis not rejected* is the conclusion from a study where no significant inter-group difference in outcome/s is evident ($P > 0.05$). In most cases, these conclusions have been based on the authors' own reported hypothesis testing; for results obtained in a few less accessible or non-English language papers, a probability of $P \leq 0.05$ was equated with a reported odds ratio ($\pm 95\%$ confidence interval) ≥ 1 .⁶

A *balance of evidence* in favour of one of the above three categories or classes for a given medical condition is concluded if, using simple arithmetic, it contains at least two more papers than the sum of the papers in the other two categories or classes. This approach has been adopted separately for placebo-controlled and comparative trials.

Results of literature search and analysis

The database scrutinised and reported here comprises a total of 93 original articles in homeopathic research. Of this total, 79 trials were placebo-controlled, while the remaining 14 compared homeopathy with a conventional medical treatment (controlled comparative trials). Table 1 lists all those medical conditions (35 in total), in 11 broad types, for which there exists at least one published clinical research trial in homeopathy that satisfies the inclusion criteria for this analysis.

Given the above criteria, 52 of the total 93 published papers are in the category 'Null hypothesis rejected' (Table 1); the remaining 41 papers are thus in the category 'Null hypothesis not rejected' (ie no conclusive difference between homeopathy and a comparison group). Of the 52 articles, 50 are classed as 'positive' and two are 'negative'. Within the 50 'positive' reports, 47 observed a homeopathic effect superior to placebo. The three others found homeopathy to be superior to another treatment for the given condition—otitis media,⁸ osteoarthritis⁹ and back pain.¹⁰ As regards the two 'negative' articles (rheumatoid arthritis,¹¹ tissue healing after dental

surgery¹²), the placebo group had a significantly better clinical response in at least one outcome measure than patients treated with a homeopathic remedy.

Balance of evidence: placebo-controlled trials

Examining the relative number of papers published for each of the three categories or classes of evidence, the present weight of evidence favours homeopathic treatment effectiveness in eight conditions:

- childhood diarrhoea;
- fibrositis (fibromyalgia);
- hayfever/allergic rhinitis;
- influenza;
- pain (of various origins);
- side-effects of radio-/chemotherapy;
- sprains;
- upper respiratory tract infection.

A weight of evidence suggesting homeopathy has no effect above placebo is apparent in three medical conditions:

- headache;
- stroke;
- warts.

For the remaining 20 conditions in which studies have been carried out, there is insufficient weight of evidence either to favour or to find no support for homeopathy (Table 1). Some of these trials are examples of the 'double positive paradox',¹³ where a homeopathy group and a placebo group have indistinguishable results but both manifest some clinical improvement.

Balance of evidence: comparative trials

There is insufficient evidence either to favour or to find no support for homeopathy in nine of the 10 medical conditions in which studies have been carried out (Table 1). Within the group of conditions 'upper respiratory tract infection', however, a weight of evidence suggests that homeopathy and conventional medicine (aspirin in both papers concerned) are equally effective in treating the common cold.^{14,15}

Discussion

Number of published trials in homeopathy

The total number of original full research papers over a 27 year time-span ($n = 93$) is very modest, for research in homeopathy is still in an early stage of development. The largest total number of articles for any particular type of condition is 10 (upper respiratory tract infection). For 12 of the 35 included medical conditions, a single published trial is all that exists. The paucity of research literature is a serious drawback for meta-analyses and formal systematic reviews in homeopathy. In the last 5 years, however,

Table 1 Medical conditions for which there is at least one published randomised/double-blind clinical research trial in homeopathy

Condition		Total	Published trials					
			Placebo-controlled			Comparative		
			Null hypothesis rejected		Null hypothesis not rejected	Null hypothesis rejected		Null hypothesis not rejected*
			+	-	±	+	-	±
Atopy	Asthma	4	2 ^{32,33}		2 ^{34,35}			
	Hayfever/allergic rhinitis	9	6 ³⁶⁻⁴¹		2 ^{42,43}		1 ⁴⁴	
Cardiovascular	Hypertension	2			1 ⁴⁵		1 ⁴⁶	
Dermatology	Insect bite-induced erythema	2	1 ⁴⁷		1 ⁴⁸			
	Leg ulcers	1			1 ⁴⁹			
	Seborrheic dermatitis	1	1 ⁵⁰					
	Warts	2			2 ^{51,52}			
Ear Nose & Throat	Influenza	2	2 ^{53,54}					
	Otitis media	2	1 ²⁸		1 ⁸			
	Upper respiratory tract infection [^]	10	7 ⁵⁵⁻⁶¹		1 ⁶²		2 ^{14,15}	
Gastroenterology	Childhood diarrhoea	3	3 ⁶³⁻⁶⁵					
	Irritable bowel syndrome	2	1 ⁶⁶		1 ⁶⁷			
	Post-operative ileus	3	2 ^{68, 69}		1 ⁷⁰			
Gynaecology	Female infertility	1					1 ⁷¹	
	Menopausal syndrome	1					1 ⁷²	
	Pre-menstrual syndrome	2	1 ⁷³		1 ⁷⁴			
	Tissue recovery after childbirth	1			1 ⁷⁵			
Musculo-skeletal	Fibrositis (fibromyalgia)	2	2 ^{76,77}					
	Muscle soreness/stiffness/cramps	5	2 ^{78,79}		3 ⁸⁰⁻⁸²			
	Osteoarthritis	4			1 ⁸³			
	Rheumatoid arthritis	5	3 ⁸⁶⁻⁸⁸		1 ¹¹	1 ⁸⁹	2 ^{84,85}	
	Sprains	2	2 ^{90,91}					
Neurology and Mental Health	Anxiety	1	1 ⁹²					
	Attention-deficit hyperactivity disorder	1	1 ⁹³					
	Headache	2			2 ^{94,95}			
	Migraine	3	1 ⁹⁶		2 ^{97,98}			
	Stroke	2			2 ^{99,100}			
	Vertigo	1					1 ¹⁰¹	
Pain	Pain (miscellaneous)	7	4 ¹⁰²⁻¹⁰⁵		1 ¹⁰⁶	1 ¹⁰	1 ¹⁰⁷	
Tissue trauma	Minor burns	1			1 ¹⁰⁸			
	Miscellaneous tissue trauma	3	1 ¹⁰⁹		1 ¹²		1 ¹¹⁰	
	Radiotherapy/chemotherapy (side effects)	3	3 ¹¹¹⁻¹¹³					
	Superficial bruising	1			1 ¹¹⁴			
Tropical disease	Cholera	1			1 ¹¹⁵			
	Malaria	1					1 ¹¹⁶	
Total		93	47	2	30	3	0	11

References cited by superscript beside the number of articles published. *Key to symbols*: * Two studies set up formally as equivalence trials.^{44,101} + positive trial; - negative trial; ± inconclusive trial; ^includes common cold, cough, sinusitis and pharyngitis.

such syntheses of (usually very few) published trials have provided support for homeopathic treatment in hayfever,¹⁶ post-operative ileus¹⁷ and rheumatoid arthritis.¹⁸ Other meta-analyses or systematic reviews have concluded there is insufficient evidence for or against homeopathy in asthma,¹⁹ influenza,²⁰ muscle soreness,²¹ osteoarthritis,²² prophylaxis for migraine or headache²³ and in tissue trauma treated with *Arnica*.²⁴

Publication bias towards the reporting of 'positive' homeopathic treatment effects has been a well-founded concern, and is properly recognised in meta-analyses,^{6,25,26} though no single trial is individually

suspected of biased reporting.²⁷ There is thus very likely to be overall exaggeration of reported positive treatment effects in the homeopathic research literature cited in the present review.

Quality of published trials in homeopathy

This review deliberately does not categorise published trials in homeopathy by their intrinsic scientific quality, for information on this issue is already available. Only 29% of placebo-controlled trials in homeopathy published before 1997 were judged to possess 'high' methodological quality.⁶ A statistical re-evaluation

of Linde's meta-analysis noted that treatment effects were larger in smaller studies and in those with inadequate blinding of outcome assessment.²⁷ Exaggeration of treatment effect can also be expected in the 14 comparative trials highlighted in the present review: the sample sizes of these 14 studies (mean, 97 patients; range, 10–184) are broadly equivalent to those for placebo-controlled trials reported by Linde *et al* (118; 5–1270).⁶

An example of some of the key issues can be taken from the two studies that have examined the effectiveness of homeopathy in otitis media in children. In the first of these papers, more patients on homeopathy than those on standard care were found to have a normal tympanogram after a treatment period of 12 months.⁸ The second article reported decreased symptom scores in acute otitis media after 24 and 64 h in patients receiving homeopathy compared with those given placebo.²⁸ These were the only statistically significant effects observed in either investigation. Both studies were preliminary in nature and had small sample sizes—33 and 75 patients, respectively. Both study designs involved randomisation of patients, but of course the comparative trial was not double-blinded.⁸ The intrinsic quality of these studies is higher than average in the homeopathic research literature.

Balance of research evidence

The above caveats (low volume, publication bias, low quality) are important in considering the research evidence base of homeopathy. Nevertheless, positive effects of homeopathic treatment are apparent in 50 published trials (over half of the included research literature). This represents a body of research where, for at least one outcome measure per trial, the Null hypothesis has been rejected in favour of homeopathy. Three of the papers (in otitis media, osteoarthritis and back pain) provide research evidence that homeopathy can actually be superior to conventional treatment.^{8–10} Only two trials have found homeopathy to have less effect than placebo.

Based on the relative number of placebo-controlled studies with positive results, the balance of research evidence currently favours homeopathy in childhood diarrhoea, fibrositis, hayfever, influenza, pain, side-effects of radio-/chemotherapy, sprains and upper respiratory tract infection. Based on published research to date, it seems unlikely that homeopathy is efficacious for headache, stroke or warts.

Insufficient research in 20 medical conditions prevents clear conclusions from being drawn. There has been no research at all in homeopathy for many other ailments. It is thus not surprising that comprehensive meta-analyses or systematic reviews in homeopathy have not discerned any clear pattern of medical conditions that appear especially promising for effective homeopathic intervention.²⁹ Meanwhile, homeopathic practitioners continue to chronicle their successful clinical cases.³⁰

Future opportunities and direction in homeopathic research

Key issues that must be addressed in future research development in homeopathy include: the research question, the associated trial design and the outcome measures chosen. Fresh research should consider carefully whether placebo-controlled trials and physical determinants of health are necessarily the wisest approach. Such approaches may be particularly inappropriate in researching homeopathy for chronic illness or where the treatment does not address a named disease. Conditions of this nature are nearly always treated by individualised homeopathy, where remedy selection is based on a person's 'constitutional' character, and so non-placebo-controlled designs using 'quality of life' measures, for example, might be the most relevant. The most appropriate place for placebo-controlled trials in homeopathy might be in examining acute (as opposed to chronic) medical conditions, where any homeopathic treatment effect is likely to be swift acting, and thus better discernable. The fact that prescribing is relatively simple (minimal range of indicated remedies) in some acute conditions could offer useful advantages in study design. It may be noteworthy that acute, rather than chronic, conditions feature prominently among those for which homeopathy has the greatest weight of positive research evidence in placebo-controlled trials.

Investigators might also consider testing the effects of homeopathy as an adjunct to conventional medication, thus reflecting its complementary nature. Equivalence trials offer another promising way forward. In these, a conclusion of 'similar clinical outcome' between homeopathy and an orthodox treatment would be based on an ability to accept statistically equivalent confidence intervals in the two groups of data.³¹ This approach would be greatly preferable to assuming equivalence based merely on failure to reject the Null hypothesis in a typical superiority trial, as is the case in nearly all of the 41 examples presented here. Formal equivalence trials could enable researchers to examine more robustly the relative safety and cost-effectiveness of homeopathy compared with a conventional medicine that was shown to possess similar treatment effectiveness in a particular clinical situation.

It remains to be seen whether passage of time sees the publication of increased numbers and quality of published research papers relevant to homeopathy that report *clinically* significant findings in its favour. For its practitioners, such robust research data would have an important impact in improving the credibility as well as the intrinsic quality of the homeopathy that they provide to their patients.

Acknowledgements

It is a pleasure to thank Conrad Harris, Peter Fisher and Bob Leckridge for their helpful comments on the manuscript in the early stages of its preparation.

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