Homeopathy In Upper Respiratory Tract Infections ? The Impact Of Plausibility Bias

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My opinion

A meta-analysis of a subset of eight 'larger higher quality' randomised controlled trials (RCTs), drawn from 110 matched RCTs each of homeopathy and conventional medicine, concluded that the results of the trials were consistent with the hypothesis that homeopathy is a placebo effect [1]. This meta-analysis was criticised for the heterogeneity of the trials on which its conclusion was based (all eight were for different conditions).

In an apparent paradox, the same meta-analysis concluded that homeopathy had a 'substantial beneficial effect' in acute upper respiratory tract infections (URTI), without evidence of positive bias. Other meta-analyses have reached similar conclusions [2, 3]. There is evidence from clinical studies of varying designs that homeopathy may be effective in treating acute otitis media [4-6]. Homeopathy is frequently prescribed for URTI by homeopathic GPs [7]. There is also some evidence from western Europe that general practitioners (GPs) with homeopathic training prescribe fewer antibiotics than their counterparts in conventional medicine [8-10].

The plausibility paradox

The problem with homeopathy for most doctors and scientists is the inherent implausibility of the idea that ultra-diluted solutions can have chemical effects [11]. Clearly it is highly unlikely that a medicine that does not contain a single molecule of the original substance could work like a conventional medicine. Sometimes the outcome of RCTs overturns theory, but at other times evidence is dismissed because of theory. Vandenbroucke states "Accepting that infinite dilutions work would subvert more than conventional medicine; it wrecks a whole edifice of chemistry and physics" [12].

An early systematic review of clinical trials stated, "we would accept that homoeopathy can be efficacious, if its mechanism of action were more plausible" [13]. Contrary views have also been expressed: demanding more evidence may itself be considered unscientific; the same level of supporting clinical trial evidence should be accepted for all scientific developments. If a lower level of proof is set for hypotheses that fit prior beliefs then we bias our view of science in favour of such beliefs and may be easily misled [14].

Does the fact that it is highly unlikely that many homeopathic medicines have a chemical effect really wreck a 'whole edifice of chemistry and physics'? Chaplin mentions a number of possible mechanisms of action that are more likely than chemical effects, like water clustering and nanobubbles [14]. 'Inherent implausibility' is a poor guide to future understanding. History is littered with examples of ideas that at one time appeared highly implausible but are now accepted as fundamental truths: the Copernican revolution and quantum physics are well-known examples [15].

The possibility of other mechanisms, the opinions of users and prescribers, fundamental research and epidemiological evidence are all ignored because of the implausibility of a chemical effect of extremely high dilutions. Goodman used Bayes' theorem to illustrate that the usual proof is not sufficient for belief in efficacy [16]. Rosendaal and Bouter illustrated this by assigning one significantly positive RCT a likelihood ratio (LR) of 16 [17]. This LR is then entered into Bayes' formula:

Posterior odds = LR x prior odds#

Their estimate of the prior that homeopathy 'works' was one in a million; implying that 'works' actually meant 'works in an accepted pharmacological way'. Then they calculate using Bayes' formula that the chance that homeopathy works goes from one in a million to less than one in ten thousand after one positive RCT.

The principal weakness of Bayesian statistics is the subjectivity in estimating the prior chance [18]. Priors are usually estimated by experts in the field. Should the prior for homeopathy be the chance that it has a chemical effect or the chance of other effects? In Bayesian reasoning all evidence should be used for sequential updating with the Bayes' formula, and very low priors especially are particularly influenced by this updating [19]. If we suppose that the proof of one RCT has LR=16, sequential updating for eight positive trials proceeds as in table 1.

Illustration 1: Table 1

This example merely shows that evidence consisting of a considerable number of RCTs and a variety of other evidence cannot be dismissed by a simple Bayesian argument. A complete Bayesian discourse about proof is much more complex [20]. We see that 7 consecutive, positive, trials suffice to bring belief from one in a million to very nearly 100%, and that there is a 'ceiling effect': additional positive studies have very little impact. The 8 trials on homeopathy for URTI have certainly not had such an impact on beliefs in the medical community. This might be due to suspicion of bias based on the plausibility fallacy.

Sources of bias

Sterne et al assumed that quality bias accounted for the positive results of RCTs of homeopathy [21], but several authors have concluded that the quality of evidence for homeopathy is not inferior to that for conventional medicine [12, 13]. Shang's analysis was the first to make direct comparison of homeopathy trials with conventional trials. Plots of odds ratio versus the standard error of RCTs show a picture that is not consistent with a placebo effect and a similar pattern for homeopathy and conventional medicine (figure 1)[12]. There was no statistically significant difference in asymmetry.

But there is incommensurability between the homeopathic and conventional data sets: for instance it excluded some larger homeopathy trials with positive effect because no matching trial could be found [22-24]. The plot for homeopathy included 16 unpublished trials, the conventional plot none. There was an additional difference in quality: homeopathy had 21 out of 110 (19%) good quality trials, conventional medicine had 9 out of 110 (8%). Both publication bias and quality bias lead to exaggerated effects. Adding the difference in quality for 12 trials results in a less biased effect in 28 out of 110 (25%) of the homeopathy trials.

Comparison of 110 homeopathy trials with 110 matched conventional trials does not indicate a difference in efficacy of both methods. Several authors show statistically non-significant results with subsets of trials. Reconstruction of the meta-analysis shows that other, equally justifiable, subsets of high quality trials yield statistically significant positive results [25]. Considering the plot of both methods, this would also be a common occurrence with subsets of conventional medical trails.

Illustration 2: Figure 1

Plausibility bias

The differing conclusions of the meta-analyses of the homeopathy and conventional medicine subsets, and particularly for the homeopathy URTI subset, do not reflect the nature of the evidence, nor its quality, but negative 'plausibility bias'. There is growing evidence that antibiotics do more harm than good in URTI, despite a plausible rationale for their use; their continued use reflects positive plausibility bias. Plausibility bias obstructs a fair evaluation of the evidence around homeopathy; its extent and implications have not been adequately recognised or discussed. In the current circumstances, negative plausibility bias concerning homeopathy should not impede further research. Nevertheless, such new research in homeopathy, if positive, may have limited impact on practice unless and until homeopathy can be established within a plausible theoretical framework.

Treatment of URTI and further research in homeopathy

The use of homeopathy for URTI, on the available evidence, demands further investigation. URTI is an 'effectiveness gap' condition, a common clinical problem for which there is a lack of effective treatments [26]. Extensive discussions about RCT evidence in homeopathy are so far inconclusive, but do these discussions not mirror the problems with the interpretation of conventional evidence?

Antibiotics have saved countless lives, but it is clear that there is little place for them in uncomplicated URTI: they do not reduce the risk of serious complications [27, 28] and they are ineffective in otitis media [29]. Bezáková et al suggest that acute otitis media recurs more frequently in young children treated with antibiotics than in those given placebo, perhaps due to selection of more virulent microflora [30], and the use of antibiotics for respiratory tract infections leads to increased antibiotic resistance [31]. Despite widespread awareness of the need to reduce the use of antibiotics for URTI, they are still frequently prescribed [32-25]. URTI is the most prevalent disease category in general practice [36]. As the problems associated with antibiotic use are increasingly recognised there is a need to consider alternative treatments such as homeopathy.

The specific research we propose, conducted in primary care, is to test the hypothesis that homeopathy averts, reduces or delays antibiotic prescriptions in the management of acute otitis media or other URTI.

There are a number of considerations to be taken into account in designing such a study. These include:

Trials using an antibiotic treated group in uncomplicated URTI are unethical since the evidence suggests that they do more harm than good in this situation.

-Trials should be of relatively long duration: URTI are often recurrent and the disadvantages of antibiotics are most evident in this context.

-Homeopathic prescribing requires skilled practitioners.

-Homeopathy is associated with strong patient preferences; previous RCTs in primary care have foundered on this issue [37].

The research question would not be: 'Can ultra-diluted medicines exert physiological effects?'. A clinical trial is a clumsy and expensive way of answering such a question, which would be much better answered by biological models. A number of such models have been described [38], and their further development might enable homeopathy to become framed in the plausible theoretical background that it requires.

Odds = chance / (1 – chance); in words, the chance that something will happen divided by the chance that it will not happen. Odds = 1 means: chance is fifty-fifty.

LR = Likelihood ratio = True positives / False positives

Conclusion

We conclude therefore that a controlled clinical trial on homeopathy for otitis media (or other URTI) should be of pragmatic design and large-scale in nature. If viewed against a background of enhanced plausibility through new basic research, the results of such a trial might have far-reaching impact on the treatment of otitis media (URTI) and on the contribution of homeopathy in primary care practice.

Abbreviation(s)

RCT: randomised controlled trial
URTI: upper respiratory tract infections
LR: Likelihood Ratio

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Illustrations

Illustration 1

Table 1: Sequential updating of belief; the posterior chance from evidence No. 1 becomes the prior chance for evidence No. 2, etc.

RCT number	Prior chance	Posterior chance	LR
1	0.000001	0.000016	16
2	0.000016	0.000256	16
3	0.000256	0.004079	16
4	0.004079	0.061505	16
5	0.061505	0.511856	16
6	0.511856	0.943748	16
7	0.943748	0.996289	16
8	0.996289	0.999767	16

Illustration 2

Figure 1: Plots of 110 homeopathy trials (top panel) and 110 conventional trials (lower panel, matched on medical indication.
(source Shang; Lancet 2005; 366:726-732, with permission from Elsevier)