

Sublingual Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and Asthma

A Systematic 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

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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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 provocation 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-

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.

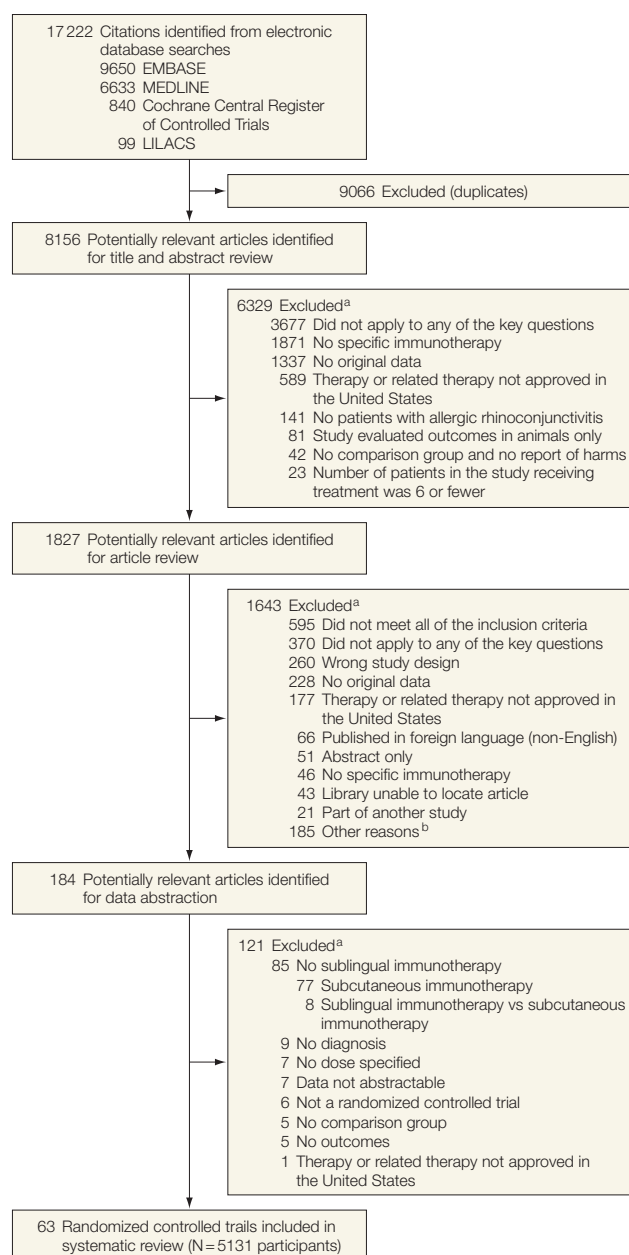
To reduce the risk of publication bias in our results, we searched public registries of clinical trials and requested scientific information packets from relevant pharmaceutical companies to search for unpublished trials. Because measures of variance were not reported in most of the included studies,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

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

Figure. Flow Diagram of Sublingual Immunotherapy Studies



^aArticles were excluded by 2 reviewers at this level so this number is exceeded by the total for all of the exclusions listed.

^bThe 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.

(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* involv-

ing 2985 participants. The most frequently studied allergens were grass mix (10 studies; 28%) and dust mite (8 studies; 22%). All studies demonstrated greater improvement in the sublingual immunotherapy groups than in the comparison groups; in 21 studies (58%), this difference was statistically significant. 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 statisti-

cally 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-

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 9-12, 14-17, 19, 24, 28-32, 35-39, 41,

§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.

ferred 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 comprehensive

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} <i>Alternaria</i> ^{22,45} Grass mix ⁴⁶ Tree mix ⁴¹ Birch ⁴⁷ <i>Parietaria</i> 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} <i>Parietaria</i> ^{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}	All studies showed greater improvement in symptoms in the sublingual immunotherapy group vs placebo.	Moderate
Asthma symptoms plus rhinitis or rhinoconjunctivitis symptom scores	515	6	<i>Alternaria</i> 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} <i>Parietaria</i> ^{48,52} Timothy grass ⁵⁶ Ragweed ¹⁰ Cedar ⁶⁵ 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

(continued)

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} <i>Parietaria</i> ^{30,38,52,64} Cedar ^{34,55,65} <i>Alternaria</i> ^{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} <i>Parietaria</i> ^{52,64,70} Dust mite ¹⁵ <i>Alternaria</i> 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 ⁹)	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 strong 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

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

	Total No. of Patients	No. of Patients ^a	Range of Patients, % ^a	Adverse Events	
				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} <i>Parietaria</i> , ^{30,48} <i>Alternaria</i> , 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} <i>Parietaria</i> , 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 <i>Parietaria</i> , 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

(continued)

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 conjunctivitis⁷⁸ 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)

	Total No. of Patients	No. of Patients ^a	Range of Patients, % ^a	Adverse Events	
				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} <i>Parietaria</i> , ³⁰ ragweed, ⁴³ multiple allergens ^{13,24,34} Sublingual immunotherapy groups (n = 20 studies)	1704	281	0.3-74	Unspecified Mild Moderate	91.0 8.9 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} <i>Parietaria</i> , ³⁰ multiple allergens ^{21,24} Sublingual immunotherapy groups (n = 11 studies)	763	308	1.5-73.4	Unspecified Mild Severe	98 1 1
Control groups (n = 7 studies)	428	182	3-65	Unspecified Mild Moderate	98 1 1
General symptoms by allergen ^j : grass mix, ^{11,19,32,33,49,50} dust mite, ^{25,27-29,35} <i>Parietaria</i> , ⁴⁸ trees, ⁴¹ Timothy grass, ⁵⁶ multiple allergens ^{14,21} Sublingual immunotherapy groups (n = 17 studies)	763	149	1-60	Unspecified Mild Moderate	74 22 4
Control groups (n = 10 studies)	435	21	6-67	Unspecified Mild Moderate	86 13 1

^aUnless otherwise indicated.

^bThere were 25 studies that reported adverse events in the control (placebo) group.

^cBased on 1 study that did not report the number of injections.

^dThirteen studies reported adverse events in the control (placebo) group; 2 studies had adverse events only in the placebo group.^{15,62}

^eTen studies reported adverse events in the control (placebo) group; 1 study had adverse events only in the placebo group.¹⁵

^fNine studies reported adverse events in the control (placebo) group; 1 study had adverse events only in the placebo group.¹²

^gEleven 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

^hOne study reported adverse events in the control (placebo) group.

ⁱNine studies reported adverse events in the control (placebo) group; 1 study had adverse events only in the placebo group.⁵⁵

^jTen 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 50% modified and 50% unspecified.

Other systematic reviews of sublingual immunotherapy have focused on a particular allergen such as dust mite⁸⁰ 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 micro-

grams 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 rel-

evant 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.

Author Contributions: Dr Lin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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

Acquisition of data: Lin, Erekosima, Kim, Ramanathan, Suarez-Cuervo, Chelladurai, Ward.

Analysis and interpretation of data: Lin, Erekosima, Kim, Ramanathan, Suarez-Cuervo, Chelladurai, Segal.

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Obtained funding: Lin, Segal.

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Online-Only Material: The eMethods and eTables 1 and 2 are available at <http://www.jama.com>.

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Supplementary Online Content

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eMethods. Search strategy and quality assessment of each article

eTable 1. Study inclusion and exclusion criteria

eTable 2. SLIT included studies summary and outcomes reported

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Search Strategy and Quality Assessment of Each Article

Search Strategy

MEDLINE (PubMed 6498)

(allergen-specific immunotherapy[tiab] OR allergen immunotherapy[tiab] OR immunotherapy[tiab] OR immunotherapy[mesh] OR immunotherap*[tiab]) AND ((rhinitis[mh] OR rhinitis[tiab] OR hay fever[mh] OR hay fever[tiab] OR rhinoconjunctivitis[tiab] OR conjunctivitis[mh] OR "allergic conjunctivitis"[tiab] OR pollinosis[mh] OR pollinosis[tiab] OR pollenosis[tiab] OR asthma[mh] OR asthma[tiab]) NOT ("occupational diseases"[mh] OR "trachoma"[mh])) NOT (animals[mh] NOT humans[mh])

1	allergen-specific immunotherapy[tiab] OR allergen immunotherapy[tiab] OR immunotherapy[tiab] OR immunotherapy[mesh] OR immunotherap*[tiab]
2	rhinitis[mh] OR rhinitis[tiab] OR hay fever[mh] OR hay fever[tiab] OR rhinoconjunctivitis[tiab] OR conjunctivitis[mh] OR "allergic conjunctivitis"[tiab] OR pollinosis[mh] OR pollinosis[tiab] OR pollenosis[tiab] OR asthma[mh] OR asthma [tiab]
3	"occupational diseases"[mh] OR "trachoma"[mh]
4	2 NOT 3
5	(animals[mh] NOT humans[mh])
6	1 AND 4
7	6 NOT 5

EMBASE (9327)

('immunotherapy'/exp OR desensiti*ation) AND ('rhinitis'/exp OR 'allergic rhinitis'/exp OR 'hay'/exp AND 'fever'/exp OR 'rhinoconjunctivitis'/exp OR 'conjunctivitis'/exp OR 'allergic conjunctivitis'/exp OR 'asthma'/exp) AND [humans]/lim AND [embase]/lim

1	'immunotherapy'/exp OR desensiti*ation
2	'rhinitis'/exp OR 'allergic rhinitis'/exp OR 'hay'/exp AND 'fever'/exp OR 'rhinoconjunctivitis'/exp OR 'conjunctivitis'/exp OR 'allergic conjunctivitis'/exp OR 'asthma'/exp
3	[humans]/lim
4	embase]/lim
5	3 AND 4
6	1 AND 2 AND 5

COCHRANE (840)

Immunotherapy AND (rhinitis OR allergic rhinitis OR rhinoconjunctivitis OR conjunctivitis OR allergic conjunctivitis OR asthma)

LILACS (99)

Immunotherapy AND (rhinitis OR allergic rhinitis OR rhinoconjunctivitis OR conjunctivitis OR allergic conjunctivitis OR asthma

Quality Assessment of Each Article

Scoring of Potential Sources of Bias	
Potential Sources of Bias	Scoring per item (Points) Minimum possible score - 0 Maximum possible score - 6
1. Was there random allocation of subjects?	Random allocation - 0 Non-random allocation - 1
2. Was the allocation scheme concealed?	Allocation scheme concealed - 0 Allocation scheme not concealed - 1
3. Were the interventions concealed from study personnel and participants?	Complete blinding - 0 Incomplete blinding - 1
4. Was incomplete data adequately addressed?	Incomplete data addressed - 0 Incomplete data no addressed - 1
5. Did the sponsoring company participate in study design, or interpretation?	No sponsor company involvement - 0 Sponsor company involvement - 1
6. Were there any other important sources of bias?	No other sources of bias - 0 Other sources of bias - 1
Interpretation of Numeric Score*	
<u>Low Risk of Bias</u> : least bias, best quality study with valid results	0-1 point
<u>Medium Risk of Bias</u> : susceptible to some bias, but no enough to invalidate results	2-3 points
<u>High Risk of Bias</u> : most bias, worst quality study, with significant flaws	4-6 points

*Note: Studies remained in the **Low risk of bias** category if the single point was due to sponsorship or “other sources of bias”; studies were assigned to the **Medium Risk of Bias** category if the single point came from lack of allocation concealment, lack of blinding or incomplete data reporting.

eTable 1. Study Inclusion and Exclusion Criteria

PICO criteria	Inclusion and exclusion criteria
Population and condition of interest	Studies enrolled patients with allergic rhinoconjunctivitis and/or allergic asthma due to airborne allergies Allergic rhinoconjunctivitis must have been confirmed by skin tests or RAST. In studies reporting asthma outcomes, asthma must confirmed by pulmonary lung function (FEV₁; methacholine challenge) or accepted clinical guidelines. Studies included adults, children, and mixed age population (adult and children).
Interventions	All studies included were randomized controlled trials. The intervention was SLIT alone or with usual care. Similar preparation must be available for off-label SLIT use in the U.S. No study of SLIT was excluded because of timing or duration of treatment. Studies were excluded where dosage units were NOT specified
Comparisons of interest	Included studies compared SLIT to any of the following: 1. Placebo 2. Any other SLIT 3. Pharmacotherapy (positive control) 4. Environmental control 5. Usual care (for example, environmental control, pharmacotherapy) We included studies where SLIT was used alone or in combination with any other treatment and compared with the listed comparators or any other treatment
Outcomes	We included studies that reported the following outcomes: Primary outcomes 1. Symptom scores (for rhinitis, conjunctivitis, or asthma) 2. Medication scores 3. Combined symptom and medication scores 4. Quality of life 5. Safety or harms Secondary outcomes 1. Functional test results (PFT, FEV₁) 2. Provocational test results (for nasal, conjunctival, or bronchial challenges)

eTable 2. SLIT Included Studies Summary and Outcomes Reported

STUDY CHARACTERISTICS															
CLINICAL OUTCOMES REPORTED														QUALITY	
Study	Allergen	No. Patients	Mono-Sensitized Patients	Children Only	Treatment Duration	µg per month of allergen	Asthma	Asthma+ Rhinitis/ RC	Rhinitis RC	Ocular	Medication	Medication+ Symptoms	QOL	PFT	Risk of Bias
DUST MITES															
Bahceciler 2001 ³⁷	Dust mites: D.pter/ D.far	15 SLIT 8 Plac 7	X	X	6 months	93.3 Der p1 81.67Der f1	X	NR	X	NR	X	NR	NR	NR	Medium
Bush 2011 ⁵⁹	Dust mites: D. far	31 SLIT High 10 SLIT Low 10 Plac 11	-	-	12-18 months	2100 Der f1	NR	X	NR	NR	X	NR	NR	X	Medium
deBot 2011 ²⁹	Dust mites: D. pter	257• SLIT 125 Plac 126	-	X	2 years	16.24 Der p1	X	NR	X	X	X	NR	X	NR	High
Guez 2000 ¹⁵	Dust mites: D.pter/ D.far	72 SLIT 36 Plac 36	-	-	24 months	91.6 Der p1 70.83Der f1	NR	NR	X	NR	X	X	NR	NR	Medium
Hirsch 1997 ³⁵	Dust mites: D.pter	30 SLIT 15 Plac 15	-	X	1 year	47.5 Der p1	X	NR	X	NR	X	NR	NR	NR	Low
Ippoliti 2003 ⁴²	Dust mites: D.pter	86 SLIT 47 Plac 39	X	X	6 months	9.6 Der p1 4.8 Der p2	X	NR	X	NR	NR	NR	NR	X	Medium
Lue 2006 ²⁶	Dust mites: D.pter/ D.far	20 SLIT 10 Plac 10	X	X	6 months	500 Der f 283.3 Der p	X	NR	NR	NR	X	NR	NR	X	Medium
Marogna 2010 ⁶⁴	Dust mites: D. pter	78 SLIT 3y 19 SLIT 4y 21 SLIT 5y 17 Control 21	-	-	3,4, or 5 years	NR	NR	NR	NR	NR	P values NR	P values NR	NR	X	Medium

STUDY CHARACTERISTICS								CLINICAL OUTCOMES REPORTED						QUALITY	
Study	Allergen	No. Patients	Mono-Sensitized Patients	Children Only	Treatment Duration	µg per month of allergen	Asthma	Asthma+ Rhinitis/ RC	Rhinitis RC	Ocular	Medication	Medication+ Symptoms	QOL	PFT	Risk of Bias
Niu 2006 ²⁷	Dust mites: D.pter/ D.far	110 SLIT 56 Plac 54	X	-	24 weeks	500 Der F 283.3 DerP	X	X	NR	NR	P values NR	P values NR	NR	X	Medium
O'Hehir 2009 ⁵⁰	Dust mites: D.pter	30 SLIT 15 Plac 15	X	-	1 year	1425 Der p1 283 Der p2	NR	NR	X	NR	NR	NR	X	NR	High
Pajno 2000 ²⁵	Dust mites: D.pter	24 SLIT 12 Plac 12	X	X	2 years	9.6 Der p1 4.8 Der f	X	NR	NR	NR	X	NR	NR	NR	Low
Tahamiler 2007 ⁹	Dust mites: D.pter/ D.far	137 SLIT 67 Plac 70 DropoutsNR	-	-	2-3 years	NR	NR	NR	X	NR	NR	NR	NR	NR	High
Tari 1990 ³⁶	Dust mites: D.pter/ D.far	66 SLIT 34 Plac 32	-	X	18 months	NR	X	NR	X	X	NR	NR	NR	X	Low
Tseng 2008 ²⁸	Dust mites: D.pter/ D.far	63 SLIT 30 Plac 33	X	X	3 weeks induction, 21 weeks maintenance	260 Der p 451.7Der f	NR	NR	X	NR	NR	NR	NR	NR	Medium
GRASS															
Ahmadi afshar 2012 ⁴⁴	Grass: Rye	24 SLIT 12 Plac 12	X	X	8 months	NR	NR	NR	NR	NR	X	NR	NR	NR	Medium
Lima 2002 ⁴⁸	Grass: Timothy	56 SLIT 28 Plac 28	-	-	18 months	900 Phl p5	X	X	X	X	X	NR	NR	NR	Low
Pajno 2011 ⁴⁰	Grass: Timothy	80 SLIT 40 Plac 40	-	X	4 months/ year for 2 years	NR	X	NR	NR	NR	X	X	NR	NR	Medium
De Blay 2007 ¹⁹	Grass: Grass Mix	118 SLIT 61 Plac 57	-	-	10 months	275 Group III grass	NR	NR	X	NR	NR	NR	NR	NR	Medium

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STUDY CHARACTERISTICS								CLINICAL OUTCOMES REPORTED						QUALITY	
Study	Allergen	No. Patients	Mono-Sensitized Patients	Children Only	Treatment Duration	µg per month of allergen	Asthma	Asthma+ Rhinitis/ RC	Rhinitis RC	Ocular	Medication	Medication+ Symptoms	QOL	PFT	Risk of Bias
Feliziani 1995 ¹⁶	Grass: Grass Mix	34 SLIT 18 Plac 16	-	-	until end of pollen season	NR	NR	NR	X	NR	X	NR	NR	NR	Medium
Hordijk 1998 ⁴⁵	Grass: Grass mix	69** SLIT 35 Plac 36	-	-	10 months	NR	NR	NR	X	NR	NR	NR	NR	NR	Medium
Marogna 2009 ^{*46}	Grass: Grass mix	51 SLIT 25 Plac 26	X	-	5 years	70 Phl p1	X	NR	X	NR	X	NR	NR	X	Medium
Novembre 2004 ^{*31}	Grass: Grass mix	113 SLIT 54 Plac 59	-	X	3 years	12.0 Group V grass	NR	NR	X	NR	X	X	NR	NR	High
Ott 2008 ⁴⁷	Grass: Grass mix	213 SLIT 142 Plac 71	-	-	3 seasons	500 Group V grass	NR	NR	X	NR	NS	X	NR	NR	Medium
Panzer 2008 ¹¹	Grass: Grass mix	35 SLIT 20 Plac 15	-	-	1 year	NR	X	X	X	X	X	NR	NR	NR	Low
Pfaar 2007 ⁶⁸	Grass: Grass mix	185 SLIT 94 Plac 91	X	-	1.5 years	1200 Group V grass	NR	NR	NR	NR	NR	X	NR	NR	Medium
Pradaliér 1999 ¹⁷	Grass: Grass mix	126● SLIT 62 Plac 61	-	-	4 months	233.75 Phl p5	NR	NR	X	NR	X	NR	NR	NR	Medium
Roder 2007 ³²	Grass: Grass mix	204 SLIT 108 Plac 96	-	X	2 years	1260 Lol p5	NR	NR	X	NR	X	NR	X	X	Low
Sabbah 1994 ¹²	Grass: Grass mix	58 SLIT 29 Plac 29	-	-	120 days	NR	NR	NR	X	X	X	NR	NR	NR	Medium

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STUDY CHARACTERISTICS								CLINICAL OUTCOMES REPORTED							QUALITY
Study	Allergen	No. Patients	Mono-Sensitized Patients	Children Only	Treatment Duration	µg per month of allergen	Asthma	Asthma+ Rhinitis/ RC	Rhinitis RC	Ocular	Medication	Medication+ Symp toms	QOL	PFT	Risk of Bias
Stelmach 2009 ⁷¹	Grass: Grass Mix	50 SLIT 25 Plac 25	-	X	24 months	120 Group V grass	NR	NR	NR	NR	NR	NR	NR	P value NR	Medium
Stelmach 2011 ³³	Grass: Grass Mix	60 SLIT Pre 20 SLIT Cont 20 Plac 20	X	X	12 months	300 Group V grass	NR	NR	NR	NR	NR	NR	NR	P value NR	Low
Wahn 2012 ⁴³	Grass: Grass Mix	207 SLIT 159 Plac 49	-	X	8 months	1200 Group V grass	X	NR	NR	NR	X	X	NR	NR	Low
TREES															
Horak 1998 ⁷²	Trees: White birch	41 SLIT 20 Plac 21	-	-	3 months	75 STU	NR	NR	NR	NR	NR	NR	NR	NR	Medium
Marogna 2005 ⁶²	Trees: White birch	79 SLIT 39 Plac 40	X	-	3.5 years	8.5 Bet v1	NR	X	NR	NR	X	NR	NR	NR	Medium
Marogna 2010 ⁵⁵	Trees: Birch	33 SLIT 17 Plac 16	-	-	5 year	8.3 Bet v1	X	NR	X	NR	X	NR	NR	X	High
Voltolini 2010 ⁷⁹	Trees: Birch	24 SLIT 14 Plac 10	-	-	2 courses of 4 months (pre/co-seasonal)	1.725 BetV1	X	NR	X	NR	NR	NR	NR	X	Medium
Fujimura 2011 ⁶⁶	Trees: Japanese cedar	103 SLIT 66 Plac 47	-	-	20 months	6-16.8 Cry j1	NR	NR	NR	NR	NR	X	X	NR	Low
Horiguchi 2008 ⁵³	Trees: Japanese cedar	67 SLIT 43 Plac 24	-	-	7 months	6.0 Cry j1	NR	NR	X	NR	NR	NR	NR	NR	Medium
Makino 2010 ⁶¹	Trees: Japanese cedar	25 SLIT 9 Plac 16	-	-	5 months	60 Cry j1, 8-20 Cry j2	NR	NR	NR	NR	X	X	X	NR	Medium

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STUDY CHARACTERISTICS								CLINICAL OUTCOMES REPORTED						QUALITY	
Study	Allergen	No. Patients	Mono-Sensitized Patients	Children Only	Treatment Duration	µg per month of allergen	Asthma	Asthma+ Rhinitis/ RC	Rhinitis RC	Ocular	Medication	Medication+ Symptoms	QOL	PFT	Risk of Bias
Okubo 2008 ⁵⁴	Trees: Japanese cedar	61● SLIT 37 Plac 22	-	-	6 months	NR	NR	NR	X	NR	X	X	X	NR	Medium
Di Rienzo 2006 ⁶⁷	Trees: Mountain cedar	34 SLIT 19 Plac 15	-	-	4 to 5 months (preseason Dec - April)	NR	NR	NR	NR	NR	NR	X	X	NR	High
Vervloet 2007 ⁵⁶	Trees: Bald-cypress	76 SLIT 38 Plac 38	X	-	120 days	6840 Jun a1	NR	X	X	X	X	NR	NR	NR	High
Vourdas 1998 ³⁹	Trees: Olive	69● SLIT 34 Plac 32	-	X	seasonal (5 to 6 months each year) for 2 years	736.3 Ole e1	NR	NR	X	NR	X	NR	NR	NR	Medium
Valovirta 2006 ⁴¹	Trees: Tree mix	98 SLIT High 32 SLIT Low 33 Plac 33	-	X	5 weeks build-up 18 months maintenance	High: 120 Bet v1/Aln g1/Cor a1 Low: 14.4 Bet v1/Aln g1/Cor a1	X	X	X	NR	X	NR	NR	NR	Medium
Voltolini 2001 ²³	Trees: Tree mix	30 SLIT 15 Plac 15	-	-	5 months per year for 2 years (co-seasonal)	89 BetV1	NR	NR	NR	NR	X	X	NR	X	Medium
WEEDS															
D'Ambrosio 1996 ⁶⁹	Weed: Parietaria	40 SLIT 20 Plac 20	X	-	8 months (mid Jan - end Sep)	1.44 Par j1	NR	X	NR	NR	NR	X	NR	NR	High
D'Ambrosio 1999 ⁵¹	Weed: Parietaria	30 SLIT 14 Plac 16	X	-	9 months	1.52Par j1	NR	X	X	X	X	X	NR	NR	Medium

STUDY CHARACTERISTICS								CLINICAL OUTCOMES REPORTED						QUALITY	
Study	Allergen	No. Patients	Mono-Sensitized Patients	Children Only	Treatment Duration	µg per month of allergen	Asthma	Asthma+ Rhinitis/ RC	Rhinitis RC	Ocular	Medication	Medication+ Symptoms	QOL	PFT	Risk of Bias
la Rosa 1999 ³⁰	Weed: Parietaria	41 SLIT 20 Plac 21	X	X	2 years	2.2 Par j1	NR	NR	X	NR	X	NR	NR	NR	Low
Pajno 2004 ⁵⁸	Weed: Parietaria	30 SLIT 15 Plac 15	-	X	13 months	1.56 Par j1	X	NR	X	X	X	NR	NR	NR	Low
Passalacqua 1999 ⁶⁰	Weed: Parietaria	30 SLIT 15 Plac 15	-	-	8 months	1.0 Par j1	NR	NR	NR	NR	X	X	NR	NR	Low
Bowen 2004 ¹⁰	Weed: Ragweed	83 SLIT 43 Plac 40	X	-	3 months (estimate duration)	3480 Amb a1	NR	NR	X	X	X	NR	NR	NR	Medium
Skoner, 2010 ⁵²	Weed: Ragweed	115 SLIT High 36 SLIT Low 39 Plac 40	-	-	17 +/- 3 weeks	High 1440 Amb a1, Low: 144	NR	NR	NR	NR	X	X	NR	NR	Low
ANIMAL															
Nelson 1993 ⁵⁷	Animal: cat	44 SLIT 22 Plac 22	-	-	105 days	12.9-257.1 Fel d1	NR	NR	X	NR	NR	NR	NR	NR	Medium
Alvarez-Cuesta 2007 ²⁰	Animal: cats Note: outcomes reported only during challenges	50 SLIT 25 Plac 25	-	-	12 months	15.3 Fel d1	NR	NR	NR	NR	NR	NR	NR	NR	High
MOLD															
Cortellini 2010 ²²	Mold: Alternaria	27 SLIT 15 Plac 12	-	-	10 months	6 Alt a1	X	NR	NR	NR	X	X	NR	NR	High

STUDY CHARACTERISTICS								CLINICAL OUTCOMES REPORTED						QUALITY	
Study	Allergen	No. Patients	Mono-Sensitized Patients	Children Only	Treatment Duration	µg per month of allergen	Asthma	Asthma+ Rhinitis/ RC	Rhinitis RC	Ocular	Medication	Medication+ Symptoms	QOL	PFT	Risk of Bias
Pozzan 2010 ⁶⁵	Mold: Alternaria	52 SLIT 34 Plac 18	-	-	3 years	3.6 Alt a1	NR	X	NR	NR	X	NR	NR	NR	Medium
MULTIPLE ALLERGENS															
Marogna 2007 ^{*63}	Trees: White birch Grass: Grass mix	48 SLIT Birch12 SLITGrass12 SLIT Mix 12 Control 12	-	-	4 years	100 Bet v1	NR	X	NR	NR	X	X	NR	X	Medium
Moreno-Ancillo 2007 ¹⁴	Grass: Grass mix Trees: Olive	105 SLIT 52 Plac 53	X	-	10 months	60 Grp V grass, 90 Ole e1	X	NR	X	X	X	X	X	X	Low
Sambugaro 2003 ^{*8}	Dust mites: Dpter/Dfar Grass: Grass mix Weeds: Ragweed Parietaria	58 8d ind 18 15d ind 18 20d ind 12 No Tx 10	-	-	2 years	4.8 Der p1, 2.4 Der p2, 12.0 GrpV grass, 27 Bet v1, 0.7 Par j1	NR	NR	NR	NR	NR	X	NR	X	Medium
Amar 2009 ⁴⁹	Grass: Timothy Trees: Ash,Maple, Red/green American elm Cottonwood Weeds: Kochia, ragweed, Sagebrush Russian thistle	58 SLITMono 19 SLITMult 20 Plac 19	-	-	15 months	570 Phl p5	NR	NR	X	NR	X	NR	NR	NR	Low
Marogna 2004 ^{*13}	Dust mites: D.pter Grass: Grass mix Trees: White birch Weeds: Mugwort/ Parietaria	511 SLIT 319 Plac 192	-	-	3 years	3.25 Der f1/f2, 5.83 Phl p1 5.83 Par j1, 8,33 Bet v1	NR	NR	NR	NR	NR	NR	NR	X	Medium

STUDY CHARACTERISTICS							CLINICAL OUTCOMES REPORTED								QUALITY
Study	Allergen	No. Patients	Mono-Sensitized Patients	Children Only	Treatment Duration	µg per month of allergen	Asthma	Asthma+ Rhinitis/ RC	Rhinitis RC	Ocular	Medication	Medication+ Symp toms	QOL	PFT	Risk of Bias
Marogna 2008 ^{*34}	Dust mite Trees: White birch Grass: Grass mix Weed: Parietaria	216 SLIT 144 Plac 72	-	X	3 years	40 Der p1 40 Der p2 3.33 Phl p1 3.33 Par j1, 8.33 Bet v1	NR	NR	NR	NR	NR	X	NR	X	Medium
Rodriguez 2006 ²¹	Dust mite Grass mix *This study reported adverse events only	135 SLIT 69 Plac 66	-	-	3 months	60 Grp V grass 24 Der p1/2	NR	NR	NR	NR	NR	NR	NR	NR	Medium
Swamy 2012 ²⁴	Dust Mite Grass: Timothy	30 SLIT 15 Plac 15	-	-	12 months	600 D Far 450 Phl p5	NR	NR	X	NR	X	NR	NR	X	Medium

SLIT: Sublingual Immunotherapy RC: Rhinoconjunctivitis, QOL: Quality of Life, PFT: Pulmonary Function Testing, D.Pter: Dermatophagoides pteronyssinus, D.Far: Dermatophagoides farina, Plac: Placebo *Denotes studies in which comparator is other than a placebo group. These studies use pharmacotherapy/conventional therapy as a comparator: Sambugaro, D'Ambrosio 1996, Novembre, Roder, Marogna 2004, 2007, 2008 and 2009. Tahamiler compared 3 years of sublingual immunotherapy to 2 years of sublingual immunotherapy. Rodriguez compared two groups of sublingual immunotherapy with identical maintenance dose, one group with updosing and the other without updosing. ** Numbers as reported in the paper, even if totals do not correspond • In these studies the numbers of patients do not correspond with total since dropouts happened after randomization but before allocation
X=outcome reported in this study
NR=not reported