The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis
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CRD summary
The authors concluded that this review provided encouraging evidence which suggested that sublingual immunotherapy using house dust mite extract might be efficacious in treating patients with allergic rhinitis and asthma, but that further research is required. These findings should be interpreted with caution given the potential for missing data and the likely poor reliability of the pooled data.

Authors' objectives
To assess the efficacy of sublingual immunotherapy using house dust mite extracts in patients with allergic rhinitis and asthma

Searching
MEDLINE, EMBASE, LILACS and SCOPUS were searched for studies published up to March 2008. Search terms were reported. In addition, reference lists of reviews and published trials were searched for further studies, along with the abstracts of relevant meetings.

Study selection
Double-blind randomised controlled trials (RCTs) that compared any sublingual immunotherapy using house dust mite extracts with placebo, in patients with allergic rhinitis or asthma, were eligible for inclusion in the review. Patients of any age were eligible for inclusion, but the causal allergen had to be identified and immunoglobulin-E sensitisation confirmed by prick test and/or specific immunoglobulin-E assays. Intervention extracts may or may not be subsequently swallowed.

Eligible primary outcomes were allergic rhinitis and/or asthma symptoms or medication requirements, regardless of how these were recorded.

Three quarters of the included trials evaluated extracts in the form of drops and remainder evaluated tablets. Studies evaluated different doses of immunotherapy. Treatments were administered for between six and 24 months (median 18 months). Roughly equal numbers of studies assessed allergic rhinitis and allergic asthma. Just less than half of the included studies included both patients with allergic rhinitis and allergic asthma. Included participants ranged in age from five to 56 years.

Two reviewers independently assessed each study for inclusion and decisions were checked by the principal investigator.

Assessment of study quality
Two reviewers assessed the methodological quality of each study using the Jadad scale; a score was awarded out of a maximum of 5 points. In addition, the concealment of allocation and detection bias was assessed using the criteria of the Cochrane Collaboration, and scored as 'A' for adequate, 'B' for unclear and 'C' for unmet. Attrition bias was considered as adequate (drop-out rate was less than 20% after one year in all treatment arms), unclear (more than 20% after one year or large differences in drop-out rates between treatment arms) or unmet (drop-out rate not reported and an intention-to-treat analysis was not possible). Trials which failed to meet the criteria for allocation concealment were excluded. Where all criteria were considered as adequate, the trial was defined as having a low risk of bias; where one or more criteria were unclear, and the rest adequate, the trial was defined as having a medium risk of bias; and where one or more criteria were unmet, the trial was defined as having a high risk of bias.

Data extraction
Two reviewers independently extracted quantitative and continuous (mean and standard deviation) data for symptom
scores and medication use; disagreements were resolved through consensus. The authors of the primary trials were contacted in order to clarify/confirm the accuracy of the data extraction.

**Methods of synthesis**

Trials were grouped by outcome and pooled standardised mean differences (SMDs) with 95% confidence intervals (CIs) calculated for continuous outcomes, using a random-effects model. Statistical heterogeneity was assessed using the $X^2$ and $I^2$ statistics. The risk of publication bias was assessed using funnel plots.

Subgroup analyses were performed for adults and children. Post-hoc sensitivity analyses were also performed to determine the influence of sample size, meta-analysis method (i.e. fixed-effect versus random-effects models), drop-out rate (i.e. less than 20% versus 20% or more), and trial outliers.

**Results of the review**

Twelve placebo-controlled RCTs (382 patients with allergic rhinitis and 476 with allergic asthma) were included in the review. Sample sizes ranged from 14 to 72 (median 44) patients for allergic rhinitis and from 14 to 109 (median 50) for allergic asthma. Drop-out rates ranged from 0% to 23%. Four trials were awarded a maximum Jadad score of 5 out of 5 points for quality; eight were awarded a score of 4 out of 5 points. Overall the risk of bias from allocation concealment, attrition bias and detection bias was described as medium level.

There was a statistically significant difference in favour of sublingual immunotherapy using house dust mite extract in comparison with placebo for: nasal symptom scores (SMD -0.95, 95% CI -1.77 to -0.14; eight RCTs; $I^2=92\%$); bronchial symptom scores of allergic asthma (SMD -0.95, 95% CI -1.74 to -0.15; nine RCTs; $I^2=93.0\%$); rescue drug use in allergic rhinitis (SMD -1.88, 95% CI -3.65 to -0.12; four RCTs; $I^2=95\%$); and rescue drug use in allergic asthma (SMD -1.48, 95% CI -2.70 to -0.26; 7 studies; $I^2=96\%$).

Subgroup analysis showed a significant reduction in symptom scores for allergic asthma in children (SMD -1.09, 95% CI -1.96 to -0.22; eight RCTs; $I^2=93\%$) and asthma medication use in children (SMD -1.86, 95% CI -3.34 to -0.38; six RCTs, $I^2=96\%$). No statistically significant differences between sublingual immunotherapy and placebo were found for any outcome in adults.

All of the analyses were associated with significant statistical heterogeneity.

A post-hoc sensitivity analysis using the fixed-effect model did not significantly alter the findings. Other post-hoc sensitivity analyses were also reported and in general showed that differences in outcomes were no longer statistically significant when smaller trials were removed from the analyses.

Funnel plots suggested a risk of publication bias, but may not be reliable due to the small number of included trials.

**Authors’ conclusions**

This review provided encouraging results which suggested that sublingual immunotherapy using house dust mite extract might be efficacious in treating patients with allergic rhinitis and asthma, but further research is required.

**CRD commentary**

This review addressed a clearly defined research question. A number of databases were searched for relevant data. The authors did not state whether any limitations were placed on the publication status or language of articles, so it was difficult to determine whether there was a risk of publication and/or language bias. The authors reported that funnel plots suggested a risk of publication bias, but that these may not be reliable given the small number of included trials. Attempts were made to reduce the risk of reviewer error and bias throughout the review process and the risk of bias in the trials was assessed using relevant criteria.

All of the trials appeared to be of high methodological quality. However, there were differences between the trials, particularly in terms of their populations and interventions, as acknowledged by the authors. Statistical tests also suggested that the majority of analyses were associated with significant levels of statistical heterogeneity, so the pooled data may not be reliable. Some attempts were made to investigate the source of this heterogeneity between trials.
Overall, the findings of the review should be interpreted with caution given the potential for missing data and the likely poor reliability of the pooled data.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further research in the form of homogeneous, large, well-designed clinical trials, using appropriate statistical methods and objective and consistent outcomes, are required to further confirm the conclusions of the review.

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