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SPECIAL ARTICLE

M. Cucherat · M. C. Haugh · M. Gooch
J.-P. Boissel, for the HMRAG group

# Evidence of clinical efficacy of homeopathy

## A meta-analysis of clinical trials

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**Abstract** *Objective*: To establish, using a systematic review and meta-analysis, whether there is any evidence from randomised controlled clinical trials of the efficacy of homeopathic treatment in patients with any disease.
*Data sources*: Published and unpublished reports of controlled clinical trials available up to June 1998, identified by searching bibliographic databases (Medline, Embase, Biosis, PsychInfo, Cinahl, British Library Stock Alert Service, SIGLE, Amed), references lists of selected papers, hand searching homeopathic journals and conference abstracts, and contacting pharmaceutical companies.
*Trials selection*: Trials were selected using an unblinded process by two reviewers. The selection criteria were randomised, controlled trials in which the efficacy of homeopathic treatment was assessed relative to placebo in patients using clinical or surrogate endpoints. Prevention trials or those evaluating only biological effects were excluded. One hundred and eighteen randomised trials were identified and evaluated for inclusion. Sixteen trials, representing 17 comparisons and including a total of 2617 evaluated patients, fulfilled the inclusion criteria.
*Data extraction*: Data were extracted by two reviewers independently, using a summary form. Disagreements were resolved by a third person.
*Data synthesis*: The evidence was synthesised by combining the significance levels ($P$ values) for the primary outcomes from the individual trials. The combined $P$ value for the 17 comparisons was highly significant $P = 0.000036$. However, sensitivity analysis showed that the $P$ value tended towards a non-significant value ($P = 0.08$) as trials were excluded in a stepwise manner based on their level of quality.
*Conclusions*: There is some evidence that homeopathic treatments are more effective than placebo; however, the strength of this evidence is low because of the low methodological quality of the trials. Studies of high methodological quality were more likely to be negative than the lower quality studies. Further high quality studies are needed to confirm these results.

**Key words** Homeopathy · Meta-analysis · Randomised clinical trial

M. Cucherat (✉) · M. C. Haugh · J.-P. Boissel
Department of Clinical Pharmacology,
Hospitals of Lyon and University Claude Bernard,
Faculté RTH Laennec, BP 8071,
F-69376 Lyon, France
e-mail: mcu@upcl.univ-lyonl.fr
Tel.: +33-478-785757; Fax: +33-478-776917

M. Gooch
Academic Departments,
Glasgow Homeopathic Hospital,
Glasgow, Scotland, UK

## Introduction

Although homeopathic treatments have been commonly used for many decades, their efficacy is still controversial. No scientific explanation for the mechanism of action of homeopathy is currently universally accepted, despite wide and often controversial debate [1–5]. One question that is often asked is a very broad one: is homeopathy efficacious? This question may seem too general, but it is in these terms that the problem is often posed.

The aim of our study was to determine, using a systematic review and meta-analysis, whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans. An unbiased conclusion is of utmost importance in this domain because it is a scientific, emotional and political issue in many areas of the world. Given that the question asked in this meta-analysis is broad, we examined evidence from all trials in which a homeopathic treatment was compared with placebo, irrespective of the nature of the treatment and the disease treated.

This project was undertaken as one component of a report prepared for the European Parliament by the Brussels Commission.

## aterials and methods

### Search strategy

Published and unpublished eligible trials, available up to June 1998, were identified using full text searches in bibliographic databases (Medline 1968–June 1998, Embase 1985–June 1998, Biosis 1970–June 1998, PsychInfo 1967–1995, Cinahl 1983–1995, British Library Stock Alert Service, SIGLE, Amed 1986–1995); reference lists of the selected papers; references provided by colleagues; hand searching of homeopathic journals and conference abstracts; and contacting pharmaceutical companies. There were no language restrictions. These search activities were co-ordinated by the British Homeopathic Library in Glasgow, and more complete details are available on request.

### Eligibility of clinical trials

We considered all randomised controlled clinical trials in which the efficacy of a homeopathic treatment was compared with that of a placebo or a treatment without active constituent. A preparation was considered to be homeopathic if the dilution was greater than 3C (one molecule of the original principle in $10^6$ molecules of solvent) or if it was presented as homeopathic by the manufacturer. Although homeopathic treatments are widely used in prevention, we restricted this analysis to treatment of diseases because the extent of the treatment effect is likely to be very different between the two settings.

Only randomised trials with a clearly defined primary outcome were included (see Statistical methods). Both unblinded and blinded studies were included, and sensitivity analysis was performed to assess the effect of blinding on the results.

Several schools of homeopathy exist making it often difficult to obtain a consensus about what treatment should be given in a particular situation. It was, therefore, impossible to judge with certainty whether, in a given trial, the patients received the most suitable substances for their symptoms. Hence, we did not try to assess the conformity of the homeopathic treatment given. The only criterion for quality used for selection was adequate concealment of treatment allocation (by a suitable randomisation method). However, sensitivity analyses were planned to examine the effects of the other quality criteria, such as percentage of lost to follow-up, and double blind follow-up, on the result.

### Data extraction

A data extraction form was designed and tested by four readers (homeopathic and non-homeopathic backgrounds). For each trial, the main characteristics and results were extracted independently by two reviewers among the 11 readers participating in the project (see Acknowledgements), with the relevant linguistic competence. Any disagreements between the readers were resolved by a third person (M.C. or M.H. assisted if needed by a different linguistic competent reader).

### Statistical methods

The broad nature of the question asked in this meta-analysis makes it difficult to use conventional meta-analytical techniques, such as Peto or Mantel-Haenszel. These conventional methods estimate the size of the treatment effects and then pool these estimates. They rely on the assumption that there is an underlying common treatment effect size across the combined trials. The pooled treatment effect size only has a clear meaning when all the trials included in the meta-analysis enrolled similar patients and endpoints. A frequent criticism of meta-analysis is that a common estimate is obtained for heterogeneous trials, combining apples, oranges and cabbages. To answer the question asked in this present meta-analysis, we needed to combine very different trials, in which the efficacy of different homeopathic treatments had been assessed in various disease settings using different endpoints. In this situation, the assumption of a common underlying treatment effect size used in conventional meta-analytical techniques is clearly not true, since this would be similar to making the assumption that streptomycin in tuberculosis and streptokinase in acute myocardial infarction have a common underlying treatment effect size.

The statistical approach used, therefore, was the combination of the significance levels ($P$ values) [6–8]. The rationale for this choice is that all the trials explored the same broad question, i.e. "is homeopathic treatment efficacious?", even if, for individual trials, the question asked expressed more specific terms and focused on a given treatment of a particular disease. Thus, unlike in the conventional meta-analytical methods, the method used does not involve pooling the numerical estimates of treatment effect sizes obtained, in our case, in very different situations. Using this approach, the null hypothesis tested is that the effect of interest (in this case, the efficacy of homeopathic treatment) is not present in any of the trials considered. If the null hypothesis is rejected, we can conclude that in at least one trial there is a non-null effect. This point is crucial and, unfortunately, the results from analysis using this approach are often misinterpreted. We cannot say in how many trials homeopathy is efficacious and we cannot estimate the size of the effect. The major advantage of this approach is that $P$ values from any statistical test for the hypothesis of interest can be combined. If the results are interpreted with sufficient precaution, this approach provides a way to combine results from very dissimilar trials with differing outcomes and statistical tests.

There is no rational basis for selecting one of the numerous methods available for combining significance levels [6, 9]. Thus, we used seven methods: the sum of logs, the sum of Z, the weighted sum of Z, the sum of t, the mean Z, the mean $P$, the count test and the logit procedure. We present the results obtained with the method that gave the most conservative (least optimistic) results. A two-sided approach was adopted because of the format of the tested hypothesis (i.e. the effect could be either "negative" or "positive").

When possible, the $P$ value was re-calculated using the most powerful test suitable for the nature of the outcomes tested in the individual trials (i.e. Fisher's exact test for the binary outcomes; Student's $t$-test for the continuous outcomes).

### Primary outcome

When several outcomes are tested in a given trial, the possibility that one of them is significant by chance alone increases with the number of tests performed. In trials with several outcomes, often only those with a "positive" result are reported in publications. In the absence of a clearly defined primary outcome, the arbitrary choice of one of these outcomes could lead to bias in the statistical approach used in this analysis. This bias can be avoided by taking into account only trials with a clearly defined primary outcome. This essential precaution ensures that the $P$ value associated with the primary outcome is the "true" $P$ value, and that it is not a $P$ value potentially less than the "true" $P$ value due to the inflation of the type-I error rate arising from multiple statistical tests. We considered that a primary outcome was "clearly" defined when this was explicitly stated in the publication or report.

### Sensitivity analyses and sub-group analyses

Sensitivity analyses based on the methodological quality of the trials were performed. The trials were divided into four groups on the basis of their quality, from low to high: single blind or unblind randomised trials; randomised double-blind trials; randomised double-blind trials, with less than 10% of patients lost to follow-up; and randomised double-blind trials, with less than 5% of patients lost to follow-up.

The likelihood of publication bias was assessed by adding fictive, non-significant trials to the real trials. The size of these fictive trials was equal to the mean of the real trials and they had a $P$ value

of 0.5, which corresponds to the expected $P$ value of an infinite set of trials with no effect. Trials were added until the combined $P$ value became greater than 0.05.

We also analysed separately those trials evaluating fixed prescription and those evaluating individualised prescriptions, since these are two important homeopathic approaches.

## Results

### General description of trial reports identified

We identified a total of 150 reports (published and unpublished) representing 118 randomised controlled trials (addressing one or more treatment comparisons). Only 16 of these trials satisfied the inclusion criteria; this corresponds to 17 comparisons, as one trial had three treatment groups. The reasons for exclusion of the remaining 102 trials were primary outcome not clearly defined (92, 90%) and methodological defects (10, 10%). Complete details of the excluded trials are available from the authors on request.

Among the 150 reports, 19 (14%) were unpublished reports (16 were thesis dissertations [10–25] and 3 were internal reports [26–28]). Although we were informed about one other unpublished trial, the data are protected by industrial property protection laws and were unavailable. We found reports in a total of eight languages (English, German, Dutch, French, Portuguese, Norwegian, Italian, Spanish). Multiple publications were identified for 26 trials, sometimes in several languages, with up to four papers for a given trial. Fifty-one trials (43%) were published for the first time before or during 1989 and 67 thereafter (57%).

### Characteristics of eligible trials

The main characteristics of the eligible trials are summarised in Table 1. One trial had three treatment groups and, therefore, data for two comparisons were analysed, giving a total of 17 comparisons. Eleven of the 17 comparisons (65%) were statistically significant results in favour of the homeopathic treatment. A non-significant trend in favour of the placebo was observed in three comparisons [29–31].

### Combining data

Table 2 shows the results of the pooling of the 17 comparisons obtained from the eight methods. We selected the weighted sum of Zs method, which appears to be the most conservative, for the subsequent analyses. This method has the advantage of taking into account the relative size of the trials (see the Appendix for details of this method). The results of the sensitivity analyses performed on subgroups of trials defined by their methodological quality are shown in Table 3. Only five comparisons were analysed in the highest quality subgroup and the resulting combined $P$ value decreased from 0.000036 for all 17 comparisons to 0.082 for the highest quality subgroup. The results for the subgroups of trials assessing fixed or individualised prescriptions are shown in Table 4. However, since only three trials used individualised prescribing, this subgroup had a lower statistical power than the fixed prescribing subgroup.

#### *Publication bias*

The addition of 63 fictive non-significant comparisons was needed to obtain a $P$ value greater than 0.01 and 155 to obtain a $P$ value greater than 0.05, suggesting that publication bias is unlikely.

#### *Comment*

The significant combined $P$ value obtained in the main analysis does not imply that the homeopathic treatments were efficacious in all the pooled comparisons. This result provides evidence that in at least one trial the homeopathic treatment was more efficacious than placebo. In other words, more trials had a positive result than would be expected due to chance alone. For clinical practice, we need to know whether a particular treatment is efficacious in a given disease setting for a specific outcome. The results of this analysis do not provide this information but suggest that it could be worthwhile to perform well-designed and suitably sized randomised controlled trials.

### Primary endpoint

The exclusion of trials without a clearly defined primary outcome resulted in several trials of otherwise good methodological quality not being included in the analysis. The trials were excluded irrespective of the results and in compliance with defined selection criteria described in the protocol for this project. The rationale for this criterion has been explained in the Materials and methods section. This relatively high rate of excluded trials results only in a loss of statistical power, but this did not prevent a significant result being obtained in the meta-analysis.

#### *Publication bias*

We identified only a few unpublished trials. Although we cannot exclude the possibly that the results of the meta-analysis are affected by publication bias, the results of the sensitivity analysis suggest that this is unlikely. It could also be argued that publication bias is less likely to exist in the homeopathy field than in other areas of medicine. Homeopathy trials with "negative" results

**Table 1** Description of the study designs and patients' characteristics for trials included in the meta-analysis. *NA* not available

| Trials | Disease setting | Homeopathic treatment | Primary outcome | No. of patients evaluated/ randomised | Result (*P* value) | Blinding | Lost to follow-up (%)[a] | Placebo |
|---|---|---|---|---|---|---|---|---|
| Mössinger 1980 [39] | Boils and pyoderma | Hepar sulfuris calcareum D4 | Healing time | 46/NA | 0.318 | Double | NA | NA |
| Coudert 1981 [40] | Dystocia | Caulophyllum 5 °C | Success within 2 h | 34/34 | 0.00055 | Double | 0 | Identical pellet |
| Reilly 1986 [41] | Active hay fever | Fixed, mixed grass pollens 30 °C | Visual analogue scale of overall symptom intensity | 102/158 | 0.018 | Double | 35 | NA |
| Grecho 1988 [29, 31, 42, 43] | Post-surgery ileus | Opium 15 °C | Delay to the first stool | 300/300 | 0.699 | Double | 0 | Identically prepared globules but without active constituent |
| Grecho 1988 [29] | Post-surgery ileus | Raphanus 15 °C + Opium 15 °C | Delay to the first stool | 300/300b | 0.358 | Double | 0 | Identically prepared globules but without active constituent |
| Zell 1988 [44, 45] | Acute ankle sprains | Traumel ointment | Composite criteria of treatment success | 69/NA | 0.028 | Double | NA | Ointment base without active constituent |
| Ferley 1989 [46] | Influenza-like syndrome | Fixed, Oscillococcinum | Recovery rate with in 48 h of treatment | 462/478 | 0.032 | Double | 3 | Identical pellet |
| Alibeu 1990 [47] | Post-operative pain agitation | Aconit 4 °C | Sedation within 15 min | 47/50 | 0.002 | Double | 6 | NA |
| Thiel 1991 [48] | Knee joint haematoma | Intraarticular Traumel R | Joint mobility | 73/80 | 0.026 | Double | 9 | Intraarticular injection of NaCl |
| Lièvre 1992 [49] | 2nd and 3rd degree burns | Calendula | Composite criteria of treatment success | 103/103 | 0.147 | Open | 0 | Vaseline |
| Gaus 1993 [50–52] | Rheumatoid arthritis | Rheumaselect | Composite criteria of treatment success | 176/176 | 0.018 | Double | 0 | NA |
| Whitmarsh 1993 [53] | Headache | Individualised | Change in mean attack frequency over the course of the trial | NA/64 | 0.83 | Double | NA | Identical pellet |
| Jacobs 1994 [54] | Acute childhood diarrhoea | Individualised | Duration of diarrhoea | 81/92 | 0.048 | Double | 12 | Identical pellet |
| Reilly 1994 [55] | Allergic asthma | Individualised homeopathic immunotherapy | Visual analogue scale of overall symptom intensity | 24/28 | 0.003 | Double | 14 | Identically prepared globules but without active constituent |
| Weiser 1995 [56, 57] | Chronic sinusitis | Euphorbium compositum S nasal spray | Cumulative score | 155/172 | 0.016 | Double | 10 | NA |
| Diefenbach 1997 [30] | Bronchitis | Bronchiselect | Length of productive cough | 209/258 | 0.86 | Double | 19 | NA |
| Papp 1998 [58] | Influenza-like syndromes | Oscillococcinum | Multiple endpoint: rate of patients affected and duration of disease | 334/372 | 0.0257 | Double | 10 | Identical pellet |

[a] Randomised patients for whom the outcome measure was missing were considered as 'lost to follow-up'
[b] Same control group as in Grecho[a]
[c] Holm's procedure was used to perform simultaneous inference. The *P* value given is an adjusted *P* value to take into account the two statistical tests performed

Table 2 Pooled *P* values obtained from all eight methods investigated for the 17 comparisons

| Method | *P* value (two tailed) |
|---|---|
| Weighted sum Z | 0.000036 |
| Mean *P* | $1.7 \times 10^{-6}$ |
| Mean Z | $7.8 \times 10^{-8}$ |
| Logit | $8.7 \times 10^{-12}$ |
| Sum log | $4.7 \times 10^{-12}$ |
| Sum Z | $5.9 \times 10^{-12}$ |
| Sum t | $3.2 \times 10^{-13}$ |
| Count | $2.8 \times 10^{-29}$ |

might be more readily accepted by non-homeopathic journals, since the lack of efficacy of homeopathy is in accordance with the belief of many non-homeopathic physicians. However, the majority of the trial reports we identified, particularly those including only a few patients, were published in homeopathy journals. We could expect that, in these journals, the "negative" trials would have been more readily rejected than the positive ones, thus leading to publication bias.

## Relationship between statistical significance and methodological quality

Although the *P* value was statistically significant when all the data were pooled, this became non-significant when the analysis was restricted to the five trials with the highest quality and, therefore, the least susceptible to potential bias. The same relationship has been also recently reported by Linde et al. [32]. Thus, the pooling of the high and medium quality trials gives a potentially flawed result. The relationship observed between the methodological quality of the trials and the statistical significance of the results has been previously described [33]. Recently, "an exaggeration of treatment efficacy when lower-quality trials were pooled" has also been reported in other areas of medicine [34].

## Other literature reviews and meta-analyses

Several attempts to assess the efficacy of homeopathic treatments have been made. Two of these were systematic reviews of clinical trials without statistical analysis [35, 36]. In 1997, a meta-analysis reviewing the evidence available up to 1995 was published [37]. The approach used in that meta-analysis is considerably different from the one we adopted. A conventional method of meta-analysis was used for combining the odds-ratios from the different trials. However, as we have stated earlier, this approach assumes that the treatment effect size for the different treatments (prevention and treatment in their case) obtained in different disease settings was comparable. This is unlikely to be true; hence, the common odds-ratio reported is difficult to interpret and it has no clear medical meaning. This pooling of the estimates of different treatment effect sizes is one of the major criticisms of meta-analysis, i.e. mixing apples and oranges [38]. Additionally, the outcome analysed in each trial was selected using an established hierarchical classification, not requiring a clearly defined primary outcome. Their approach thus does not control for the inflation of the alpha risk and could lead to potentially false-positive results. However, despite these limitations

Table 3 Sensitivity analysis by stepwise removal of lower methodological quality comparisons (weighted sum of Z)

| Class | Comparisons | No. of trials | Combined 2-tailed *P* value |
|---|---|---|---|
| Randomised, blind or open | See Table 1 | 17 | 0.000036 |
| Randomised, double blind | As above except Lièvre 1992 [49][a] | 16 | 0.000068 |
| Randomised, double blind, with less than 10% of lost to follow-up | Coudert 1981 [40], Thiel 1991 [48], Whitmarsh 1993 [53], Ferley 1989 [46], Alibeu 1990 [47], Gaus 1993 [50–52], Grecho 1988 [29], Weiser 1995 [56, 57] | 9 | 0.0084 |
| Randomised, double blind, with less than 5% of lost to follow-up | Coudert 1981 [40], Ferley 1989 [46], Gaus 1993 [50–52], Grecho 1988 [29] | 5 | 0.082 |

[a] The trial by Liévre used as control a treatment without active component but distinguishable from the active treatment

Table 4 Results by subgroup defined by treatment setting (weighted sum of Zs)

| Treatment setting | Trials | No. of trials | Combined 2-tailed *P* value |
|---|---|---|---|
| Individualised treatment | Jacobs 1994 [54], Reilly 1994 [55], Whitmarsh 1993 [53] | 3 | 0.021 |
| Fixed preparation | Mössinger 1980 [39], Coudert 1981 [40], Reilly 1986 [41], Thiel 1991 [48], Ferley 1989 [46], Alibeu 1990 [47], Gaus 1993 [50–52], Grecho 1988 [29], Weiser 1995 [56, 57], Zell 1988 [44, 45], Lièvre 1992 [49], Papp 1998 [58], Diefenbach 1997 [30] | 14 | 0.00011 |

and the inclusion of the new data available since 1995, the qualitative result obtained is the same as ours.

## Conclusion

From the available evidence, it is likely that among the tested homeopathic treatments tested at least one shows an added effect relative to placebo. The meta-analysis method used does not allow any conclusion on what homeopathic treatment is effective in which diagnosis or against which symptoms. It is of no more practical value than to answer yes to the question "are homeopathic treatments effective?" without specifying which drug?, which dose or regimen? and against which disease?

However, the strength of the evidence for this conclusion remains low because of the overall low quality of the trial designs and reporting and the limitations of the meta-analysis approach used. We cannot eliminate the possibility that the available trials were biased resulting in a meta-analysis which is also biased, although the results from the sensitivity analyses would seem to exclude this possibility.

It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective; however, homeopathy can and should be assessed using the same methodology used for allopathy. More well-designed and well-run clinical trials, including many hundreds of patients, are needed before definitive conclusions can be drawn regarding the clinical efficacy of homeopathic treatments. A clinically relevant primary outcome should be clearly defined and the intention-to-treat principle should be respected.

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## Statistical appendix

The weighted sum of Zs enables each standard normal deviate (Z) to be weighted by the size of the sample on which it is based (or by its degree of freedom). The general procedure is to multiply each Z by the weight w, add the weighted Zs and divide the sum of the weighted Zs by the square root of the sum of the squared weights as follows:

$$\bar{Z} = \frac{w_1 Z_1 + w_2 Z_2 + \cdots + w_k Z_k}{\sqrt{w_1^2 + w_2^2 + \cdots + w_k^2}}$$

A one-tail $P$ value was used to compute the Zs, taking into account the direction of the effect. So, a positive effect, i.e. the tested treatment is superior to the control, leads to a Z greater than zero, and a negative effect, i.e. the control treatment is superior to the tested treatment, leads to a Z less than zero. The combined Z thus gives the direction of the effect.

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