Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review

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CRD summary
This well-conducted review concluded that there was moderate evidence to support the effectiveness of sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma, but high-quality trials were needed to determine the best dosing strategies. These findings are likely to be reliable.

Authors' objectives
To systematically review the effectiveness and safety of aqueous sublingual immunotherapy for allergic rhinoconjunctivitis and asthma.

Searching
The following databases were searched for articles from inception to December 2012: MEDLINE, EMBASE, LILACS, and Cochrane Central Register of Controlled Trials (CENTRAL). Search strategies were reported and only articles in English were considered. Public registries of clinical trials were searched, and the reviewers requested unpublished trial data from relevant pharmaceutical companies.

Study selection
Randomised controlled trials (RCTs) that assessed sublingual immunotherapy in patients with allergic rhinoconjunctivitis, allergic asthma, or both, were eligible for inclusion. Allergic conditions had to be due to airborne allergens, and confirmed with skin or specific immunoglobulin E blood testing. The sublingual allergen doses had to be reported. Comparators could be placebo, other sublingual immunotherapy regimens, or pharmacotherapy. Trials were excluded if similar formulations were not available in the USA, even for off-label use. The primary outcomes were symptom scores (for rhinitis, conjunctivitis, or asthma), medication scores, combined symptom and medication scores, quality of life, safety or harms, and adverse events. Secondary outcomes were pulmonary function test and provocation test scores.

Within the included RCTs, participant age ranged from four to 74 years, 41% included only adults, 27% included adults and children, and 32% included only children (under 18 years old). Most trials compared sublingual immunotherapy with placebo, and all trials allowed either conventional or rescue medication for both treatment arms. The maintenance dose varied from daily to weekly, with treatment duration ranging from three months to five years. There was considerable variation in the reporting of the maintenance or cumulative dose, and various units were used.

Articles were reviewed independently by at least two investigators, and disagreements were resolved by consensus.

Assessment of study quality
The risk of bias was assessed using a modification of the Cochrane Collaboration's Tool for Assessing Risk of Bias. This considered: random allocation, allocation concealment, blinding, complete data reporting, sponsor participation in the study design or interpretation of data, and other sources of bias. Trials were rated as having a low, medium, or high risk of bias (details were reported).

The number of reviewers who assessed the risk of bias, was not stated.

The evidence for each primary outcome was graded for quantity, quality, and consistency, using GRADE criteria, to produce a rating of high, moderate, low or insufficient. This was done by the team, using discussion to achieve a consensus (details were reported).

Data extraction
Standardised data extraction forms were completed independently by paired investigators. Differences in opinion were resolved by consensus or by discussion during team meetings. Where trials recorded outcomes at multiple time points,
the data from the final assessment were used. For trials that treated and assessed patients over one season, the outcomes were extracted for the peak of the pollen season, if possible.

**Methods of synthesis**
A meta-analysis was not performed due to the extreme variation between the included trials. The trials were summarised by allergens, comparators, and outcomes, producing detailed evidence tables. The magnitude of any effect in a trial was classified according to the percentage difference from before to after therapy (<15% difference was weak, 15% to 40% difference was moderate, and >40% difference was strong), for sublingual immunotherapy versus the comparator.

Because measures of variance were not reported in most trials, it was not possible to produce a meaningful funnel plot to assess publication bias.

**Results of the review**
A total of 63 RCTs with 5,131 participants were included. Forty-three trials (68%) had a medium risk of bias; 13 (21%) had a low risk of bias; and seven (11%) had a high risk of bias.

**Symptoms:** High strength evidence (13 RCTs; 625 participants; most trials were placebo controlled, with a medium risk of bias) supported a benefit of sublingual immunotherapy for asthma symptoms. Moderate strength evidence (36 RCTs; 2,985 participants; with a medium risk of bias) supported a benefit of sublingual immunotherapy for rhinitis symptoms. Moderate strength evidence (13 RCTs; 1,074 participants; with a medium or low risk of bias) supported a benefit of sublingual immunotherapy for conjunctivitis symptoms.

**Other outcomes:** Moderate evidence (41 RCTs; 2,162 participants) supported sublingual immunotherapy for decreasing medication use. Moderate evidence (eight RCTs; 819 participants; with a medium risk of bias) supported sublingual immunotherapy for improving disease-specific quality of life. Other outcomes, including those relating specifically to children, were reported in the paper or the full report (see Other Publications of Related Interest).

**Authors’ conclusions**
There was moderate evidence to support the effectiveness of sublingual immunotherapy, for the treatment of allergic rhinitis and asthma, but high-quality trials were needed to determine the best dosages.

**CRD commentary**
This well-conducted review addressed a clearly defined research question, with reasonable searches and appropriate inclusion criteria. A language restriction was applied, but this seems reasonable given the research aim, which was specific to the USA. Processes to minimise reviewer error and bias were implemented throughout the review. The included trials were assessed for quality, and a narrative synthesis was used to summarise the results, taking note of the clinical and methodological diversity between trials.

The conclusions appear to reflect the evidence presented and should be regarded as reliable.

**Implications of the review for practice and research**
**Research:** The authors made several detailed recommendations for future research, including the need for RCTs directly comparing sublingual with subcutaneous immunotherapy. They recommended standardised methods of diagnosis for asthmatic patients, and of reporting and scoring of symptoms, adverse events and dosing.

**Practice:** The authors made no recommendations for practice.

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Other publications of related interest

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.