Sublingual Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and Asthma

A Systematic Review

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Importance Allergic rhinitis affects up to 40% of the US population. To desensitize allergic individuals, subcutaneous injection immunotherapy or sublingual immunotherapy may be administered. In the United States, sublingual immunotherapy is not approved by the Food and Drug Administration. However, some US physicians use aqueous allergens, off-label, for sublingual desensitization.

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

Evidence Acquisition The databases of MEDLINE, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials were searched through December 22, 2012. English-language randomized controlled trials were included if they compared sublingual immunotherapy with placebo, pharmacotherapy, or other sublingual immunotherapy regimens and reported clinical outcomes. Studies of sublingual immunotherapy that are unavailable in the United States and for which a related immunotherapy is unavailable in the United States were excluded. Paired reviewers selected articles and extracted the data. The strength of the evidence for each comparison and outcome was graded based on the risk of bias (scored on allocation, concealment of intervention, incomplete data, sponsor company involvement, and other bias), consistency, magnitude of effect, and the directness of the evidence.

Results Sixty-three studies with 5131 participants met the inclusion criteria. Participants' ages ranged from 4 to 74 years. Twenty studies (n=1814 patients) enrolled only children. The risk of bias was medium in 43 studies (68%). Strong evidence supports that sublingual immunotherapy improves asthma symptoms, with 8 of 13 studies reporting greater than 40% improvement vs the comparator. Moderate evidence supports that sublingual immunotherapy use decreases rhinitis or rhinoconjunctivitis symptoms, with 9 of 36 studies demonstrating greater than 40% improvement vs the comparator. Medication use for asthma and allergies decreased by more than 40% in 16 of 41 studies of sublingual immunotherapy with moderate grade evidence. Moderate evidence supports that sublingual immunotherapy improves conjunctivitis symptoms (13 studies), combined symptom and medication scores (20 studies), and disease-specific quality of life (8 studies). Local reactions were frequent, but anaphylaxis was not reported.

Conclusions and Relevance The overall evidence provides a moderate grade level of evidence to support the effectiveness of sublingual immunotherapy for the treatment of allergic rhinitis and asthma, but high-quality studies are still needed to answer questions regarding optimal dosing strategies. There were limitations in the standardization of adverse events reporting, but no life-threatening adverse events were noted in this review.

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Allergic rhinitis affects approximately 20% to 40% of the US population.[1] Currently, 2 forms of specific immunotherapy (subcutaneous immunotherapy and sublingual immunotherapy) are used clinically in the United States. Considerable interest has emerged in sublingual immunotherapy, which involves placement of the allergen under the tongue for local absorption to desensitize the allergic individual over an extended treatment period to diminish allergic symptoms. Compared with subcutaneous immunotherapy, sublingual immunotherapy is easy to administer, does not involve administration of injections, and may be administered at home, avoiding the inconvenience of office visits. The opportunity for home-based therapy makes it potentially suitable for use in medically underserved areas.

In 1996, a World Health Organization Task Force on Immunotherapy cited the

For editorial comment see p 1297.

CME available online at www.jamanetworkcme.com and questions on p 1299.

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emerging clinical data on sublingual immunotherapy, and recognized its potential as a viable alternative to subcutaneous therapy.[2] In Europe, approximately 45% of specific immunotherapy consists of sublingual immunotherapy, with up to 80% in Southern Europe.[3] Sublingual tablet and aqueous immunotherapy have been approved by European regulatory authorities.

In the United States, there are no sublingual forms of immunotherapy approved for use by the Food and Drug Administration. However, some physicians in the United States use subcutaneous aqueous allergens, off-label, for sublingual desensitization. Physicians are supported in using this desensitization approach by the European Medicines Agency's approval of certain sublingual products; however, due to the differing standardization of potency in Europe and the United States, doses are hard to compare among countries.

The primary objective of this systematic review was to review the clinical efficacy and safety of sublingual immunotherapy delivered as an aqueous solution as can potentially be done in the United States. This study was derived from work done for an evidence report commissioned by the US Agency for Healthcare Research and Quality to determine effectiveness of specific immunotherapy for allergic rhinitis and asthma (Agency for Healthcare Research and Quality publication 13-EHC061-EF).

METHODS

A protocol for this review was developed and posted online (http://effectivehealthcare.ahrq.gov/ehc/products/270/665/SIT_Protocol_20110824.pdf), following guidelines for systematic review.[4,5] We searched the following databases: MEDLINE (from 1950 to December 22, 2012), EMBASE (from 1947 to December 22, 2012), LILACS (from 1982 to December 22, 2012), and the Cochrane Central Register of Controlled Trials (inception to December 22, 2012) with a specific search strategy (eMethods at http://www.jama.com).

Titles, abstracts, and articles were reviewed independently by at least 2 separate investigators from the study team, with various study members assigned to review portions of the literature, and disagreements were resolved by consensus. We searched for English-language randomized controlled trials (RCTs) reporting on the effects of sublingual immunotherapy. We required that the RCTs enrolled patients with allergic rhinoconjunctivitis and/or allergic asthma due to airborne allergens confirmed with skin or specific immunoglobulin E blood testing, and clearly stated the dose of allergen delivered. Allowed comparators were placebo, other sublingual immunotherapy regimens, or pharmacotherapy. Studies were excluded if they did not report on our outcomes of interest (eTable 1). Studies also were excluded for which similar formulations are not obtainable in the United States, even for off-label use.

The primary outcomes of interest included symptom scores (for rhinitis, conjunctivitis, or asthma), medication scores, combined symptom and medication scores, quality of life, safety or harms, and adverse events. Asthma outcomes were extracted only if patients in the study were diagnosed as having asthma by using objective criteria (such as pulmonary function testing), or according to established clinical guidelines. Secondary outcomes included pulmonary function test results and provocational test results (allergen challenge).

Standardized forms for data extraction were completed independently by paired investigators. Data were abstracted from the published text or tables, and if necessary, from figures. Differences in opinion were resolved through consensus adjudication and by discussion during team meetings. For studies that recorded outcomes at multiple time points, we used the data from the final time point reported. For studies that treated and assessed patients during a single season, we extracted the outcomes at peak pollen seasons when available. Articles were also reviewed from duplicative data, and studies reporting follow-up data from an earlier study were abstracted with the original report.

The risk of bias was assessed using a modification of the Cochrane Collaboration Tool for Assessing Risk of Bias from the *Cochrane Handbook for Systematic Reviews of Interventions*.[5] We assessed 6 categories of potential bias: random allocation, lack of allocation concealment, inadequate blinding, incomplete data reporting, sponsor participation in the study design or interpretation of data, and other sources of bias. Studies were categorized as having a low, medium, or high risk of bias depending on their performance across these 6 categories (eMethods).

Studies were summarized by allergens, comparators, and outcomes producing detailed evidence tables. We graded the quantity, quality, and consistency for each primary outcome by adapting an evidence grading scheme recommended by the GRADE Working Group's guide for conducting comparative effectiveness reviews.[6] The grading incorporated the risk of biases, the consistency of the direction of the effect across studies for a given comparison and outcome, the relevance of the collection of trials to the question of interest (directness), and the magnitude of the effects reported in the trials. We could not comment on the precision of the effect size because there were seldom measures of variability within the individual studies. The magnitude of effect in a trial was classified according to the percentage difference in the post-to-pre change (<15% difference defined as weak, a 15%-40% difference defined as moderate, and >40% difference defined as a strong effect), comparing the sublingual immunotherapy group with the comparator group.

The evidence for each primary outcome was graded as (1) high grade: high confidence the evidence reflects the true effect; (2) moderate grade: moderate confidence that the evidence reflects the true effect and future research may change the estimate, (3) low grade: low confidence that the evidence reflects the true effect and further research is likely to change the estimate, or (4) insufficient evi-

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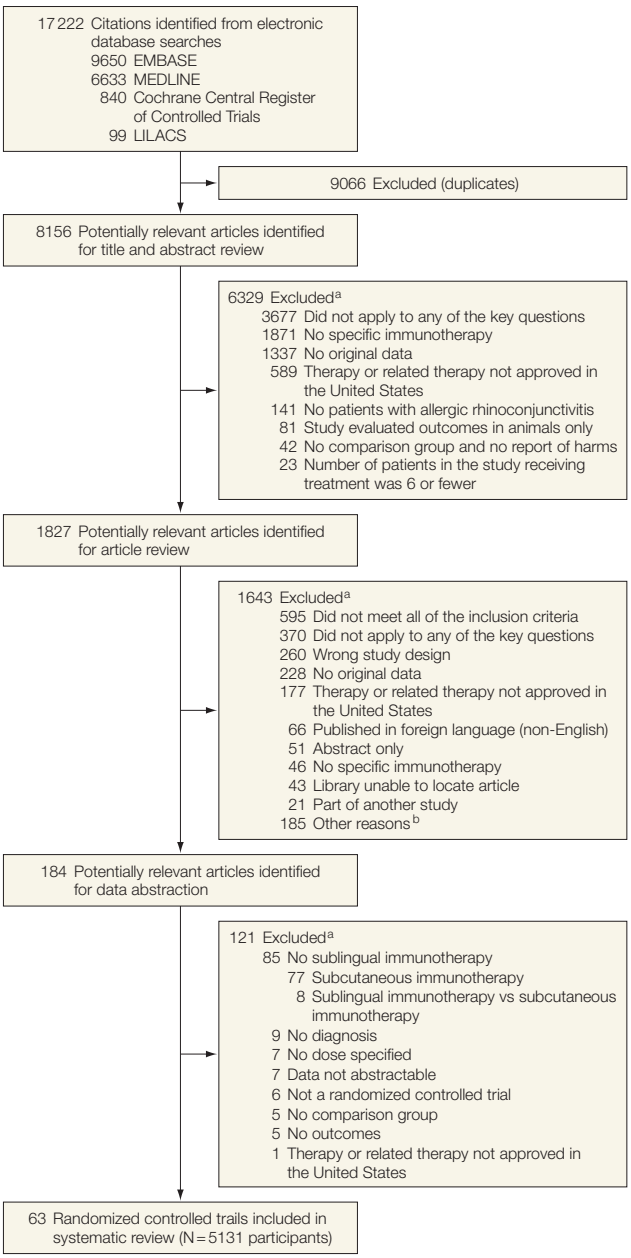
dence.[7] The following system was used to assign grade when looking at the overall evidence for each outcome: high-grade evidence required a minimum of 2 or more trials with low risk of bias, and at least 1 strong magnitude of effect in the context of largely consistent overall evidence. Moderate-grade evidence required 1 or more trials with low risk of bias or strong magnitude of effect, or 1 trial with low risk of bias or moderate magnitude plus 1 trial with medium risk of bias or strong magnitude. Evidence was low grade if it did not meet any of these categories. Insufficient evidence was assigned if there were no relevant trials. The team reviewed and came to consensus on the grades. The evidence regarding indirect outcome measures (pulmonary function test results and provocation tests) was not graded.

A meta-analysis was not performed due to the extreme heterogeneity of the included studies. There was a wide range of clinical diversity in the types of participants, their allergies, allergens treated, and geographic treatment locations. The extreme variability of the published RCTs in dosing and treatment schedules confounds meta-analysis. Methodological diversity was evident in the study designs, quality, and systems for measured outcomes. The statistical reporting was incomplete in most studies and information such as confidence intervals was rarely reported.

To reduce the risk of publication bias in our results, we searched public registries of clinical trials and requested scientific information packets from relevant pharmaceutical companies to search for unpublished trials. Because measures of variance were not reported in most of the included studies, we could not produce a meaningful funnel plot to look for evidence of publication bias.

Figure. Flow Diagram of Sublingual Immunotherapy Studies



[a] Articles were excluded by 2 reviewers at this level so this number is exceeded by the total for all of the exclusions listed.
[b] The possible other reasons included control group is a healthy population, routes of administration not included (eg, oral, nasal, lymph node), abandoned interventions, outcomes not reported, no comparator group, continued medical education reports, editorials or reviews, studies about mechanism of action, other allergies (eg, food, aspirin), study in animals or in vitro, or fewer than 6 patients per treatment group.

RESULTS

We identified 8156 potentially relevant citations. After applying exclusions and triage to other topics, 63 RCTs remained for this systematic review (FIGURE). We identified 63 RCTs testing sublingual immunotherapy with 5131 participants included. Participants' ages ranged from 4 to 74 years. Twenty-six studies (41%) enrolled adults only, 17 (27%) included both adults and children,[8-24] and 20 (32%) exclusively studied children (<18 years of age; n = 1814 patients).[25-44]

The study comparator groups were placebo (46 studies; 73%), another sublingual intervention without a placebo group (9 studies; 14%), and conventional treatment (pharmacotherapy) without placebo

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(8 studies; 13%). All studies allowed either conventional or rescue medications in all treatment groups. The maintenance dosing varied from daily to weekly, with treatment duration ranging from 3 months to 5 years. There was great heterogeneity in the reporting of the maintenance or cumulative dose delivered, and a variety of units to report dosing. Forty-three studies (68%) were assessed as having a medium risk of bias. There was a low risk of bias in 13 studies (21%) and a high risk of bias in 7 studies (11%). The reporting of outcomes was heterogeneous with diverse systems and scores for reporting on primary outcomes (eTable 2). A formal assessment of publication bias could not be performed due to lack of variability estimates from most included trials.

Evidence for Use of Sublingual Immunotherapy

We found moderate evidence across outcomes to support the use of sublingual immunotherapy to improve clinical outcomes (TABLE 1).

Asthma. Thirteen studies (n=625) evaluated sublingual immunotherapy for the control of asthma symptoms. The majority of studies (7; 54%) evaluated dust mite allergen.[25-27,35-37,42] All but 1 study were placebo-controlled studies, and all allowed pharmacotherapy for symptom relief. The placebo-controlled studies demonstrated statistically significant improvement in asthma symptoms in the sublingual immunotherapy group relative to the placebo group. The magnitude of the association was strong in 9 of these studies (69%). The remaining study, which compared sublingual immunotherapy with inhaled steroids, showed comparable improvement in both groups. The risk of bias was medium for the majority of studies (8; 62%), and favored sublingual immunotherapy in all of the studies. We graded the strength of evidence as high in support of sublingual immunotherapy for improving asthma symptoms.

Rhinitis. Rhinitis or rhinoconjunctivitis symptom scores were reported in 36 placebo-controlled studies* involving 2985 participants. The most frequently studied allergens were grass mix (10 studies; 28%) and dust mite (8 studies; 22%). The majority of studies (94%) demonstrated greater improvement in the sublingual immunotherapy groups vs placebo. The overall risk of bias was medium for this group. The magnitude of association was moderate or strong in 14 studies (39%). We concluded that the strength of evidence was moderate in support of using sublingual immunotherapy for improving rhinitis or rhinoconjunctivitis symptom scores.

Conjunctivitis. Conjunctivitis outcomes were reported in 13 studies involving 1074 patients.† All but 1 study demonstrated an improvement compared with the placebo group; and the majority of studies (11; 85%) had medium or low risk of bias. A strong magnitude of association was demonstrated in 3 studies (23%). We concluded that the evidence was of moderate strength in support of sublingual immunotherapy for treating allergic conjunctivitis.

Medication Scores. Medication scores were reported in 41 studies involving 2162 patients.‡ Grass mix (10 studies; 24%) and dust mite (9 studies; 22%) were the most commonly studied allergens. Thirty-eight studies (93%) demonstrated greater improvement in symptoms in the sublingual immunotherapy group vs the comparator group, with 16 studies demonstrating a strong magnitude of association. We graded the strength of evidence as moderate in support of sublingual immunotherapy for decreasing medication use.

Quality of Life. Disease-specific quality of life was reported in 8 studies involving 819 patients.[14,29,32,51,54,65,67,68] Half of these studies showed statistically significant gains in quality of life after treatment with sublingual immunotherapy compared with placebo. All used validated disease-specific instruments. These studies demonstrated a medium risk of bias overall, with 7 of 8 demonstrating a favorable change with sublingual immunotherapy. Two studies (25%) had a strong magnitude of association. We concluded that the strength of evidence was moderate in support of sublingual immunotherapy to improve disease-specific quality of life.

Other Outcomes. Some studies reported outcomes as a combined score: (1) medication use plus symptom scores§ and (2) asthma plus rhinitis or rhinoconjunctivitis symptoms.[41,43,45,61-63] The evidence was graded as moderate to support the use of sublingual immunotherapy for these outcomes. Indirect outcomes such as pulmonary function[8,26,27,33,36,42,66] and allergen challenges‖ were not graded, but sublingual immunotherapy was consistently associated with improvements in both.

Outcomes in Children. Evidence was similar in strength to support the use of sublingual immunotherapy in children (<18 years of age) for allergic rhinitis and asthma. The strength of evidence was high to support sublingual immunotherapy use for the improvement of asthma in children based on 9 studies[25-27,35-38,41,42] involving 471 participants. A strong magnitude of association for asthma outcomes was identified in 6 of 9 pediatric studies (67%) compared with 3 of 4 mixed-age/adult studies (75%). Rhinitis or rhinoconjunctivitis outcomes were reported in 12 trials[28-32,35-39,41,42] involving 1065 children, with moderately strong evidence to support sublingual immunotherapy use; strong magnitude of effect was present in 2 of 12 pediatric studies (17%) compared with 7 of 23 mixed-age/adult studies (30%). However, the strength of the evidence in children dif-

*References 9-12, 14-17, 19, 24, 28-32, 35-39, 41, 42, 46, 49-60.
†References 10-12, 14, 19, 29, 36, 39, 41, 48, 52, 55, 56.
‡References 10-12, 14-17, 19, 22-32, 35, 37-39, 41, 43-46, 50, 52, 54-58, 60-66.
§References 8, 14, 15, 22, 23, 31, 34, 43, 50, 52-54, 57, 63-65, 67-70. ‖References 9, 20, 23, 30, 34-36, 46, 56, 58, 60, 62-64, 66, 71, 72.

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fered in 2 outcomes from our larger report. First, there was insufficient evidence to grade disease-specific quality of life based on 2 studies[29,32] involving 461 participants. Second, the data for the evidence for the combined symptom plus medication score were graded as low based on 2 studies[31,34] involving 329 participants. A comprehen-

Table 1. Sublingual Immunotherapy Evidence Summary

Outcome	No. of Participants	No. of Studies	Allergens	Comparators	Summary of Grading Data	Findings	Strength of the Evidence
Asthma symptoms	625	13	Dust mite[25-27,35-37,42] *Alternaria*[22,45] Grass mix[46] Tree mix[41] Birch[47] *Parietaria*[48]	Sublingual immunotherapy vs placebo[22,25-27,35-37,42,45,47,48] vs inhaled steroids[46] vs placebo-controlled trial of sublingual immunotherapy[41]	Two studies with low risk of bias and strong magnitude of effect.[25,35]	All placebo-controlled studies demonstrated greater improvement in the sublingual immunotherapy group. The study[46] of sublingual immunotherapy vs inhaled steroids showed improvement in both groups.	High
Rhinitis or rhinoconjunctivitis symptom scores	2985	36	Grass mix[11,12,16,17,19,31,32,46,49,50] Dust mite[15,28,29,35-37,42,51] *Parietaria*[30,38,48,52] Cedar[53-55] Timothy grass[56] Ragweed[10,57] Birch[47,58] Olive[39] Cat[59] Tree mix[41] Multiple allergens[14,60]	Sublingual immunotherapy vs placebo[10,12,14-17,19,28-32,35-37,39,42,47-52,54-57,59] vs pharmacotherapy[46,58] vs placebo-controlled trials of sublingual immunotherapy[11,41,57,60]	One study with low risk of bias and strong magnitude.[11] Six studies with medium risk of bias and strong magnitude.[16,39,42,46,49,50]	The majority of studies showed greater improvement in symptoms in the sublingual immunotherapy group vs placebo.	Moderate
Asthma symptoms plus rhinitis or rhinoconjunctivitis symptom scores	515	6	*Alternaria*[45] Birch[61] Tree mix[41] Grass mix[43] Dust mite[62] Multiple allergens[63]	Sublingual immunotherapy vs placebo[4,45,61] vs 2 placebo-controlled and 1 pharmacotherapy-controlled trials of sublingual immunotherapy[41,62,63]	Two studies with medium risk of bias and strong magnitude.[41,63] One study with medium risk of bias and moderate magnitude.[61] Two studies with medium risk of bias and insufficient data to determine magnitude of effect.[45,62] One study with low risk of bias and moderate magnitude of effect.[43]	Five studies demonstrated greater improvement in the sublingual immunotherapy group.[41,43,45,61,63] One placebo-controlled study[62] found no improvement in symptoms.	Moderate
Conjunctivitis symptom scores	1074	13	Grass mix[11,12,19] Dust mite[29,36] *Parietaria*[48,52] Timothy grass[56] Ragweed[10] Cedar[55] Olive[39] Tree mix[41] Multiple allergens[14]	Sublingual immunotherapy vs placebo[10-12,14,19,29,36,39,48,52,55,56] vs a placebo-controlled trial of sublingual immunotherapy[41]	Five studies with low risk of bias[11,14,36,48,56]; 1 of these had strong magnitude.[11] Six studies with medium risk of bias[10,12,19,39,41,52]; 1 of these had strong magnitude.[41] Seven studies with insufficient data to determine magnitude of effect.[10,12,19,29,48,52,56]	All but 2 studies showed greater improvement in symptoms in the sublingual immunotherapy group vs placebo. One study showed greater improvement with placebo.[10] The direction of change could not be determined in 1 study.[48]	Moderate

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sive description and subanalysis of the pediatric studies are available in the full Agency for Healthcare Research and Quality report on effectiveness of specific immunotherapy for allergic rhinitis and asthma.

Safety Outcomes. The studies did not uniformly or consistently report safety information, although 47 studies (75%)

Table 1. Sublingual Immunotherapy Evidence Summary (continued)

Outcome	No. of Participants	No. of Studies	Allergens	Comparators	Summary of Grading Data	Findings	Strength of the Evidence
Medication use scores	2162	41	Grass mix[11,12,16,17,19,31,32,43,46,50] Dust mite[15,25-29,35,37,62] *Parietaria*[30,38,52,64] Cedar[54,55,65] *Alternaria*[22,45] Tree mix[23,41] Timothy grass[56,60] Ragweed[10,57] Birch[58,61] Olive[39] Rye[44] Multiple allergens[14,24,63]	Sublingual immunotherapy vs placebo[10,12,14-17,19,22,24-32,35,37-39,43-45,50,52,54-56,58,64,65] vs pharmacotherapy[23,46,61,66] vs 5 placebo-controlled trials of sublingual immunotherapy[11,41,57,60,62]	Ten studies with low risk of bias[11,14,25,30,32,38,56,57,60,64]; 2 of these had strong magnitude of effect[11,25]; 2 had weak magnitude.[14,60] Twenty-two studies with medium risk of bias[10,12,15-17,19,23,24,26,28,35,37,39,41,45,46,50,52,54,61,63,65]; 7 of these had strong magnitude,[12,23,24,45,46,52,61]; 6 of these had weak magnitude of effect.[10,15,50,54,62,65] Six studies with high risk of bias[22,27,29,31,55,58]; 3 of these had strong magnitude.[22,55,58] Ten studies with insufficient data to determine magnitude of effect.[16,17,25,29-32,35,39,56]	Sublingual immunotherapy did better than comparator in all but 1 study.[32] The direction of change could not be determined in 1 study.[30] There was a strong magnitude of effect in 16 studies.[11,12,22,23,25,27,37,44-46,52,55,57,58,61,63]	Moderate
Medication use plus symptom scores	1669	20	Cedar[53,54,65,67,68] Grass mix[31,43,50,69] *Parietaria*[52,64,70] Dust mite[15] *Alternaria*[22] Ragweed[57] Tree mix[23] Multiple allergens[8,14,34,63]	Sublingual immunotherapy vs placebo[14,15,22,43,50,53,54,64,65,67-70] vs pharmacotherapy[23,52] vs no treatment[31,34] vs sublingual immunotherapy (1 placebo-controlled trial,[57] 1 pharmacotherapy-controlled trial,[63] and 1 trial vs no treatment[8])	Four studies with low risk of bias[14,57,64,67]; 1 of these had strong magnitude[57]; 2 had low magnitude.[14,64] Eleven studies with medium risk of bias[8,15,23,34,50,52-54,63,65,69]; 5 of these had strong magnitude.[8,43,52,63,69] Four studies with high risk of bias.[22,31,68,70] Eight studies with insufficient data to determine magnitude of effect.[2,23,31,53,54,65,67,70]	All studies but one[67] (in which direction of change could not be determined) showed greater improvement with sublingual immunotherapy than comparator. Six studies demonstrated a stong magnitude of effect.[8,34,52,57,63,69]	Moderate
Disease-specific quality of life	819	8	Cedar[54,65,67,68] Dust mite[29,51] Grass mix[32] Multiple allergens[14]	Sublingual immunotherapy vs placebo[14,29,32,51,54,65,67,68]	Four studies with medium risk of bias[14,54,65,68]; 2 of these had strong magnitude.[14,65] Two studies with low risk of bias and insufficient data to determine magnitude of effect.[2,67] Five studies with insufficient data to determine magnitude of effect.[29,32,51,65,67]	Four studies reported significant improvement in disease-specific quality of life vs placebo.[54,65,67,68] Two studies reported significant improvement with sublingual immunotherapy when comparing the initial with the final quality-of-life scores.[14,51]	Moderate

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mentioned safety.¶ The lack of a standard grading system and the heterogeneous reporting systems used by the different studies required that safety outcomes be presented descriptively. We concluded that the evidence was insufficient to comment further about safety (TABLE 2). Because our safety review was limited to RCTs, the safety data presented herein should not be considered representative of all the existing sublingual immunotherapy safety literature.

¶References 8-15, 17-19, 21, 24, 25, 27-36, 38, 39, 41, 43-45, 49-51, 53-56, 59-63, 66, 68, 69, 73-75.

Local reactions were more frequent in patients receiving sublingual immunotherapy (range, 0.2%-97%) than in the comparator groups (range, 3%-38.5%). Systemic reactions were rarely reported, but were more common in the groups receiving sublingual immunotherapy than in comparator groups. There were no reported episodes of anaphylaxis, life-threatening reactions, or death in any treated patients across studies.

COMMENT

We found that the evidence is of moderate strength overall and it supports the position that aqueous sublingual immunotherapy is associated with improvement in allergic rhinitis and asthma outcomes. By definition in this review, moderate grade indicates moderate confidence that the evidence reflects the true effect. However, future research may change this estimate. Standardization of safety data reporting was lacking across studies, but there were no reports of life-threatening adverse events in this review. The results of this systematic review are applicable to patients with allergic rhinoconjunctivitis and/or asthma because we included only

Table 2. Sublingual Immunotherapy Safety Summary of Studies Reporting Adverse Events

		Adverse Events			
				Severity	
	Total No. of Patients	No. of Patients[a]	Range of Patients, %[a]	Description	% of Total Reported Events
Local reactions by allergen[b]: grass mix,[11,12,17,19,30,31,33,43,49,50,60,69] dust mite,[9,15,25,29,35,51,62,66] trees,[39,41,53-55,61,68,73] multiple allergens,[13,14,21,24,34,63] *Parietaria*,[30,48] *Alternaria*,[45] ragweed,[10] cat[59]					
Sublingual immunotherapy groups (n = 39 studies)	2520	681	0.2-97	Unspecified	45
				Mild	54
				Moderate	1
Placebo groups (n = 24 studies)	933	191	3-38.5	Unspecified	26
				Mild	74
Local reactions to Timothy grass[56,c]					
Sublingual immunotherapy group	28	380 reactions	4.75 events per patient	Mild	100
Control group	28				
Upper respiratory reactions by allergen[d]: grass mix,[11,12,17,32,43,49,50] dust mite,[9,29,36] trees,[41,55,73] *Parietaria*,[30] multiple allergens[8,21,24]					
Sublingual immunotherapy groups (n = 19 studies)	1201	347	3-92	Unspecified	73
				Mild	25
				Severe	2
Control groups (n = 12 studies)	572	228	1.6-93	Unspecified	94
				Mild	5
				Moderate	1
Lower respiratory reactions by allergen[e]: grass mix,[11,17,32,43,49,50] dust mite,[29,36,51,62] trees,[55] cat,[59] *Parietaria*,[30] multiple allergens[13,34]					
Sublingual immunotherapy groups (n = 16 studies)	1229	197	0.3-69 of doses	Unspecified	93
				Mild	5
				Moderate	1
				Severe	1
Control groups (n = 10 studies)	522	145	3-67 of doses	Unspecified	94
				Mild	4
				Moderate	1
				Severe	1
Cutaneous reactions by allergen[f]: grass mix,[17,31,43,50] dust mite,[29,36,66] trees,[53,55] multiple allergens[13,14,24,34]					
Sublingual immunotherapy groups (n = 15 studies)	1336	151	0.7-57	Unspecified	93
				Mild	7
Control groups (n = 6 studies)	535	135	2-65	Unspecified	96
				Mild	4

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studies that confirmed the diagnosis of allergy with testing.

Our systematic review is the most comprehensive in 2 aspects: it reports on the widest breadth of allergic symptom outcomes compared with previous reviews, and it includes a significantly larger number of RCTs compared with previous reviews because the search extends to December 2012. Our systematic review included RCTs of all age groups and all environmental allergens, evaluated the efficacy of sublingual immunotherapy, and performed grading of evidence for the largest number of direct (n=7) and indirect (n=2) clinical outcomes. Prior to our current review, the largest scale systematic reviews of sublingual immunotherapy, which reported on 2 primary outcomes, were performed in 2003,[76] updated in 2010,[77] and published in the Cochrane Collaboration Database. Our study included RCTs through December 2012, which allowed inclusion of 11 new RCTs not included in the last large Cochrane review.[77] Our findings are congruent with previous reviews of sublingual immunotherapy,[76-79] which found sublingual immunotherapy to be an effective treatment without serious adverse events, with all authors noting the wide heterogeneity in the literature.

Some prior systematic reviews have focused on a single outcome, such as allergic conjunctivitis[78] or asthma.[79] A review published in 2008 concluded that sublingual immunotherapy was associated with efficacy for treatment of asthma, but the magnitude of association was not large.[79] Our analysis found high-grade evidence to support that sublingual immunotherapy was associated with improved asthma symptoms. Of note, our study included 5 studies[22,43,45-47] published after 2008 that were included for asthma evidence grading in which 3 had strong magnitude of association,[22,46,47] which may explain the greater evidence in our report.

Table 2. Sublingual Immunotherapy Safety Summary of Studies Reporting Adverse Events (continued)

		Adverse Events			
				Severity	
	Total No. of Patients	No. of Patients[a]	Range of Patients, %[a]	Description	% of Total Reported Events
Gastrointestinal reactions by allergen[g]: grass mix,[12,17,19,31-33,43,49,50] dust mite,[9,29,36,62] trees,[41,55] *Parietaria*,[30] ragweed,[43] multiple allergens[13,24,34]					
Sublingual immunotherapy groups (n = 20 studies)	1704	281	0.3-74	Unspecified	91.0
				Mild	8.9
				Moderate	0.1
Control groups (n = 11 studies)	636	244	3-73	Unspecified	100
Cardiovascular reactions by allergen[h]: grass mix,[49] tree (cypress)[55]					
Sublingual immunotherapy groups (n = 2 studies)	65	2	2-4	Mild	100
Control group (n = 1 study)	30	1	2-4	Mild	100
Ocular reactions by allergen[i]: grass mix,[11,32,43,69] dust mite,[29,36] trees,[39,73] *Parietaria*,[30] multiple allergens[21,24]					
Sublingual immunotherapy groups (n = 11 studies)	763	308	1.5-73.4	Unspecified	98
				Mild	1
				Severe	1
Control groups (n = 7 studies)	428	182	3-65	Unspecified	98
				Mild	1
				Moderate	1
General symptoms by allergen[j]: grass mix,[11,19,32,33,49,50] dust mite,[25,27-29,35] *Parietaria*,[48] trees,[41] Timothy grass,[56] multiple allergens[14,21]					
Sublingual immunotherapy groups (n = 17 studies)	763	149	1-60	Unspecified	74
				Mild	22
				Moderate	4
Control groups (n = 10 studies)	435	21	6-67	Unspecified	86
				Mild	13
				Moderate	1

[a] Unless otherwise indicated.
[b] There were 25 studies that reported adverse events in the control (placebo) group.
[c] Based on 1 study that did not report the number of injections.
[d] Thirteen studies reported adverse events in the control (placebo) group; 2 studies had adverse events only in the placebo group.[15,62]
[e] Ten studies reported adverse events in the control (placebo) group; 1 study had adverse events only in the placebo group.[15]
[f] Nine studies reported adverse events in the control (placebo) group; 1 study had adverse events only in the placebo group.[12]
[g] Eleven studies reported adverse events in the control (placebo) group; 1 study with 60 patients did not report the number of doses or the number of events so the percentage or range of adverse events was not quantifiable and severity was 100% unspecified.[33]
[h] One study reported adverse events in the control (placebo) group.
[i] Nine studies reported adverse events in the control (placebo) group; 1 study had adverse events only in the placebo group.[55]
[j] Ten studies reported adverse events in the control (placebo) group; 1 study had adverse events only in the placebo group[62]; 2 studies with 116 patients did not report the number of doses or the number of events so the percentage or range of adverse events was not quantifiable and severity was 50% modified and 50% unspecified.

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Other systematic reviews of sublingual immunotherapy have focused on a particular allergen such as dust mite[80] or grass.[81] Our review similarly found that sublingual immunotherapy treatment for these allergens was associated with improvement in a variety of outcomes.

Challenges

We encountered several challenges during our review process. We included only RCTs in this review; however, the studies varied substantially in their risk of bias. Among 46 studies (73%) that received industry support, few described the extent of involvement of their sponsors. For these reasons, most studies were considered to have a moderate or high risk of bias.

The literature was heterogeneous. The inconsistent scoring and lack of standardized reporting systems for clinical outcomes and harms made comparisons difficult among studies. The studies used varying criteria for diagnosing asthma and assessing asthma severity. The use of combined scores such as asthma plus rhinitis may not accurately reflect the degree of control for both disease processes. Studies with multiple allergens presented a similar dilemma; response to 1 allergen may have determined the overall clinical score, with little effect from a second allergen. The heterogeneity of the data on symptoms and medication use precluded pooling the data for further analysis.

Most challenging to this review was the extreme variability in the dosing and treatment schedules from study to study. The doses were reported in varying units (biological units, index of reactivity units, standardized quality units, micrograms, bioequivalent allergy unit, specific treatment units, etc). Indeed, without a common unit of dose measurement, it is impossible to compare dose effect among studies. In several studies, major allergen content was not reported. To illustrate, dust mite was the most widely used sublingual allergen in 5 studies. When considering the dosing for dust mite in micrograms per month, the highest dose used was more than 50 times greater than the lowest dose, yet clinical efficacy was reported at both ends of the spectrum (eTable 2). The extreme variability in sublingual doses and treatment schedules makes it impossible to comment on the strength of the evidence regarding dosing and treatment schedule.

Another significant limitation of the current review in regard to dosing was the difficulty in comparing European allergens with US allergens.[82] In the United States, the Food and Drug Administration establishes for each standardized allergen an in vitro potency test that all manufacturers must use to compare their extracts; in Europe, each allergen manufacturer has its own reference standards rather than a European standard. Another difference is that the in vivo potency in the United States is quantified by intradermal testing methods, which is not the case in Europe. This current review has attempted to express, when possible, sublingual dosing in micrograms of major allergen (eTable 2). However, it must be emphasized that due to these differences between allergen standardization and potency in the United States vs Europe, caution must be exercised when attempting to translate European dosing to the United States.

There were deficiencies in the statistical reporting provided in the included studies. Most of the studies had small sample sizes and small amounts of relevant statistical information on the outcomes reported because scores were frequently unavailable (such as standard deviation, standard error, or confidence intervals). Therefore, precision of the point estimates could not be assessed.

As in most fields, there may be publication bias in the sublingual immunotherapy literature, with studies reporting positive results being more likely to be published than studies reporting negative results. Our study aimed to overcome publication bias by searching for registered and yet unreported clinical trials and requesting scientific information packets from relevant pharmaceutical companies to look for unpublished trials; however, our report includes studies in the periods before clinical trial registration was required. The incomplete statistical reporting in the majority of included studies made it impossible to prepare a meaningful funnel plot to further assess publication bias. One of the major limitations when considering the validity of the conclusions of this systematic review is the potential for publication bias.

Future Research

Additional RCTs are needed to examine the efficacy and safety of sublingual immunotherapy. There is a particular need for additional high-quality studies that directly compare sublingual with subcutaneous immunotherapy. Future studies should use standardized methods to report and score symptoms, adverse events, and dosing. Studies including patients with asthma should describe how asthma was diagnosed and how severity was determined. This will allow assessment of whether there is a particular subgroup of patients with asthma that may benefit from sublingual immunotherapy. In addition, the target maintenance dose, dosing strategies, duration of treatment, and use of single vs multiple allergen therapy have not been fully determined.

CONCLUSIONS

Our review found moderate strength in the evidence to support the use of sublingual immunotherapy for allergic rhinitis and asthma. This indicates moderate confidence that the evidence reflects a true efficacy. However, future research could change the estimate. High-quality studies are needed to answer questions of optimal dosing strategies. There were limitations in the standardization of adverse event reporting, but no life-threatening adverse events were noted.

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Study concept and design: Lin, Suarez-Cuervo, Ward, Segal.

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