

## Use of ultramolecular potencies of allergen to treat asthmatic people allergic to house dust mite: double blind randomised controlled clinical trial

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### Abstract

**Objective** To evaluate the efficacy of homoeopathic immunotherapy on lung function and respiratory symptoms in asthmatic people allergic to house dust mite.

**Design** Double blind randomised controlled trial.

**Setting** 38 general practices in Hampshire and Dorset.

**Participants** 242 people with asthma and positive results to skin prick test for house dust mite; 202 completed clinic based assessments, and 186 completed diary based assessments.

**Intervention** After a four week baseline assessment, participants were randomised to receive oral homoeopathic immunotherapy or placebo and then assessed over 16 weeks with three clinic visits and diary assessments every other week.

**Outcome measure** Clinic based assessments: forced expiratory volume in one second ( $FEV_1$ ), quality of life, and mood. Diary based assessments: morning and evening peak expiratory flow, visual analogue scale of severity of asthma, quality of life, and daily mood.

**Results** There was no difference in most outcomes between placebo and homoeopathic immunotherapy. There was a different pattern of change over the trial for three of the diary assessments: morning peak expiratory flow ( $P=0.025$ ), visual analogue scale ( $P=0.017$ ), and mood ( $P=0.035$ ). At week three there was significant deterioration for visual analogue scale ( $P=0.047$ ) and mood ( $P=0.013$ ) in the homoeopathic immunotherapy group compared with the placebo group. Any improvement in participants' asthma was independent of belief in complementary medicine.

**Conclusion** Homoeopathic immunotherapy is not effective in the treatment of patients with asthma. The different patterns of change between homoeopathic immunotherapy and placebo over the course of the study are unexplained.

### Introduction

A thorough evaluation of homoeopathic treatment for asthma is needed because homoeopathy is increasing in popularity<sup>1-4</sup> and because several uncontrolled studies (without placebo control) have reported that such treatments are efficacious.<sup>3-7</sup> Several organisa-

tions have called for further research.<sup>8-12</sup> A recent review of placebo controlled homoeopathic clinical trials in general concluded that the effects of treatment cannot be attributed entirely to a placebo response but that there was insufficient evidence to support the use of homoeopathic treatment for any single disease.<sup>13</sup>

Data on the use of homoeopathy to treat asthma are particularly limited. In a previous study 28 patients with allergic asthma, primarily to house dust mite, were treated for 12 weeks with homoeopathic doses of allergen (homoeopathic immunotherapy) given as an ultramolecular preparation—that is, in dilutions in which there were probably no molecules of active ingredient present.<sup>14</sup> This treatment is not usual homoeopathic practice but offers a testable model for differentiating between infinitesimal homoeopathic dilutions and placebo. There seems to be some preliminary evidence to support the hypothesis that we can differentiate between placebo and homoeopathic treatment using this model.<sup>13-15</sup> In the studies by Reilly et al participants recorded how they perceived their symptoms of asthma on a visual analogue scale.<sup>14-16</sup> There was a gradual and significant improvement in those who received homoeopathic immunotherapy compared with placebo over the course of the study. There was also a non-significant but positive trend in results of spirometry in the clinic but not for diary measures of peak expiratory flow.<sup>14</sup>

In two larger studies of allergic rhinitis Reilly and colleagues reported a significant clinical benefit with homoeopathic treatment (homoeopathic immunotherapy) compared with placebo. They also observed an occasional initial aggravation in symptoms with homoeopathy.<sup>15 16</sup> A Norwegian study of 66 participants with hay fever due to birch pollen found a mid-study difference in symptoms between those treated with a homoeopathic potency of birch pollen and placebo.<sup>17</sup> However, there was no difference at the end of the study.

We examined the clinical efficacy of homoeopathic potencies of house dust mite (homoeopathic immunotherapy) in asthmatic people allergic to house dust mite in a placebo controlled, randomised, double blind trial.

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## Methods

### Design

The study took place from September to April (outside the pollen season). After a run-in period of four weeks participants received homoeopathic immunotherapy or placebo orally on three occasions over 24 hours. We then assessed participants for 16 weeks. We followed the principles of participant selection and homoeopathic treatment used in previous studies. The study nurse witnessed the first administration of study medication, and participants were instructed to give themselves the two remaining doses, which is standard homoeopathic practice.<sup>14</sup>

We collected data on clinic assessments at the start and end of the run-in period (that is, at randomisation) and at the start of the sixth, 12th, and 16th week after randomisation. Participants completed diaries in the first and third weeks of run-in (two diaries of seven days) and in the first and every other week (eight diaries of seven days) after randomisation. Concurrent medication for all disorders, including asthma, was unchanged. Any participants who needed oral corticosteroids were withdrawn from the study and any available data used in the intention to treat analysis. Ethical approval was obtained from the Southampton and South West Hampshire joint research ethics committee and Bournemouth ethics committee.

### Recruitment of participants

We received lists of patients with asthma from 38 general practices. We wrote to those aged 18-55 years on headed notepaper from each practice. If patients did not respond to the first letter we sent a reminder letter. Over 1000 patients subsequently underwent skin prick tests for nine common allergens. Those eligible and prepared to consent to this prolonged clinical trial were then entered into the baseline recording period. Throughout the study all participants were seen in their own general practitioner's surgery. We included only those people with a positive result to house dust mite (wheal diameter 3 mm greater than the negative control 15 minutes after test) that was greater than for other aeroallergen extracts tested.

We considered patients to have asthma if they had a 15% improvement in forced expiratory volume in one second (FEV<sub>1</sub>) or peak expiratory flow 15 minutes after a 200 µg inhalation of salbutamol before randomisation and two of three criteria of an asthma symptom diary score of > 1 on at least seven of the 14 baseline days during the run-in period or a diurnal variation in peak expiratory flow of > 15% on at least seven of the 14 baseline days or a need for inhaled salbutamol on at least seven of the 14 baseline days.

Some variability in the participants' asthma was essential if we were to observe improvement or deterioration during the trial. We excluded participants if they recorded no impairment in quality of life in their diaries during the run-in period or if they filled in their diaries on fewer than 10 days during that period. We also excluded participants if they had taken part in another drug trial within the previous 30 days, had previously been treated with homoeopathic immunotherapy, were pregnant or lactating, were unlikely to comply with the trial requirements, had experienced a respiratory tract infection within the last three weeks,

or had changed their concurrent medication in the two weeks before entry.

### Treatment, blinding, and randomisation

Homoeopathic immunotherapy and placebo were prepared by Laboratoire Boiron, Lyons, France, using the same method of multiple dilutions with shaking (homoeopathic potentiation) to produce an ultramolecular dose of house dust mite as a 30C potency (30 dilutions of 1:100) as described by Reilly et al.<sup>14</sup> The placebo was made with the same method of dilution but without the house dust mite. The indistinguishable preparations were sent directly to the pharmacy at Southampton General Hospital, along with a sealed code indicating which package contained active or placebo treatment. The vials were stored in a secure area in accordance with the standard operating procedures of good clinical practice. The individual treatment vials were recoded as A or B by an independent researcher not involved with the study and not aware whether a vial contained active or placebo treatment.

We randomised the first 10 participants to treatment A or to B using a sealed envelope. All subsequent participants were allocated to A or B by a process of minimisation according to age, sex, smoking status, and severity of asthma, with severity assessed from the diaries (see below).<sup>18</sup> The participants and research nurses recorded whether treatment A or B had been given the day after dosing. The randomisation codes were broken only after the study had been completed.

### Measures

We recorded measures taken in the clinic and those noted by the participant on diary cards.

#### *Clinic based measures*

At baseline we recorded results of skin prick tests, concentration of total serum IgE, concentration of IgE specific for house dust mite, the participant's attitude to complementary and alternative medicine,<sup>19, 20</sup> and results of routine blood screening for undetected systemic illness. As a check for blinding, one day after randomisation we asked participants and investigators separately to guess whether the treatment was homoeopathic immunotherapy or placebo. At randomisation we recorded FEV<sub>1</sub> as the maximum of three blows. We calculated predicted FEV<sub>1</sub> from standard tables.<sup>21</sup> At randomisation and during clinic visits after treatment participants completed questionnaires on negative and positive trait mood<sup>22-24</sup> and quality of life specific to asthma (the asthma bother profile).<sup>25</sup>

#### *Diary measures*

In the diaries participants recorded morning and evening peak expiratory flow as the best of three attempts; perceived asthma severity on a visual analogue scale with high scores indicating worse asthma; and perceived mood on a bipolar scale with high scores indicating better mood. We calculated mean scores for the run-in period and for each of the eight weeks of assessment after randomisation. We calculated variability in mood by the variance of mood within each participant in each of the assessment periods and variability in peak expiratory flow by taking the difference between previous evening and morning

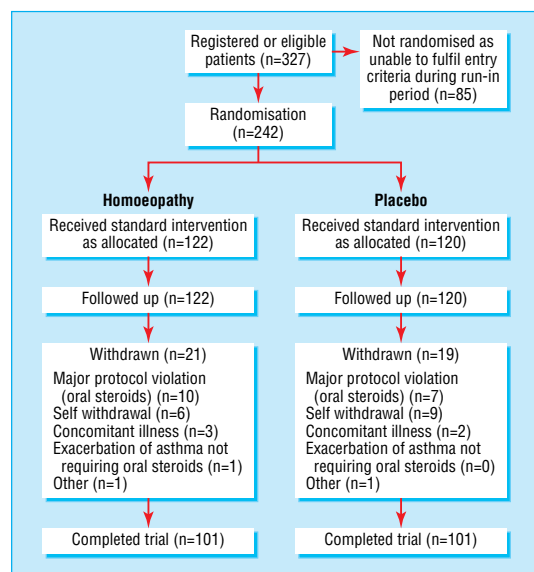


Fig 1 Patients entered, randomised, and withdrawn from trial

peak expiratory flow and dividing by previous evening peak expiratory flow multiplied by 100.<sup>26</sup>

We used the diaries to assess quality of life using the proportion of days in each of the assessment periods when no problem was reported in six categories of life.<sup>27</sup> Participants assessed symptoms at night, first thing in the morning, and during the day. We calculated the proportion of symptom-free days (no symptom of any kind) for each assessment period. Participants used inhaled bronchodilators as required. We assessed bronchodilator consumption by the frequency of daily use of the prescribed bronchodilator during each of the assessment periods.

### Analysis

An initial sample size of 270, with a 25% dropout rate (giving a final number of 202), would give a power of 80% for detecting an 8% difference in mean predicted FEV<sub>1</sub>, based on SD 20% and a two tailed test at the 5% level. FEV<sub>1</sub> and quality of life from diaries were the primary outcome variables; all other variables were designated as secondary. A sample size of 270 would give a power of 80% for detecting a difference in quality of life of 0.12 (SD 0.3).

We examined all outcome measures for suitability for parametric analysis. We tested blinding with  $\chi^2$  test. We tested clinical efficacy by comparing the two treatment groups at the end of the study (week 16 for clinic assessments and week 15 for diary assessments) using analysis of covariance. For FEV<sub>1</sub> the covariate was the average assessment at the start and end of the run-in period. For the other clinic based outcomes the covariate was the value obtained at the start of the run-in period. For outcome measures assessed from diaries the covariate was the value obtained from the average of values during the run-in period.

Because research in homoeopathy predicts an initial deterioration followed by improvement, we undertook a secondary analysis using the interaction term in a repeated measures analysis of covariance.<sup>28</sup> The interaction value in the analysis of covariance shows whether changes in outcome are significantly different between the two groups by comparing a series

of differences over the treatment period. Significance in the interaction value for analysis of covariance may occur if homoeopathy is having either a short term effect or a non-therapeutic effect. To interpret the pattern of any interaction effects we carried out individual analyses of covariance to compare each week after treatment with baseline for the two treatment groups. We examined only significant interactions in this way to avoid increasing the risk of a type I error due to multiple comparisons. We carried out the interaction test using only those participants who completed all diary or clinic assessments. Individual analyses of covariance were carried out on all participants who completed that particular assessment.

We used correlated Spearman's correlation coefficient to test whether belief in homoeopathy affected outcome. We correlated the total score on attitudes to complementary and alternative medicine with the change scores—that is, differences between baseline and point of maximum average improvement—but only for those variables where there was a significant effect. Probabilities of <0.05 were considered as significant.

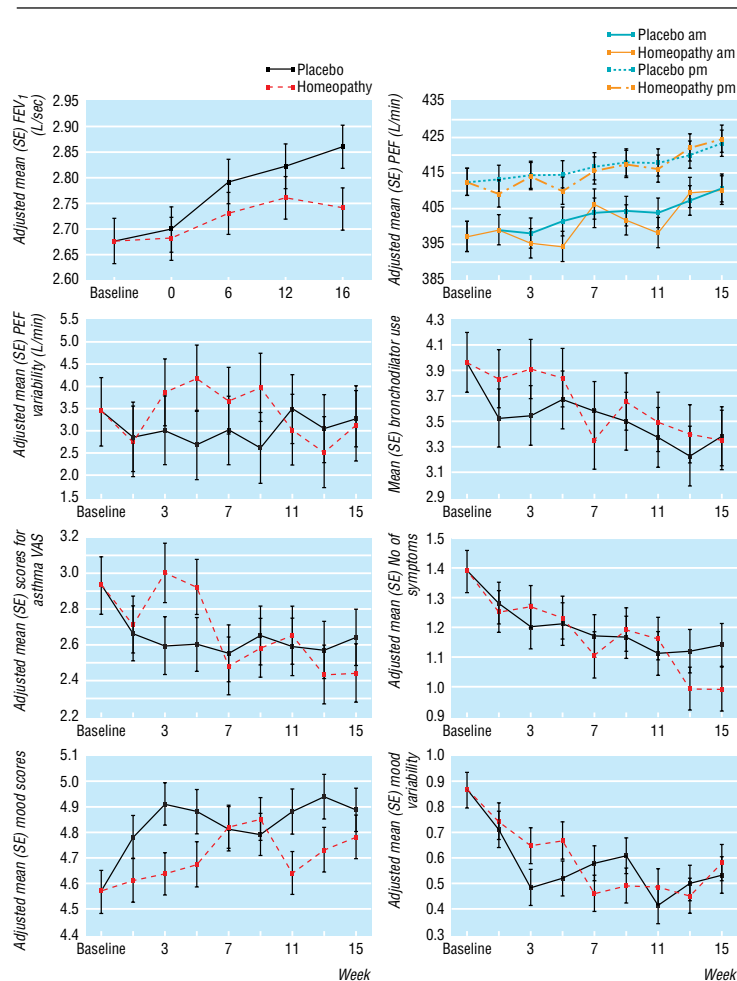
## Results

### Sample characteristics at baseline and blinding

We recorded baseline data from 327 people from 38 general practices (fig 1). Eighty five failed to fulfil the entry criteria before randomisation and dosing because their asthma was either too mild or too well

Baseline values for weeks before randomisation for all patients. Figures are means (SD) unless stated otherwise

Variable	Placebo (n=120)	Homoeopathy (n=122)
No of women	75	78
Mean (SD) age (years)	37.9 (10.4)	38.2 (9.0)
Smokers	29	29
FEV <sub>1</sub> (average of three measures) (l/sec)	2.68 (0.817)	2.67 (0.826)
FEV <sub>1</sub> (maximum of three measures) (l/sec)	2.77 (0.839)	2.76 (0.852)
Predicted FEV <sub>1</sub> (%)	79.9 (18.4)	80.9 (19.9)
Red cell magnesium (mmol/l)	1.93 (0.165)	1.94 (0.220)
Severity of asthma:		
1 (mild)	40	44
2 (moderate)	58	61
3 (severe)	23	17
Attitudes to alternative medicine (aggregated scores; high=positive attitude)	17.6 (7.28)	17.5 (6.99)
Asthma bother <sup>25</sup> (aggregated scores; high=more bother)	27.3 (11.9)	29.3 (12.6)
PANAS <sup>22</sup> (positive affect subscale)	30.0 (6.50)	29.3 (7.37)
PANAS <sup>22</sup> (negative affect subscale)	19.4 (6.97)	20.2 (7.53)
Mood (scale 0 (poor mood)-7 (good mood))	4.64 (0.79)	4.50 (0.80)
Mood variability	0.55	0.69
Peak expiratory flow (l/min):		
Morning	404.0 (103.7)	390.0 (106.3)
Evening	418.8 (104.8)	405.7 (102.2)
Median (range) diurnal variation (%)	2.55 (-9.98-26.2)	1.58 (-12.8-23.2)
Asthma (visual analogue score; high score is worse asthma as perceived by patient)	2.85 (2.07)	3.02 (2.19)
Problem-free days (proportion)	0.35	0.34
Median (range) No of puffs of bronchodilator per week	3.4 (0-14)	3.2 (0-10)
No not using bronchodilators	11	5
Median (range) serum IgE concentration (KU/l)	126 (5-14400)	112 (5-4250)
Proportion in each fifth of distribution of house dust mite specific IgE (KU/l):		
0 (least)	11	8
1	8	5
2	16	17
3	35	31
4 (greatest)	31	39



**Fig 2** Variables measured at clinic visits (FEV<sub>1</sub>) and from diaries (asthma visual analogue score (VAS), peak expiratory flow (PEF), mood, symptoms, use of bronchodilator). Error bars for each graph are same because of method of analysis used. Baseline figures are averages of two recordings for each variable

controlled. Therefore 242 participants were given homeopathic immunotherapy or placebo, and 202 completed all clinic assessments. Figure 1 shows details of participant flow. Diary completion decreased over the course of the study, and only 186 participants completed all diary assessments. Those who withdrew from the study were more troubled by their asthma (P=0.033), had worse scores on the visual analogue scale (P=0.048), and had worse morning peak flows (P=0.042) at baseline. No participant reported an adverse drug reaction due to homeopathic immunotherapy during the course of the study.

Baseline details of the two groups were similar (table). Forty six participants were not taking inhaled steroids (25 in the homeopathy group and 21 in the placebo group). Neither participants nor investigators were better than chance at guessing treatment (114 (47%) participants and 116 (48%) investigators guessed correctly).

**Clinical efficacy of homeopathy**

There was a significant increase from baseline in FEV<sub>1</sub> (P=0.006) and a significant decrease in asthma bother score (P=0.001) in both groups. There were also significant improvements in many of the diary measures.

However, there was no significant difference between the groups in either of the two primary outcome variables. Mean improvement in FEV<sub>1</sub> from baseline was 0.414 l/sec for placebo and 0.136 l/sec for active treatment (95% confidence interval for difference 0.136 to 0.693), and mean improvement for diary quality of life was 0.117 for placebo and 0.090 for active treatment (-0.096 to 0.150). There were no significant differences for any of the secondary outcome variables at the end of the study. Figure 2 shows mean values over time of testing.

**Diary assessments**

*Secondary statistical analysis*

We found significant interactions between the treatments and week of assessment for three secondary outcome variables (morning peak expiratory flow (P=0.025); asthma visual analogue scale (P=0.017); mood (P=0.035)), indicating differences between the two groups over the course of the study. There were no significant differences for the remaining variables. As the data for mood variability and bronchodilator use deviated from criteria for parametric testing (no suitable transformation was found) the inference of non-significance in these two cases may be invalid. There was no evidence of significant change in bronchodilator use in either group, although participants in the homeopathy group were using less bronchodilator than the placebo group in the last four weeks of the study. There was no evidence that homeopathic immunotherapy was better at treating asthma than placebo. There was no significant correlation between attitudes to complementary and alternative medicine and improvement on any of the outcome variables.

**Discussion**

This randomised placebo controlled trial shows that homeopathic immunotherapy is no better than placebo for the treatment of people with asthma who are allergic to house dust mite. Previous studies have suggested that homeopathy is efficacious in the treatment of rhinitis and possibly asthma.<sup>14-16</sup> Our study was substantially larger than any of the earlier studies and included a wider range of outcome measures. We found no evidence of difference measures between placebo and homeopathy in our primary outcome at the end of the study but in both arms there were large treatment effects. This “trial effect” remains unexplained.

Although there was some evidence of difference between treatments during the course of the study in three outcome variables from the diaries, these results should be treated with caution. Overall, differences between the treatments failed to achieve significance. However, there was a different pattern of response within the homeopathy group, characterised by alternating deterioration and improvement. This pattern is inconsistent with homeopathic theory and with previous reports of data in related studies, in which there was aggravation of symptoms or mid-study improvement.<sup>15 17 29</sup> The cause of this significant oscillating pattern is unknown, but we cannot exclude a type 1 error arising from the use of the multiple outcome variables.

### What is already known on this topic

Homoeopathic remedies probably have an effect that is greater than placebo

Some of the better quality homoeopathic studies involve homoeopathic doses of allergens used to treat allergic disease

### What this study adds

In this study homoeopathic remedies were no better than placebo in the treatment of asthmatic patients who are allergic to house dust mite

Several other studies have shown clinical effectiveness of homoeopathy in rhinitis. However, only one study of 28 patients showed efficacy based on perception of symptoms.<sup>14</sup> We used a similar homoeopathic intervention to that used in an earlier asthma study and used the same outcome variable that previously indicated a significant difference (visual analogue scale).<sup>14</sup> Although we measured diary outcome on only alternate weeks, it is unlikely that this could explain the difference between results.

Other than attributing a type 1 error to the earlier study, which we believe was underpowered, one possible reason for the difference between the two studies may be because in the earlier study a homoeopath was involved in patient selection and could veto entry for any individual patient, though no details of entry criteria were given.<sup>14</sup> Perhaps differences in patient recruitment or other unknown factors may explain the inconsistency of the results between these two studies. However, in view of the much larger sample used in our study compared with the earlier one, the proposal that homoeopathic immunotherapy is efficacious in selected patients with asthma should be treated with some caution.

The purpose of clinical trials involving homoeopathic immunotherapy has been to develop a model that allows us to demonstrate differences between homoeopathic immunotherapy, involving ultramolecular homoeopathic dilutions, and placebo.<sup>20</sup> We did not observe the same response as that described by Reilly et al and Taylor et al, but there were some differences between homoeopathic immunotherapy and placebo for which we have no explanation.<sup>14, 16</sup> In conclusion, in this large, double blind, randomised controlled trial of homoeopathic immunotherapy we have failed to confirm that this treatment is therapeutically efficacious in allergic asthma in an assessment that used previously validated objective and subjective outcome measures.

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Contributors: GTL conceived and managed the project; ADW helped to develop the protocol; MEH was involved in

protocol development and data analysis; SS oversaw data analysis; and JAB and GD were research assistants who carried out the study. STH was involved in protocol development. All authors were involved in the preparation of the final paper. GTL is the guarantor.

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