

tion use) should be supplemented by objective measures such as provocation threshold measures or skin test responses. Moreover, we believe that studies of non-conventional treatment should compare the test medication with the best available conventional therapy, so that results can be translated to mainstream clinical practice.

References

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We thank you for your interest in our work 5 years after its publication in the *Lancet* [1]. Unfortunately there are a number of inaccuracies in your analysis of our clinical trial which undermine your assumptions and therefore invalidate your conclusions.

Firstly, you state that 'readers might conclude that this study supports the use of homoeopathic medication for hayfever'. In fact our conclusion was that 'no evidence emerged to support the idea that placebo action fully explains the clinical responses to homoeopathic drugs'. We avoided generalizations or issues of external validity, rather the emphasis of this study was on its internal validity. 'We aimed simply to ask whether the effect of a potency differed from that of placebo' (quoted from [1]).

Internal validity was ensured by the use of identical

placebo, proper randomization and double blinding [2]. The large numbers in this trial increased precision and reduced the risk of dissimilarities between the groups which can occur in any trial despite randomization [3]. This work was based on designs of hayfever trials at that time [4-6] with the collaboration of statisticians from Glasgow University who also analysed the data triple blind. The methodology of this trial was examined recently by an unbiased team from the Department of Epidemiology from Limburg University who reviewed 105 clinical trials of homoeopathy and gave our work joint top rating for methodological quality (90 out of a possible 100 points) [7].

Moving from your general to your more specific points, you state that there could be potential bias in the patients as they 'were likely to be believers in homoeopathy'. This misses the point that such 'believers' would *increase* the placebo response and so *reduce* the likelihood of demonstrating a treatment effect (P. Knipchild, personal communication). Most people participate in a study because they believe the treatment might help—what is different here? Further the randomized double blind design ensures that such possible confounding variables are evenly spread between the groups.

You questioned the accuracy of our diagnoses. The admission criteria clearly stated that each patient had to have a past history of hayfever (hardly a difficult diagnosis to make) and current clearly defined symptoms. This followed standard trial procedure, but we decided to go further and check the accuracy of this clinical selection by testing a randomly selected subgroup with supplementary objective testing (the sensitivity and specificity still being less than 100%). The results were very reassuring. Only two patients (not several as you state) with negative skin tests were entered into the study: they had active symptoms and were found to have positive IgE to pollen (RAST tests > 0.7 10.0 units/ml). It was clearly stated in the paper that 'the purity of the sample was reflected in the fact that RAST screening of 96 patients showed evidence of allergies besides pollen in only 12 patients'. Indeed in all of these 12 patients pollen was the most significant allergen. Even if this validation of these criteria had been disappointing it would have pointed to a loss of accuracy but not a loss of internal validity. Indeed had there been a loss of power it would likely produce bias in the direction of an *underestimate* of the actual effect.

Thank you for pointing out the typesetters error over the dates of entry—patients entered the trial up till July 18.

We agree with you that failure to analyse on 'intention to treat' basis can introduce bias and that is why all available data were included. Therefore it is inaccurate to state that 30% of patients were omitted from the final

analysis. The 11 patients who had minor omissions in their diaries were not omitted but simply did not have complete 5 week data (as stated in Table II).

Turning to the analysis of visual analogue scores (VAS) we do not agree that the Kolmogorov-Smirnov test is a more appropriate analysis even if we restricted it to the changes in symptom score from weeks 1 to 5. The changes in the groups can clearly be seen in Figure 2 to adequately follow the pattern of normally distributed data. Indeed probability plots and tests of Normality confirm this assumption. Therefore to use a non-parametric procedure on Normal data is wholly inappropriate since the power of the Kolmogorov-Smirnov test is likely to be very poor. Further we must emphasize that the major analysis of our data was the repeated measures analysis of variance with a follow-up Bonferroni multiple comparisons procedure across the time-points using the baseline VAS, week of entry into study and pollen counts, when available, as potential covariates. Figure 2 represents a simple (numbers rounded to nearest 10) descriptive analysis. Interestingly, a recent study co-authored by some of you [8] did not use the Kolmogorov-Smirnov test as a way of circumventing the difficulties of analysing non-normally distributed VAS scores in hayfever trials.

You state that the doctor assessed scores (which were not the main measure of outcome) were not statistically significant. The P value was 0.05—we assume from the sophistication of your statistical arguments elsewhere that you are not drawing conclusion from the arbitrary difference between $P=$ and $P<0.05$ [9].

You refer to the washout periods for drugs used before the trial. We used the appropriate and generally accepted standards—no patient was on any long-term acting antihistamines.

As regards our pilot study, it is inaccurate to state there was a temporal bias in the randomization—the first placebo patient was entered on June 6, the first active June 8 and random entry continued throughout the trial. The alternate design was 'an attempt to have pairs of patients entered at approximately the same time from the same geographical area who would be exposed to similar pollen counts at the same stage of their treatment'. We carefully analysed on a day-to-day basis the average pollen exposure for each group (unpublished data) and were satisfied that the proportion of pollen >50 days and >200 were the same for each group. The smaller numbers on active treatment made the improvement demonstrated all the more surprising: it began during the first week of treatment and by week 3 the active group had improved 63% more than placebo ($P=0.002$). This improvement merited further study.

We agree that any form of anti-allergic therapy should be evaluated in rigorous trials. However, testing of non-

conventional treatments with conventional treatments is a few stages down the road of scientific investigation, as efficacy, then optimum treatment, have to be established first. These studies are not sufficient in themselves to recommend homoeopathic substitutes for conventional desensitization—but they do raise the question.

Taken in isolation a single trial proves nothing, but the recent review of over a hundred clinical trials [7] suggests our result does not stand in isolation.

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Route of administration of adrenaline for the treatment of anaphylactic reactions to bee or wasp stings

Sir, Dr Müller and colleagues gave an excellent review of the treatment of allergic reactions to bee and wasp stings [1]. I would like to comment on one point.

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