

## The best studies show individualised homeopathic treatment has beneficial effects beyond placebo

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Several systematic reviews and meta-analyses of homeopathy have been performed. However, none had looked solely at placebo-controlled trials of individualised homeopathic treatment as delivered by homeopaths in practice. The research team of Mathie *et al.*<sup>1</sup> have now performed such an analysis and found that homeopathic medicines, when prescribed during individualised treatment, are 1.5- to 2-times more likely to have a beneficial effect than placebo. Use of a rigorous and transparent methodology, including a sensitivity analysis, gives credibility to these findings, which fundamentally challenge claims that homeopathy is purely a placebo effect.

### Introduction

To date, many of the systematic reviews of clinical studies on homeopathy have analysed studies on all forms of homeopathic treatment together, in an attempt to answer the general question, "Is *homeopathy* better than placebo?". However, homeopathy takes several forms. '*Individualised homeopathic treatment*', consisting of a consultation plus personalised prescription, is considered to be usual care as provided by homeopaths in real world clinics. In contrast, '*non-individualised homeopathy*' involves the same remedy being used by all patients, based on a clinical diagnosis only (e.g. over-the-counter homeopathic preparations containing multiple remedies for conditions such as hay fever or travel sickness).

There is no reason to assume that different homeopathic treatment approaches are equally effective or ineffective. It is therefore not surprising that studies combining the results of all homeopathy trials, with little or no attempt to disentangle the different types of treatment involved, have led to some negative studies and reports<sup>2,3</sup> and ensuing heated debate. In Mathie *et al.*'s study, placebo-controlled trials of individualised homeopathy have been analysed in isolation<sup>1</sup>, allowing us to explore the key question - do homeopathic medicines, when prescribed during individualised homeopathic treatment (IHT) have an effect beyond placebo?

### Meta-analysis of Individualised Homeopathic Treatment (IHT)

Mathie *et al.*<sup>1</sup> identified 22 eligible clinical trials comparing Individualised Homeopathic Treatment (IHT) to placebo for a range of clinical conditions. To ensure that the results would be recognised by the wider academic world, Mathie's team used state-of-the-art methods for analysing a large body of clinical trial data, namely a systematic review and meta-analysis (see Definition box).

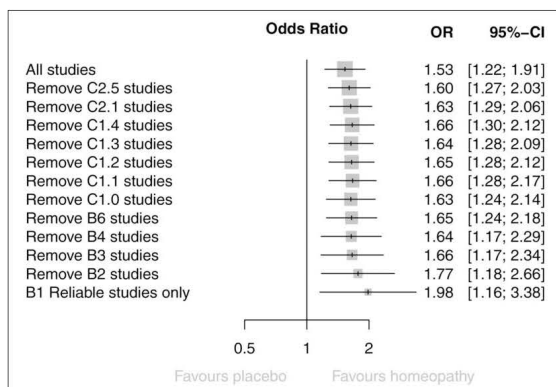
All 22 trials were assessed for quality using the well-recognised Cochrane collaboration's assessment tool<sup>4</sup> and given an overall 'reliability' rating of A, B or C. Three of the 22 trials met the strict criteria set by Mathie *et al.* to be designated as the most 'reliable' evidence (i.e. rated B1 and above); a meta-analysis of these three top trials found that IHT is more beneficial than placebo. It is important to note that this definition of 'reliable' is more stringent than that used in previous meta-analyses of homeopathy performed by other groups (e.g. Shang *et al.*<sup>5</sup>). Also, this method of classifying study quality and 'reliability' should not be misinterpreted as suggesting that the remaining 19 trials are not meaningful; rather, they are simply lower down the scale of relative reliability.

### Key findings

Overall, IHT had a positive effect that was statistically different from placebo. Specifically, individually prescribed homeopathic medicines were found to be 1.5- to 2- times more likely to have a beneficial effect than placebo. The size of the treatment effect was measured by the '*Odds Ratio*' (OR); if an OR is greater than 1.0, the effect of the intervention is positive, and the greater the OR, the greater the size of that positive effect.

The treatment effect seen in the 3 trials designated as most 'reliable' was calculated to be OR=1.98 (95% CI [1.16 - 3.38]; p = 0.013.) As these results were based on only 3 studies, Mathie *et al.* performed a '*sensitivity analysis*' to check that they were robust i.e. the choice of trials analysed was changed in multiple ways according to their quality rating to see whether this caused the final result to alter (see Figure 1).

When analysing the 12 trials rated as B6 and above, the OR did not change significantly; OR=1.63 (95% CI [1.24 - 2.14]; p < 0.001) (Fig. 1. Remove C1.0 studies); and when all 22 trials were analysed together, regardless of quality, the result was again not significantly different: OR=1.53 (CI [1.22 - 1.91]; p < 0.001) (Fig. 1. All studies). This sensitivity analysis demonstrates that Mathie *et al.*'s findings are robust. It is also important to note that there is no evidence of larger treatment effects being found in lower-quality trials, contradicting the notion that only poor quality studies on homeopathy show positive results.



**Figure 1:** Sensitivity analysis. Meta-analysis results for various sub-groups of the 22 eligible trials. Each line represents a different sub-group of trials according to their quality/reliability rating (C2.5 being the lowest and B1 the highest). The top line ('All studies') represents the odds ratio (OR) results from all 22 studies pooled together. Successive lines from top to bottom represent the results after step-wise removal of trials with the next reliability rating. The bottom line ('B1 Reliable studies only') represents the results when analysing the three 'best' trials only. (Figure reproduced with permission from Mathie *et al.*<sup>1</sup>).

When testing the efficacy of IHT for several different clinical conditions, one might expect the results to vary depending on the condition being treated, making it more difficult to detect a specific effect when all conditions are pooled: interestingly this was not the case. Additionally, two of the three most 'reliable' trials used homeopathic remedies that were diluted beyond the Avogadro limit, yet a significant specific effect was still detected. This is a striking finding considering that many detractors of homeopathy argue that this is either scientifically implausible or simply impossible.

While the effect of individually prescribed homeopathic medicines was greater than placebo, the clinical 'effect size' detected was 'small'. To put this into context, conventional drugs with a similar effect size include sumatriptan for migraine, fluoxetine for major depressive disorder and cholinesterase inhibitors for dementia<sup>5</sup>.

### Comparison with other studies

Two previous systematic reviews of IHT have been performed<sup>6</sup>. Ernst *et al.* (published in 1999) located 3 randomised controlled trials comparing IHT to conventional medicine and the low trial quality prevented any conclusions from being drawn<sup>7</sup>. In 1998 Linde *et al.*'s study looked at 32 trials of IHT versus placebo and found a positive, but unconvincing, trend<sup>8</sup>. Mathie *et al.* added an extra level of 'significance' to these 'previous' systematic 'reviews' by 'performing a state-of-the-art meta-analysis.

When the meta-analysis of Mathie *et al.* is directly compared with perhaps the most often cited meta-analysis of 'global' homeopathy performed by Shang *et al.*<sup>9</sup>, which reached negative 'conclusions, 'key' 'differences' between 'the' 'two' studies become clear:

- the criteria for reliability of the clinical trials used by Mathie *et al.* were more stringent
- the trials used by Mathie *et al.* were more up-to-date (14 of the 22 trials identified were not included in Shang *et al.*, published in 2005)
- the positive results of this study are based on trials which test individualised homeopathic care<sup>9</sup>; Shang *et al.*'s final conclusion that homeopathy does not have an effect beyond placebo was based only on trials of non-individualised homeopathy
- Mathie *et al.* performed a rigorous sensitivity analysis to confirm that despite basing their main conclusion on only 3 of 22 available studies, the findings are reliable. Shang *et al.* did not perform such an analysis on their data, but other authors have shown that their results (based on only 8 of 110 available studies) fail a rigorous sensitivity analysis and are therefore unreliable<sup>10</sup>.

### Impact of the study

In summary, Mathie *et al.* have taken the three most reliable, high quality studies of individualised homeopathic treatment available and found that when the results are analysed together, the result is positive, showing a beneficial effect of homeopathic medicines beyond placebo. The input from two highly respected, independent biostatisticians from the University of Glasgow as co-authors gives further credibility to the findings.

Although the authors remain only cautiously optimistic about their findings, the meta-analysis by Mathie *et al.* is well constructed and methodologically sound, providing a strong argument in favour of the existence of specific effects beyond placebo in real-world homeopathic treatment. The results of this meta-analysis challenge the commonly repeated argument, 'the best studies show homeopathy doesn't work', and provide strong evidence that the opposite is actually correct, i.e. the best studies show homeopathy works.

### Definition box

A **systematic review** is a highly structured scientific method used to locate, collate, critically assess and evaluate all research studies available that address a particular question. The highest quality evidence is then used to synthesise a final position and draw conclusions.

A **meta-analysis** is a statistical method used to assess overall trends in the combined data extracted from multiple individual studies identified through systematic review. A meta-analysis assigns a level of statistical significance to the combined results (i.e. how likely it is that the result is 'real' and not simply due to chance).

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