Is evidence for homoeopathy reproducible?

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Summary

We tested, under independent conditions, the reproducibility of evidence from two previous trials that homoeopathy differs from placebo. The test model was again homoeopathic immunotherapy.

28 patients with allergic asthma, most of them sensitive to house-dust mite, were randomly allocated to receive either oral homoeopathic immunotherapy to their principal allergen or identical placebo. The test treatments were given as a complement to their unaltered conventional care. A daily visual analogue scale of overall symptom intensity was the outcome measure. A difference in visual analogue score in favour of homoeopathic immunotherapy appeared within one week of starting treatment and persisted for up to 8 weeks (p=0·003). There were similar trends in respiratory function and bronchial reactivity tests.

A meta-analysis of all three trials strengthened the evidence that homoeopathy does more than placebo (p=0·0004). Is the reproducibility of evidence in favour of homoeopathy proof of its activity or proof of the clinical trial's capacity to produce false-positive results?

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Introduction

A pilot study[1] specifically designed to answer the question "Is homoeopathy a placebo response?" suggested that it was not, a result replicated in a larger trial.[2] As these findings were controversial, the original investigators approached independent colleagues in the University of Glasgow to find out if the result could be replicated in a third trial. The three studies used homoeopathic immunotherapy in inhalent allergy as a model, the first two in hay fever, the third in asthma with the same main outcome measure—a visual analogue score of overall symptom intensity. We report the results of this third study and a meta-analysis of all three.

Patients and methods

Qualification screening[3] was used to obtain a study sample from an asthma outpatient clinic treating patients from west-central Scotland. All patients gave written informed consent and the trial was approved by the Glasgow Royal Infirmary ethics committee.

Table 1 shows criteria for eligibility. Before inclusion patients had symptoms and compliance monitored over a 4-week run-in period. They continued with their usual treatments and were asked not to take any new allergen-avoidance measures for the duration of the study.

Trial design

The study was a randomised double-blind assessment of two parallel groups, one receiving homoeopathic treatment, the other placebo (figure 1). A cross-over design was not used because we wished to avoid the complications of any carry-over effect from prolonged action from homoeopathy.[6] Patients were entered over 4 consecutive weeks, beginning in the first week of February (so that the main observation period was outwith the local pollen season).

At the beginning of the run-in, each patient was assessed by a homoeopathic and an asthma-clinic doctor, a nurse did skin tests, and a respiratory physiologist measured pulmonary function and bronchial reactivity to histamine. The pharmacist checked subjects' inhaler technique and their other treatments. Patients were then given a single-blind placebo medication with the same ritual of selection and administration as at subsequent visits: the pharmacist administered the contents of a vial onto the patient's tongue.

Inclusion
Age >16 yr
Asthma: >15% improvement in FEV_1 with bronchodilators[4]
>1 year history
Atopic: reactive to inhaled allergens and positive skin tests
Exclusion
Deterioration during grass-pollen season
Allergen-avoidance within previous 6 weeks
Previous homoeopathic immunotherapy for asthma
Respiratory infection
Severe concomitant disease
Pregnancy
Antihistamines in past 4 weeks
Parenteral steroids in past 6 months[5]

Table 1: **Criteria for eligibility**

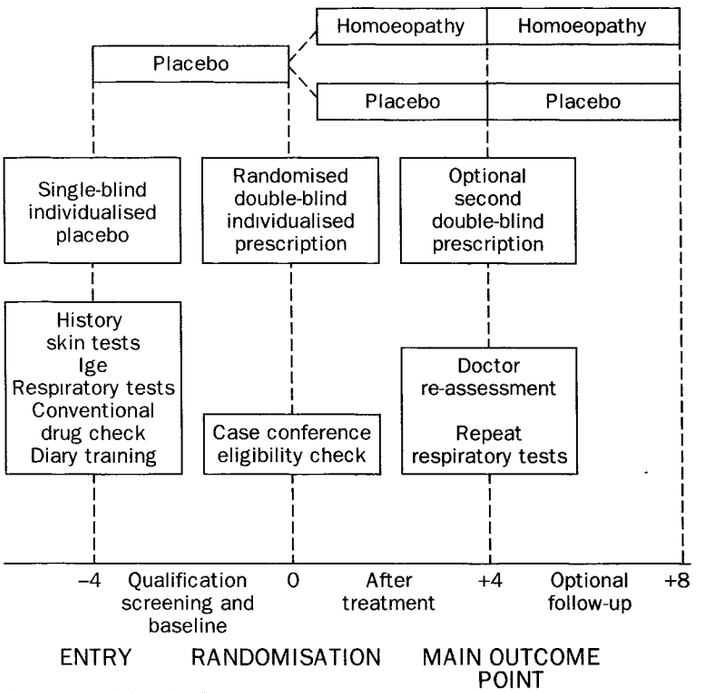

Figure 1: **Trial design**

4 weeks later a case conference was held about each patient to confirm eligibility and decide the main allergen for desensitisation. Both doctors could veto patients they considered unsuitable. The homoeopathic doctor selected the homoeopathic prescription on the basis of the largest skin-test weal concordant with the allergy history. Patients were then randomised by a restricted technique of permuted blocks of 2,[7] stratified for the indicated allergen and daily dosage of inhaled steroid. They received treatment that same morning. At the main end point 4 weeks later, patients returned for a reassessment by both doctors, a diary check, and pulmonary function tests. Patients who volunteered to continue to the optional assessment 4 weeks later were reassessed by the homoeopathic doctor to see if their prescriptions needed to be repeated or changed.

Respiratory function

Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were measured with an electronic spirometer incorporating a Fleisch type Plau-head connected to a differential pressure transducer (Vitalograph Compact, Buckingham, UK); the best of three successive measurements was recorded. All patients were asked to refrain from taking bronchodilators before the tests which were carried out at the same time of day. Reactivity to histamine was measured with a dosimeter[8] (Nebicheck, PK Morgan, Kent, UK) and a nebuliser (Aeromist, Vickers Medical, Hampshire, UK), by an adaptation of the method of Cockcroft et al.[9] After inhalation of 10 puffs of saline, patients were asked to inhale increasing doses of histamine, doubling each time from 0·03 mg/mL to 16 mg/mL. FEV_1 was measured 30 and 90 seconds after each dose. When the FEV_1 had fallen by 20% from the value after saline alone the test was stopped. The amount of histamine required to cause this 20% drop (PC_{20}) was measured by linear interpolation on a log dose-response plot. At baseline all patients had a PC_{20} of less than 2 mg/mL (moderate to severe asthma).

Skin testing and serology

Reactivity to house-dust mite, cat fur, dog hair, tree pollens, grass pollens, and *Cladesporium* was tested with preloaded lancets (Phazets, Pharmacia, UK); and reactivity to *Aspergillus*, feathers, and house-dust with a needle and allergen solution (Bencard, UK). After 15 minutes a weal reaction of 3 mm or more in its greatest diameter was taken as positive.

Allergen-specific serum IgE antibodies were measured by radio-immunoassay (RAST, Pharmacia), according to manufacturer's recommendations. Blood samples were tested in batches to avoid inter-assay variability. A value of more than 0·7 units/mL was taken as positive.

Study diaries and visual analogue scores

Patients were shown how to use a study diary. Each morning they scored the severity of night-time asthma and morning tightness on a 0–4 digital scale, and their peak-flow rate. At the end of each day they scored daytime asthma, cough, and nasal symptoms, and noted peak-flow rate and use of medications. They completed a summary 100 mm visual analogue scale using the same wording as in the previous two studies: "Overall today I felt . . .", with the minimum point labelled "Fine" and a maximum labelled "Terrible". In context, timing, and intent the scale was about asthma, but the wording may include some element of general well being. Visual analogue scales have been validated and recommended for clinical trials of breathlessness,[10] where scores are consistent within patients,[11] accurate in assessing the severity of asthma,[12] and sensitive enough to detect an effective treatment.[13] In hayfever, an average difference of 5% between groups is considered clinically relevant;[14] however, there is no clear consensus on the equivalent difference in asthma. One methodology guide comments that between-group differences in scores have to exceed 30% to be relevant.[15]

Medication preparation and administration

Allergen material was obtained from the Pasteur Institute in Paris. A homoeopathic drug laboratory (Laboratoires Boiron, Lyon, France) then made the preparations according to the French Homoeopathic Pharmacopoeia. In a controlled-atmosphere chamber (category A) the standardised allergen already in liquid form was first dissolved in a 70:30 water/alcohol solution, and was then serially diluted 1 in 99 thirty times, with vigorous automatic vibration (succussion) at each stage (a mechanical arm imparted a 4-second burst of 150 up-and-down movements, through an amplitude of 6 cm, with a resting phase of 20 seconds). Neutral glass vials were used only once (Hahnemannian method). The final dilution (30c, a theoretical dilution of 10^{-60} commonly used in homoeopathic practice) was sprayed onto 15:85 lactose/sucrose globules in a glass flask under positive pressure. The globules were then packaged in an air-filtered area and sealed into 1 g plastic vials. Placebo vials were prepared with globules impregnated with the same batch of diluent which, without the addition of any antigen, had been identically diluted and vibrated.

The drugs and sealed codes were delivered directly to the pharmacy department of Glasgow Royal Infirmary. The drug packages were recoded before the start of the trial by the pharmacist, who gave a unique number to each treatment package; the codes remained unbroken until analysis was completed.

The treatment pack contained three identical vials to be taken in 24 hours. Although a single dose is usually considered adequate we used this "split single dose" approach to ensure adequate delivery, and to cover the possibility of a diurnal rhythm in the patient's sensitivity to treatment.

Random samples of drug vials were forwarded for independent analysis. These were checked for the presence of any contaminants, or anti-asthmatic drugs, including steroids and theophylline, with gas chromatography-mass spectroscopy (MD800, Fisons, Manchester, UK).

Analysis

With the hayfever trial[2] data as best guess, the power calculation was based on a minimum difference between the placebo and homoeopathically treated groups measured by a mean change in visual analogue scale scores across all individuals within each group. The mean of 15 mm (SD 29) with a 5% significance level and 80% power suggested that 60 patients per group would be needed.[7] We did not recruit this number of patients because of qualification screening and closing recruitment before the pollen season.

Analysis was by intention to treat. The predefined main measure of outcome was the mean change from baseline over 4 weeks in visual analogue scale scores. Two-tailed two-sample *t* tests were applied to data with normal distributions (visual

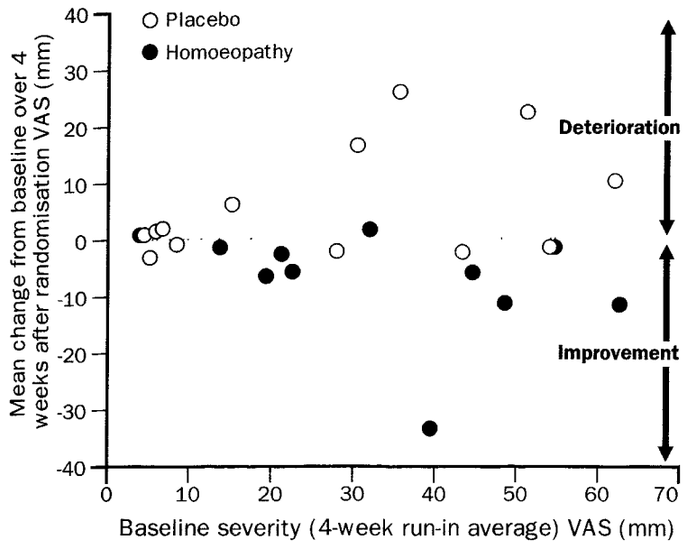

Figure 2: **Baseline visual analogue scale scores and changes with treatment**

Values in any one time period are the mean of the daily overall scale scores. VAS=visual analogue scale. Baseline VAS: Mean (SD): homoeopathy 32·9 (18·4) mm, placebo 26·8 (20·8) mm, p=0·46.

analogue scale scores and $\log_{10}$ PC_{20}) and Mann-Whitney U tests on skewed data (FVC, FEV_1). χ^2 tests and McNemar's test of symmetry were applied where appropriate to the comparison of patients' and doctors' overall perceptions of the effectiveness of treatment, and to the number of patients who showed improvement in respiratory function tests.

The chest clinic doctor verified the data given to the independent statistician who, unaware of the coding, began by checking the results of the simple analyses. He then applied repeated-measures analysis of variance to investigate treatment and time effects, followed by the regressions of the visual analogue scale score of any one week on the previous week to identify where significant changes in pattern between treatments occurred.

Meta-analysis

Meta-analysis of the three homoeopathic immunotherapy trials, including this one, was conducted to re-evaluate the placebo hypothesis that these trials were designed to address; our focus, therefore, was on the reproducibility of evidence that a homoeopathic dilution shows a greater effect than placebo, not on the examination of the daily clinical effects of homoeopathic immunotherapy; indeed the latter would require further work and a different design because, apart from our three studies, the only published data on inhalant allergy homoeopathic immunotherapy are two uncontrolled case studies[16,17] and one brief abstract of a non-randomised controlled trial.[18]

The features which allowed the three trials to be compared are: inhalant allergy, homoeopathic immunotherapy, use of a 30c potency, and an identically worded visual analogue scale as the main measure of outcome. We pooled all available visual analogue scale scores from every randomised patient over the 4 weeks after randomisation. To ease visual interpretation of overall trends the descriptive daily graphs were plotted with smoothed values, by means of simple robust non-linear procedures.[19]

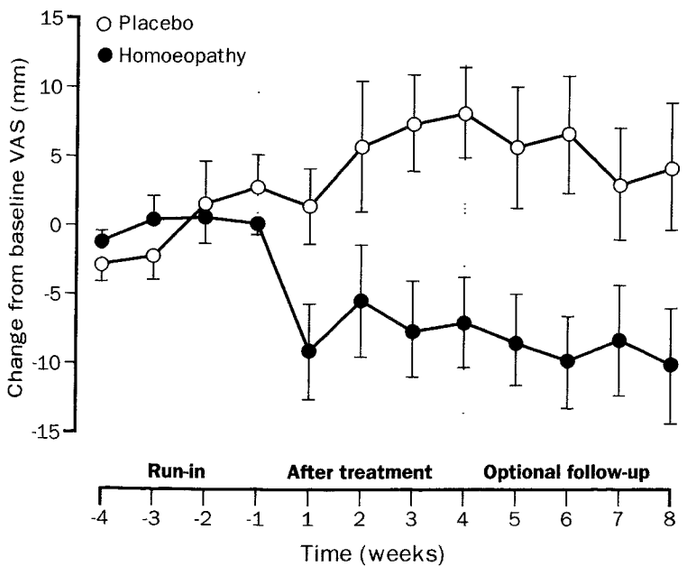

Figure 3: **Weekly comparison between groups (means and SEM)**

	Homoeopathy (n=13)	Placebo (n=15)
Age (yr)*	40 (16·3)	37 (14·3)
Sex (M/F)	8/5	7/8
Duration of asthma (yr)*	21 (17)	15 (13)
Smokers/ ex-/ non-	2/4/7	2/6/7
Patients using inhaled steroids:†		
None	3	5
<1000 μg/day	5	5
≥1000 μg/day	5	5
Prescribed allergen		
House-dust mite	11	12
Cat	0	1
Dog	0	1
Feathers	1	1
Mixed moulds	1	0
Skin testing and serology		
Specific IgE (units/mL)‡	6·0 (1·4–48·5)	5·8 (0·7–28·1)
Skin test (mm)‡	8·0 (4·8–9·8)	6·5 (5·5–8·0)

*Mean (SD); †beclomethasone or equivalent. ‡median (quartiles).

Table 2: **Baseline clinical characteristics**

Results

28 patients completed qualification screening and were randomised. 4 patients did not attend for follow-up: 3 (2 homoeopathy) gave social reasons and reported no marked change in symptoms; 1 (placebo) was withdrawn by her GP 3 days after randomisation because of worsening symptoms. Thus, 24 of 28 patients' data were used in the principal analyses of changes from baseline over 4 weeks after randomisation. All patients chose to continue into the optional follow-up period but a further 3 from the placebo group failed to attend for this assessment, with no drop-outs in the homoeopathy group. The groups were well matched in clinical characteristics (table 2) and initial respiratory function tests (table 3). Symptoms were similar during the 4-week run-in (figure 2, horizontal distribution).

Visual analogue scale

The vertical distribution of figure 2 shows the two groups separated after treatment: 5 of 13 patients on placebo improved whilst 9 of 11 patients on homoeopathic treatment improved. In general, patients with mild symptoms changed little and patients with more severe initial symptoms responded most.

Figure 3 shows a difference in favour of homoeopathy within 1 week of randomised treatment, and figure 4 the significance of that difference. For statistical analysis we averaged weeks 3 and 4; when, from previous trials, patients would be clear of any initial aggravations and any

	Homoeopathy	Placebo	p
FVC (L) median (quartiles)	3·4 (2·4–4·8)	3·7 (3·1–4·5)	0·48
FEV_1 % of predicted median (quartiles)	66 (49–77)	70·5 (56–92)	0·36
Log_{10} PC_{20} mean (SD)	−0·72 (0·34)	−0·74 (0 53)	0·93

Table 3: **Baseline pulmonary function tests**

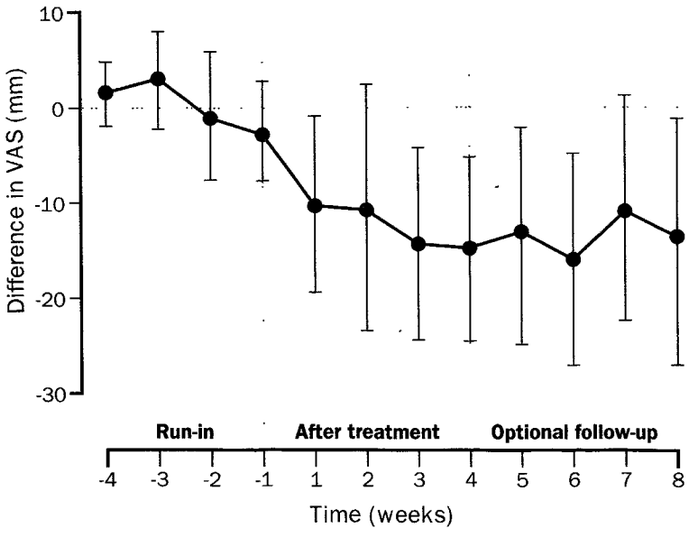

Figure 4: **Differences between groups (means and 95% CI)**

expected treatment effect would be evident. This showed a mean (SEM) reduction of 7·2 (3·2) mm for homoeopathy versus an increase of 7·8 (3·0) mm for placebo (two-sided two-sample t test p=0·003, 95% CI [−24·1 to −5·9] mm). The difference between the groups averaged 33% over the 4 weeks after treatment.

Additional independent analyses showed the visual analogue scale score to be a consistent measure with clear indications of a strong correlation between weekly measurements on the same patient. On the basis of repeated ANOVA there were no systematic time effects or time/treatment interactions. A significant baseline-corrected difference between the groups was confirmed. Further analysis on each week of the study using as covariates the mean baseline score and previous week score found that the significant change in score between the groups occurred within 1 week of homoeopathic treatment.

Respiratory function tests

Out of the 24 patients with usable clinical data, 2 (1 in each group) did not attend for follow-up respiratory function testing. A further 2 (1 in each group) had a major degree of obstruction precluding bronchial provocation at both test sessions. Of the remaining 20 patients, 2 had only one test: 1 in the homoeopathy group improved sufficiently after treatment to allow a histamine challenge during the second series of tests, the other patient was on placebo and deteriorated to the point where a second test could not be done. The results which follow may therefore underestimate the difference between the groups. In the 18 remaining patients, there was evidence of a change in favour of homoeopathy in the FVC and FEV_1 (table 4).

There was also a tendency in the homoeopathy group to a greater reduction in bronchial reactivity in the PC_{20} tests with a median increase of 53% in histamine

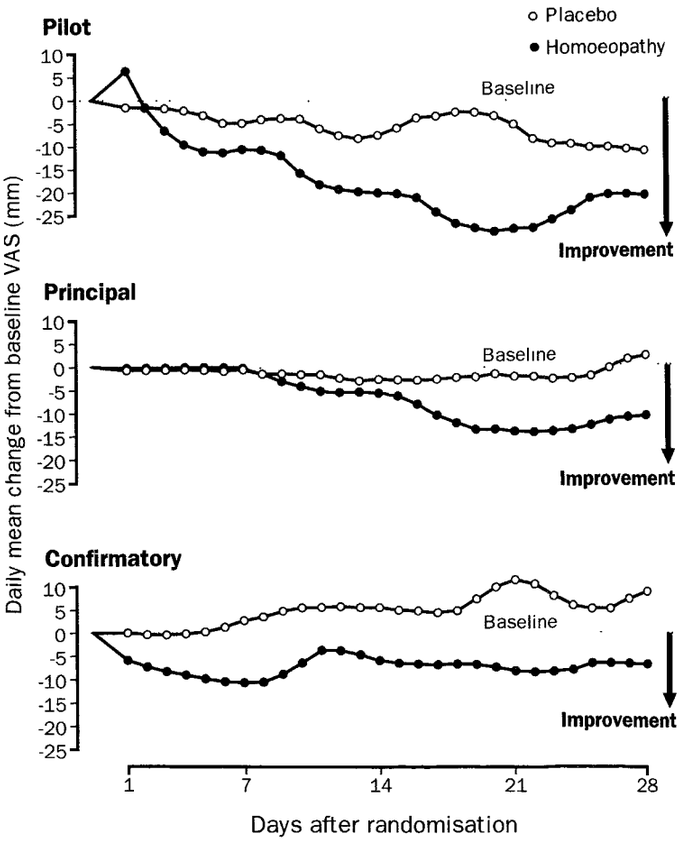

Figure 5: **Pattern of change within each trial**
The first two studies were in hayfever, the third in asthma. The baseline in each case was: pilot, the first 3 days; principal, 7 days before randomisation; confirmatory, 28 days before randomisation. The sample size in the composite is 108 placebo and 94 homoeopathy. All values are the mean change from baseline of the daily overall visual analogue scale scores for the given time period.

resistance (measured as mg/mL) compared with a median decrease of 7% in the placebo groups. The pre-treatment and post-treatment geometric means of the $\log_{10}$ transformed data were 0·19 and 0·25 respectively for homoeopathy giving a doubling dose of 0·33. The equivalent values for placebo were 0·18 and 0·22 resulting in a doubling dose of 0·22. These changes were not statistically significant at 5%. Summarising the PC_{20} results: 7 of 9 (77%) patients on homoeopathic treatment showed improvement, compared with 4 of 11 (36%) on placebo (p=0·08 Fisher's exact test).

Other measures

Daily digital scores and peak flow readings showed no significant trends. The patients complied with instructions not to alter their drug use; however, 1 placebo patient required oral prednisolone 3 and 4 weeks after treatment. IgE antibody titres tended to increase throughout the study with a greater but not statistically significant rise in the homoeopathy group.

Analysis of preparations

No contamination with anti-asthmatic drugs was detected; the limit of sensitivity was 10 μg/L. House-dust

	Within group		Between group				
	Homoeopathy	Placebo	Mean/median difference	95% CI	p	% difference*	Trends in direction of:
FVC (L) median (quartiles)	0·07 (−0·2 to 0·4)	−0·33 (−0·4 to 0·0)	0·36	0·03 to 0·73	0·03	10·2%	Homoeopathy
FEV_1 % of predicted median (quartiles)	3·0 (−3·0 to 8·3)	−7·0 (−11 to 5·0)	8·50	−3·0 to 18·0	0·08	14·9%	Homoeopathy
Log_{10} PC_{20} mean (SEM)	0·09 (0·12)	−0·02 (0·11)	0·11	−0·2 to 0·5	0·48	34·9%	Homoeopathy

*Calculated as % change from baseline for each patient expressed as difference between group means or medians.

Table 4: **Pulmonary function tests: change from baseline**

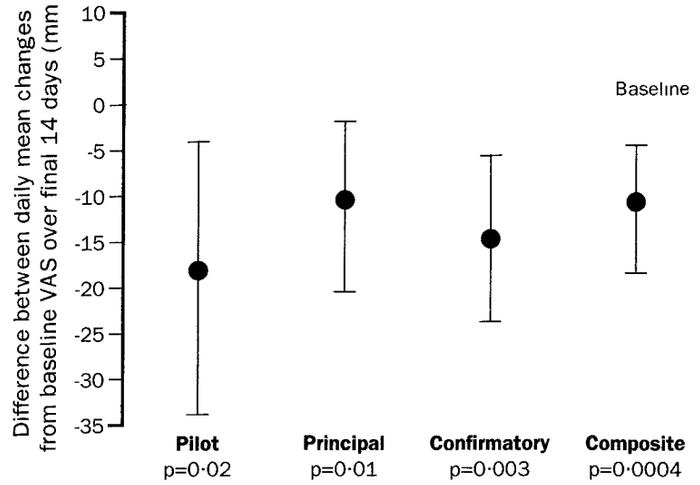

Figure 6: **Trials compared and combined**
95% CI and difference between means.

mite antigen (*der* P1) was checked with ELISA[20] (University of Virginia, Charlottesville, USA). No antigen was detected, the limit of sensitivity being 1·95 ng/mL.

Clinical perceptions

3 patients (1 homoeopathy) reported initial aggravations of asthma symptoms. 4 weeks after treatment, patients and both doctors were asked to rate effectiveness of treatment on a scale of −4 (very severe deterioration) to +4 (very good improvement), the patients' opinions being noted by the chest clinic doctor. The patients and homoeopathic doctor tended to rate the homoeopathic treatment as more effective (patients χ^2=4·0, p=0·05; homoeopathic doctor χ^2=2·8, p=0·09); no doctor or patient gave a negative score to homoeopathy. When asked if, based on their assessment of effects, the treatment prescribed had been homoeopathic or placebo, both doctors and patients tended to be correct (patients χ^2=4·2, p=0·04), although the respiratory doctor was non-committal in 8 of the 11 homoeopathy patients. Overall there was a trend for the homoeopathic doctor's accuracy to be greater than that of the non-homoeopathically trained doctor (McNemar's test p=0·06).

Meta-analysis

The meta-analysis compares the baseline corrected visual analogue scale scores across the three homoeopathic immunotherapy trials (figure 5). A similar pattern of change emerged in each—the homoeopathically treated groups showed a greater improvement in scores than the placebo groups. When the 95% CIs of these changes were compared (taking the last 2 weeks compared with the baselines) there was a clear indication of a mean advantage of homoeopathy over placebo (figure 6).

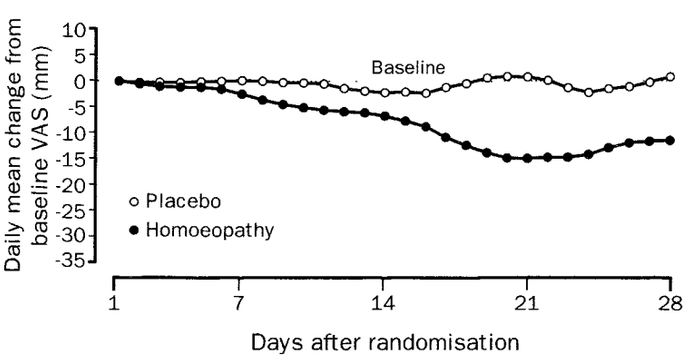

Figure 7: **Composite of three trials**

To describe the average clinical effect of homoeopathic immunotherapy we pooled the data from the three trials to give a collective sample size of 202 for the composite graph (figure 7). On average, evidence of improvement over placebo appears by the second week, and by the third and fourth week, averages a reduction of about one-third versus 10% in the placebo patients. This change is statistically significant.

Discussion

This study has reproduced the evidence from its two predecessors[1,2]—that the effects of homoeopathy differ from those of placebo. The three trials used the same model of homoeopathic immunotherapy in inhalant allergy, and an identically worded visual analogue scale score as the main measure of outcome. The trials were not designed to determine daily practice; the issue is a general one of homoeopathy versus placebo. Although the results might suggest that homoeopathic immunotherapy has a part to play in treating these diseases, with the hayfever patients reducing their antihistamines and patients with asthma showing a trend towards improvement in respiratory function tests, we think it premature to speculate further. The debate should focus on the challenge inherent in reproducing evidence that patients can detect an effect from homoeopathic medicines over and above their placebo action.

Could the explanation be three false-positive results? The patients were carefully selected, had clearly defined diagnoses, and the results were not due to any change in conventional treatments. Double blinding and randomisation rule out observer or patient bias. The patterns appear orderly, and are similar in the three studies. Analysis shows the absence of random or chance factors, and the results have proved reproducible under independent conditions. The positive results from the meta-analysis of 202 patients do not stand in isolation. An independent criteria-based review of over 100 published controlled trials of homoeopathic treatments[6] noted that 77% show a positive effect. Using current orthodox standards, this review commented that this body of evidence "would probably be sufficient for establishing homoeopathy as a regular treatment for certain conditions".

But homoeopathy is not an orthodox treatment; it has long been regarded as having "inherent implausibility".[21] So can positive trial results validate claims of biological efficacy for solutions thought to be lacking any trace of their original solute? Where should this debate now proceed: when does one "believe the unbelievable" as an editorial in *Nature* asked?[22]

Over a century ago the UK General Board of Health omitted the success of homoeopathic treatments in the London cholera epidemic in their statistical return to Parliament as they would "give an unjustifiable sanction to an empirical practice alike opposed to the maintenance of truth and to the progress of science".[23] Does this still hold true and must we likewise reject contemporary trial results as spurious? If so, we must ask if the technique of randomised controlled clinical trials is fundamentally flawed, and capable of producing evidence for effects that do not exist, by, for example, the effects of clinicians' expectation of outcome[24] transmitted by subtle effects that circumvent even double blinding? To question the tool which has built most of today's pharmacological practice is no less perplexing than asking whether homoeopathic

treatments are active. Either answer suggested by the evidence to date—homoeopathy works, or the clinical trial does not—is equally challenging to current medical science.

The usual response to the possibility that homoeopathic treatments are effective is to call for a mechanism of action—asking "how?" before asking "if?" is a bad basis for good science when dealing empirically with things that may as yet evade explanation. The speculation which follows should be considered in that light.

Opposite action at low dose—a poison becoming an aid—is not unfamiliar in conventional science and the subject of much debate, in recent times under the term hormesis.[25,26] Conventional allergen desensitisation is a form of applied hormesis, and accepted wisdom is that (like homoeopathy) it works for some patients with prolonged action from single doses through mechanisms of action as yet unknown.[27] Biological effects at microdilution, are no longer such a firm basis for rejection as they were last century. In fact, conventional researchers have moved closer towards homoeopathy, using "extraordinarily low doses", for example in oral immunotherapy.[28,29] Here, on the edge of biological sensitivity, considering qualitative information or triggers, biologically amplified after reception like the single molecules of pheromones, would seem more fruitful than pharmacological dose-response curves.

For today's science, however, the main barrier to acceptance of homoeopathy is the issue of serially vibrated dilutions that lack any molecules at all of the original substance. Can water or alcohol of fixed biochemical composition encode differing biological information? Using current metaphors,[30] does the chaos-inducing vibration, central to the production of a homoeopathic dilution, encourage biophysically different fractal-like patterns of the diluent, critically dependent upon the starting conditions? Theoretical physicists seem more at ease with such ideas than pharmacologists, considering the possibilities of isotopic stereodiversity, clathrates, or resonance and coherence within water as possible modes of transmission, while other workers are exploring the idea of electromagnetic changes.[31] Nuclear magnetic resonance changes in homoeopathic dilutions[32] have been reported and, if reproducible, may be offering us a glimpse of a future territory.

For now the critical tests remain clinical. Our results lead us to conclude that homoeopathy differs from placebo in an inexplicable but reproducible way.

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