

## Systematic review

# Sublingual immunotherapy improves symptoms of allergic rhinoconjunctivitis and asthma

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Commentary on: Lin SY, Erekosima N, Kim JM, *et al.* Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA* 2013;309:1278–88.

## Context

Allergic rhinoconjunctivitis (ARC) and asthma are among the most prevalent chronic disorders affecting the US population, and contribute significantly to morbidity, direct and indirect healthcare costs and quality-of-life issues. Specific immunotherapy remains as a mainstay of treatment for these diseases and has traditionally been administered subcutaneously over an extended treatment period to desensitise allergic patients and improve their symptoms. Over the last several years, European regulatory authorities have approved<sup>1</sup> the use of sublingual immunotherapy to treat allergic diseases and nearly 45% of allergen-specific immunotherapy is currently administered via this route in those countries.<sup>2</sup> The advantages of sublingual immunotherapy over subcutaneous immunotherapy include ease of administration, avoidance of injections and convenience of home administration. In the USA, there are currently no Food and Drug Administration (FDA) approved forms of sublingual immunotherapy, although several formulations are under review. In spite of this, some US physicians prescribe off-label use of sublingual immunotherapy citing the safety and efficacy of certain products approved by the European regulatory authorities. However, the results obtained from previously conducted European studies cannot necessarily be generalised to the US population since doses are difficult to compare among countries due to the use of numerous methods for standardising potency. Lin and colleagues systematically reviewed the available literature to assess the effectiveness and safety of sublingual immunotherapy for the treatment of ARC and asthma in the USA.

## Methods

The authors searched MEDLINE, EMBASE, LILACS and the Cochrane Central Register of Controlled Trials (CENTRAL) and included results from English-language randomised controlled trials (RCTs) that compared sublingual immunotherapy with placebo, pharmacotherapy or other sublingual immunotherapy regimens reporting clinical outcomes. Studies of sublingual immunotherapy that are unavailable, or for which a related immunotherapy is unavailable in the USA, were excluded. Paired reviewers selected articles and extracted data. The strength of the evidence for each outcome and comparison was graded on the risk of bias, consistency, effect magnitude and the directness of the evidence.

## Findings

Sixty-three trials (n=5131) met the inclusion criteria and were included in the analysis. Twenty of the studies exclusively enrolled a total of 1814 paediatric participants. The risk of bias was graded as medium in 43 (68%) of the studies. Strong evidence suggested that sublingual immunotherapy improved asthma symptoms, with 8 of 13 studies reporting greater than 40% improvement versus the comparator. Similarly, there was moderate evidence that sublingual immunotherapy decreased rhinitis or rhinoconjunctivitis scores, with 9 of 36 studies reporting greater than 40% reduction versus comparator. Moderate evidence also supported an improvement in conjunctivitis symptoms (13 studies), combined symptom and medication scores (20 studies) and disease-specific quality of life (8 studies). Safety outcomes were presented descriptively since they were neither uniformly nor consistently reported across the included trials. Local reactions were more frequent in subjects receiving sublingual immunotherapy. There were no reports of anaphylaxis in any of the participants.

## Commentary

Lin and colleagues reported evidence of moderate strength that sublingual immunotherapy is associated with improvement in ARC and asthma outcomes. Compared with previous reviews, this review is quite comprehensive since it reported on a wide breadth of allergic symptom outcomes and included a large number of recent RCTs. In general, these findings are consistent with those reported by previous reviews.<sup>3 4</sup> However, a greater improvement in asthma symptom scores was reported here than previously. This finding is predominately attributed to the inclusion of recent asthma studies which reported a higher magnitude of improvement in asthma symptoms compared with older studies.

A major challenge encountered was that the majority of trials were industry-supported and were subsequently considered to have a moderate or high risk of bias. A second challenge was inconsistent scoring and lack of standardised reporting systems for clinical outcomes and adverse events across the studies. Other significant challenges were the variability in dosing and treatment schedules across studies, as well as the difficulty in comparing doses that are not standardised across European countries. Most of the reviewed trials had deficiencies related to small sample sizes and insufficient reporting of relevant statistical information. Finally, the potential for publication bias related to selective publication of trials with only positive results cannot be ruled out. All of these deficiencies were addressed by the authors. In addition, the authors emphasised the need for future well-designed RCTs to clearly evaluate the safety and efficacy of sublingual immunotherapy in the USA. Overall, this is an excellent, comprehensive and up-to-date review of sublingual immunotherapy trials which provides clinicians with an extensive summary of established data supporting a role for the use of sublingual immunotherapy in the treatment of ARC and asthma symptoms.

Competing interests None.

## References

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