

ALLERGEN IMMUNOTHERAPY FOR THE TREATMENT OF ALLERGIC RHINITIS AND/OR ASTHMA

FINAL SYSTEMATIC REVIEW REPORT

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Conflict of Interest Statement

No study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the allergen immunotherapy for the treatment of allergic rhinitis and/or asthma Drug Class Review.

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Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

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Introduction

Rationale

Seasonal and perennial allergic rhinitis and allergic asthma represent important public health concerns, affecting up to 30% of adults (1) and up to 40% of children (2). Signs and symptoms include sneezing, stuffy or runny nose, post-nasal drip, and itchy nose (3). There is considerable cost associated with allergic rhinitis and allergic asthma, including medication cost, days of work lost, and reduced quality of life (4). Clinical practice guidelines recommend that patients who have an inadequate response to pharmacologic interventions be referred for immunotherapy (3).

Allergen immunotherapy comprises two classes of therapy: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). Subcutaneous immunotherapy involves the injection of an allergen extract, generally comprised of the allergen to which the patient is sensitive. Sublingual immunotherapy involves placement of a tablet or drops containing the allergen under the patient's tongue. Both SCIT and SLIT are potentially associated with important benefits and harms (3), although head-to-head comparisons of the two treatments are largely lacking.

A recent international consensus statement suggests that allergen immunotherapy is underused because of a lack of agreement about efficacy and insufficient data on its cost effectiveness (5). We undertook this systematic review of reviews to summarize the current evidence for the effectiveness and safety of allergen immunotherapy in the treatment of allergic rhinitis with or without allergic asthma.

Objective

This systematic review of reviews aims to rapidly summarize clinical and safety evidence from multiple systematic reviews of allergen immunotherapy for the treatment of allergic rhinitis or allergic asthma, including SCIT and SLIT.

Research questions

- RQ1. What is the current evidence for the efficacy or effectiveness of allergen immunotherapy interventions for the treatment of allergic rhinitis or allergic asthma compared to placebo, standard care or each other?
- RQ2. What is the current evidence for the safety of allergen immunotherapy interventions for the treatment of allergic rhinitis or allergic asthma compared to placebo, standard care or each other?
- RQ3. Is the efficacy and safety of allergen immunotherapy different in adult or children (< 18 yr) subpopulations with allergic rhinitis or allergic asthma?

Methods

This was a focused rapid systematic review of existing systematic reviews with a limited search. In order to adequately assess a large body of research literature within a limited time frame, the scope of the review was limited in the following ways:

1. Only secondary evidence assessments were eligible for inclusion, including health technology assessments, indirect treatment comparisons, network meta-analyses, systematic reviews and/or meta-analyses.
2. A date-limited (5 years) search strategy was developed, and a limited grey literature search was conducted.
3. Although we aimed to capture all relevant evidence syntheses regardless of language or publication status, it was not possible to retrieve all located articles and/or translate them within the timelines of this review.

Although this is a rapid assessment of existing evidence syntheses, systematic and structured methods were used throughout to limit bias and ensure a transparent, comprehensive review of the current literature.

Identifying relevant secondary studies

We included systematic reviews that met the following criteria:

- Described a search strategy and a criteria for including and excluding studies;
- Published in English (or a language that can be translated within the time frame of this review) and be retrievable within the condensed time frame of this review;
- Met the requirements of the population, intervention, comparator, and study design criteria and eligibility requirements outlined below.

PICO framework

A PICO framework was used to evaluate the relevance of eligible evidence syntheses (Exhibit 1).

Exhibit 1: Population, intervention, comparator, outcome criteria

PICO Element	Details
Population	Adult or pediatric patients with seasonal or perennial allergic rhinitis (also known as hayfever or rhinoconjunctivitis) or allergic asthma
Interventions	<ul style="list-style-type: none"> • Sublingual immunotherapy (SLIT), including Oralair, Grastek, Ragwitek • Subcutaneous immunotherapy (SCIT), including Pollinex-R, allergen extracts and serums
Comparators	<ul style="list-style-type: none"> • Placebo • Usual care • Active control (SCIT or SLIT to each other, environmental control, medications such as topical nasal corticosteroid or cromolyn preparations, oral antihistamines, decongestants, beta-agonists, oral steroids, bronchodilators, ocular corticosteroids, and montelukast) • Single or multi-allergen SLIT
Outcomes: Efficacy/ Effectiveness	All outcomes will be considered, although certain clinical outcomes may be prioritized for reporting. Outcomes will not be used to assess eligibility of relevant reviews; however, the study must report on the efficacy or effectiveness of allergen immunotherapy(ies). We will not include reviews focused on pharmacokinetic outcomes (considered out of scope) or those solely focused on economic or cost

	<p>outcomes</p> <p>Key outcomes include:</p> <ul style="list-style-type: none"> • Total combined symptom–medication score • Symptom improvement (asthma or rhinitis) • Decrease in medication use (asthma or rhinitis) • Disease-specific quality of life • Adherence/discontinuation
Outcomes: Safety	<p>All outcomes will be considered; however, we do not aim to summarize all adverse effects in depth individually. We will aim to provide a summary of local, systemic or gastrointestinal reactions, withdrawals or discontinuations due to adverse effects, and serious adverse events or death.</p> <p>Key outcomes include:</p> <ul style="list-style-type: none"> • Local (SCIT) injection site reactions including redness, swelling, pruritis, induration • Local (SLIT) oral cavity irritation, itching, swelling, irritation, pain • Systematic: respiratory, cardiovascular, gastrointestinal • Severe life-threatening reactions (anaphylaxis) • Death
Study Types	<ul style="list-style-type: none"> • Health technology assessments, indirect treatment comparisons/network meta-analyses, systematic reviews and/or meta-analyses assessing and including primary studies • A review will be considered if it presents a defined search strategy, searched two or more databases and presents explicit eligibility criteria • For efficacy, reviews must include randomized controlled trials; however, for safety, reviews may summarize any prospective controlled primary study design (randomized, quasi- or non-randomized) • Primary studies will only be included if they were published after the search date of the latest included study literature search. In this case we will narratively summarize RCTs for efficacy and effectiveness and any prospective controlled studies we locate for safety
Excluded	<ul style="list-style-type: none"> • Non-allergic or occupational rhinitis, or rhinitis caused by hormones/hypothyroidism, medication, atrophic mucosa, or other inflammatory or immunologic disorders • Non-allergic asthma • Non-systematic or simple literature or topic reviews • Reviews that have a broader approach than the current review and do not provide a specific systematic sub-analysis relevant to this review • Where a relevant systematic review is ongoing at the time searches are undertaken and/or published after the searches, it will be noted in the final manuscript but not included in the summary of findings • Reviews of reviews

Search strategy

The search strategy was developed and tested through an iterative process by an experienced medical information specialist in consultation with the review team. The database searches were executed on May 31, 2015. Using the OVID platform, we searched Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, and Embase. We also searched the Cochrane Library on Wiley (containing the Database of Systematic Reviews, DARE, HTA Database, and CENTRAL).

Strategies utilized a combination of controlled vocabulary (e.g., “Rhinitis, Allergic”, “Desensitization, Immunologic”, “Administration, Sublingual”) and keywords (e.g., seasonal allergies, hyposensitization therapies, SLIT). Vocabulary and syntax were adjusted across databases. Results were limited to the period 2010 to the present. We used a sensitive systematic review/meta-analysis filter and a validated systematic review filter to focus results. Animal-only and opinion-pieces were removed from the results. Grey literature was sought using CADTH’s Grey Matters Light (www.cadth.ca/sites/default/files/is/cadth_Handout_greymatters_light_e.pdf).

Specific details regarding the strategies appear in Appendix 1.

Article selection

Eligibility criteria were applied to each title and abstract by two independent review authors in a standardized manner using DistillerSR, an online systematic review management and screening tool. Uncertainties were resolved by discussion and consensus with a third review author. All potentially eligible studies were obtained in full-text format. Two independent review authors applied the eligibility criteria to the full-text record, and a final decision was made for inclusion. The reviewers were not blinded as to the study authors or centre of publication prior to study selection.

Quality assessment

We evaluated each systematic review by applying the AMSTAR checklist to ensure that the following requirements were met:

- A comprehensive search strategy involving two or more electronic databases;
- An explicit statement describing the inclusion (and ideally exclusion) criteria applied to candidate studies. Ideally the review mentions a priori development of this criteria and/or use of a protocol;
- Illustrate use of a formal critical appraisal or quality assessment process for all included studies and report the outcome of that process.
- Report findings on efficacy or safety outcomes of interest using details on the study and patient characteristics of two or more studies, and provide the direction of the findings from any pooled analyses (narrative or meta-analysis) carried out.

Summary of findings

From each high-quality systematic review, we extracted the following characteristics:

- Review characteristics (first author, year of publication, county of origin)
- Study design, length of treatment
- Patient characteristics, sample size
- Interventions, comparators, outcomes data

Data were extracted by a single review author and checked for accuracy and completeness by a second review author. Any disagreements were resolved through discussion and consensus with a third review author. The findings from reviews with similar topics have been grouped and synthesized using a narrative approach. Where possible, review findings are summarized and presented by clinical or safety outcome with further detail by comparison, e.g., patient-reported symptom scores for the following comparisons:

- SLIT versus placebo
- SCIT versus placebo
- SLIT versus SCIT
- SLIT or SCIT versus active control

Where possible, data for children and adults are presented separately.

Results

Study selection

The initial literature search returned 257 database abstracts, and 31 articles were identified through grey-literature searching. Of these, 90 were excluded following review of the title and abstract, and 198 were evaluated at full-text screening. Of the 198 full-text articles reviewed, 161 were excluded for a variety of reasons as described in the PRISMA flow diagram (Exhibit 2; Appendix 2). The full-text version of 9 articles could not be located (Appendix 3). The final number of included records was 36 (Appendix 4). Of these, 11 records could not be translated during the review period (Appendix 4). In total, 19 unique SRs published in English were summarized in the final review (6-24).

Characteristics of the included reviews

We assessed the characteristics of the 19 unique systematic reviews that met our PICO criteria (Exhibit 3). Included reviews were published between 2010 and 2015. Of these, 3 included patients with a primary complaint of allergic asthma (6, 18, 24), and 15 included patients with a primary complaint of allergic rhinitis (7-9, 11-17, 19-23). One review included both patients with allergic asthma or allergic rhinitis and provided the data separately by indication (10). All included RCTs, while 2 also included non-randomized studies (15, 16). The number of included studies in each review ranged from 8 to 268, and varied by the indication for allergen immunotherapy. The duration of therapy ranged from 2 week to more than 5 weeks; only 1 SR compared the efficacy and safety of immunotherapy of short (< 3 yr) and long (> 3 yr) duration (21). Of the included reviews, 4 involved only SCIT (6, 14, 16, 18), 6 involved only SLIT (11, 12, 15, 19, 22, 24), and 9 involved both SCIT and SLIT.

Most of the included systematic reviews compared either SCIT or SLIT to placebo. One systematic review included a comparison to pharmacotherapy; however, the comparison groups were not well described and data are not included in this review (17). One systematic review involved comparison between cluster and conventional administration of SCIT. This comparison was deemed outside the scope of this review.

Quality of the included reviews

The AMSTAR checklist was applied to 19 systematic reviews that met the PICO criteria at the full-text screening phase. Of these, 14 scored less than 8 points on the AMSTAR checklist (Appendix 5). Of note, one systematic review received a score of zero points (25). This review was performed as part of the development of a guideline and met our criteria for inclusion. It did not, however, provide sufficient detail to achieve a score on the AMSTAR checklist.

Exhibit 2: PRISMA flow diagram

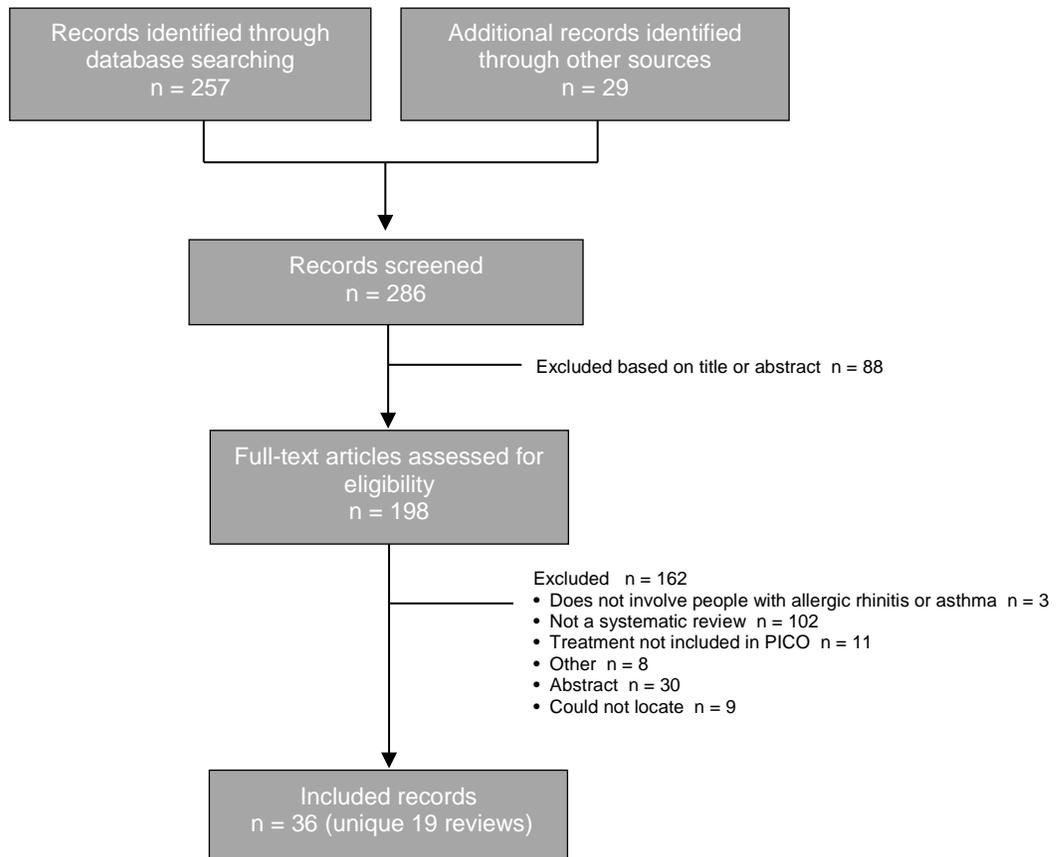


Exhibit 3: Characteristics of included systematic reviews

Study	Country of conduct	No. of included studies	Included study designs	Population	Duration	Indication	Immunotherapy evaluated	Type of analysis	Included allergens	AMSTAR Score (/11)
Allergic asthma										
Lu 2015	China	19	RCT	Mixed	4 mo–3 yr	AA	SCIT	Meta-analysis	HDM	7
Tao 2013	China	16	RCT	Mixed	10 wk–25 mo	AA +/- AR +/- conjunctivitis	SLIT	Meta-analysis	HDM, grass, birch	6
Abramson 2010	Australia	88	RCT	Mixed	≤ 3 yr	AA	SCIT	Meta-analysis	HDM, pollen, animal dander, mould, latex	7
Allergic rhinitis										
Seidman 2015	US	267	CPG,SR, RCT	Mixed	NR	Seasonal and perennial AR	SCIT, SLIT	Narrative	NR	0
CADTH, 2014	Canada	8	RCT	Mixed	9 w – 2 yr	Seasonal AR +/- conjunctivitis	SCIT, SLIT	Network meta-analysis	Grass pollen	7
Feng 2014	China	9	RCT	Mixed	2.3 mo–3 yr	AR	SCIT (cluster)	Meta-analysis	Grass pollen, cat hair	8
Devillier 2014	France	28†	RCT	Mixed	NR	Seasonal AR	SLIT	Meta-analysis	Grass pollen	5
Dranitsaris 2014	Canada	20	RCT	Mixed	1–34 mo	Seasonal AR	SCIT, SLIT	Meta-regression	Grass pollen	3
Larenas-Linnemann 2013	Mexico	28	RCT, NRS	Children and adolescents	6 mo–3 yr	AR or RC +/- AA	SLIT	Narrative	Grass or tree pollen, HDM, <i>Alternaria</i> , peanut, milk	6
Lin 2013a (Kim 2013, Erekosima 2013, Lin 2013b, Chelladurai 2013)	US	142‡	RCT	Mixed	NR	Allergic RC +/- AA	SCIT, SLIT	Narrative	Pollen, cat, dog, cockroach, HDM	11
Manzotti 2013	Italy	7	RCT	Mixed	5.3–7 mo	Seasonal allergic RC	SLIT	Narrative	Grass pollen	1
Meadows 2013 (Dretzke 2013)	UK	28	RCT	Mixed	Mean 3.6 yr	AR +/- AA	SCIT, SLIT	Meta-analysis	Grass, tree or ragweed pollen, fungi, <i>Parietaria</i>	10
Calderon 2013	UK	44	RCT	Mixed	6–28 mo	AR + AA	SCIT, SLIT	Narrative	HDM	3

Study	Country of conduct	No. of included studies	Included study designs	Population	Duration	Indication	Immunotherapy evaluated	Type of analysis	Included allergens	AMSTAR Score (/11)
Purkey 2013	US	12	RCT	NR	≤ 5 yr	Seasonal and perennial AR	SCIT, SLIT	Narrative	Pollen	3
Calderon 2011	UK	42	RCT	Mixed	3–36 mo	Seasonal and perennial allergic RC or conjunctivitis	SLIT	Meta-analysis	Pollen	11
Larenas-Linnemann 2011	Mexico	31§	RCT, NRS	Children and adolescents	3–36 mo	Seasonal or perennial AR or RC +/- AA	SCIT	Narrative	HDM, grass pollen, birch, fungus	5
Radulovic 2011 (Wilson 2003)	UK	60	RCT	Mixed	2 wk-3 yr¶	Seasonal and perennial AR	SLIT	Meta-analysis	<i>Parietaria</i> , ragweed, tree pollen, HDM, cat	10
Bousquet 2010	France	94	RCT	Mixed	NR	AR conjunctivitis, +/- AA	SCIT, SLIT	Narrative	Grass pollen	2
Calderon 201Y	UK	33	RCT	Mixed	1–84 mo	Seasonal allergic RC	SCIT, SLIT	Narrative	Grass pollen	1

Note: AA = allergic asthma, AR = allergic rhinitis, CPG = clinical practice guideline, HDM = house dust mite, NR = not reported, NRS = non-randomized study, RCT = randomized controlled trial, SCIT = subcutaneous immunotherapy, SLIT = sublingual immunotherapy, SR = systematic review, RC = rhinoconjunctivitis.

†Authors report that 28 publications were included. Unclear if this represents the number of unique RCTs.

‡Authors report that 142 articles were included. Unclear if this represents the number of unique RCTs.

§Authors report that 31 articles were included. Unclear if this represents the number of unique RCTs.

¶Three consecutive grass pollen seasons.

Efficacy

Allergic asthma

Three systematic reviews assessed the efficacy of allergen immunotherapy among patients with allergic asthma (children and adults; Exhibit 4) (6, 18, 24). Of these, two involved comparison between SCIT and placebo (6, 18), and one involved comparison between SLIT and placebo (24). The reviews by Abramson and colleagues (6) and Lu and colleagues (18) included only trials involving participants with allergic asthma, while Tao and colleagues included trials that assessed efficacy among participants with allergic asthma with or without allergic rhinitis and/or allergic conjunctivitis (24).

Exhibit 4: Efficacy of subcutaneous and sublingual immunotherapy among participants with allergic asthma

Unadjusted SMD (95% CI); I^2 ; k										
Author, year	Population	Included allergens	Comparison	TCS	Symptom score	Medication score	Disease-specific QoL	Adherence*	AMSTAR	Search date
Tao 2013	AA, with or without AR and/or conjunctivitis	HDM, grass, birch	SLIT v. placebo	—	-0.74 (-1.26 to -0.22); 91%; NR	-0.78 (-1.45 to -0.11); 93%; NR	—	—	6	March 2012
Abramson 2010	AA	HDM, pollen, dander, mould, latex	SCIT v. placebo	—	-0.59 (-0.83, -0.35), 73%; 34	—	—	—	7	August 2005
Lu 2015	AA	HDM	SCIT v. placebo	—	-0.94 (-1.58 to -0.29); 92%; 13	—	—	—	7	February 2013

Note: AA = allergic asthma, AR = allergic rhinitis, HDM = house dust mite, k = number of included studies, QoL = quality of life, SCIT = subcutaneous immunotherapy, SLIT = sublingual immunotherapy, SMD = standard mean difference, TCS = total combined symptom–medication score.
 *Treatment adherence/discontinuation, not discontinuation due to adverse events.

No data were available for total combined symptom–medication score, disease-specific quality of life, or medication adherence. Only one systematic review reported medication use among participants with allergic asthma (24). In this review, the use of asthma medication was significantly lower among participants assigned to SLIT than among those assigned to placebo. It was unclear how many systematic reviews contributed data to this score, and there was high heterogeneity between the trials ($I^2 = 93\%$).

All 3 systematic reviews reported symptom scores among participants with allergic asthma. In each review, participants assigned to either SCIT or SLIT had significantly improved symptoms relative to those assigned to placebo. The number of studies that contributed data to the review by Tao and colleagues (24) was not reported. In total, 34 and 13 trials contributed data to the effect estimates by Abramson and colleagues (6) and Lu and colleagues (18), respectively; the difference in number of included trials is likely because of the number of allergens included in each review. Both systematic

reviews reported high heterogeneity among the included trials for this outcome.

One additional study narratively assessed the efficacy of SCIT versus placebo and SLIT versus placebo (10).

One systematic review (6) reported on SCIT compared with inhaled steroid (budesonide). One trial was included in this comparison, in which the use of budesonide resulted in "...faster and more striking improvement during the first few months as compared to immunotherapy [SCIT], with an even more rapid decline in benefits on cessation of budesonide. Immunotherapy on the other hand, resulted in slow but steady improvement which did not decline as rapidly as budesonide on cessation." Whether the difference in symptom scores was statistically significant was not reported.

Allergic rhinitis

Four systematic reviews provided pooled effect estimates for the comparison of SLIT and placebo (12, 13, 20, 22), and 2 systematic reviews compared SCIT and placebo (13, 20) (Exhibit 5). Two systematic reviews provided a comparison between SCIT and SLIT (13, 20). An additional 5 reviews narratively assessed the efficacy of SLIT or SCIT in this population (9, 10, 17, 19, 21). There was wide variation in quality among the systematic reviews that provided pooled effect estimates, with AMSTAR scores ranging from 3 to 10. The literature search of the most recent systematic review was conducted in 2013 (month not reported).

Among the systematic reviews that compared SLIT with placebo, two assessed total combined symptom–medication scores (12, 20); both reported significant improvement among participants taking SLIT relative to those taking placebo. Two systematic reviews assessed symptom scores and medication scores (20, 22): both reported significant improvement among patients taking SLIT for each outcome, with moderate to high heterogeneity for both estimates (Exhibit 5). One systematic review assessed disease-specific quality of life, with a significant improvement reported among participants taking SLIT. One study assessed discontinuation among participants taking either Oralair or Grazax (13). Both SLIT products were associated with a significant increase in discontinuations compared with placebo. One systematic review performed an indirect comparison between SLIT products (Oralair and Grazax; Exhibit 5). Dranitsaris and colleagues reported that Oralair was associated with a significant improvement in symptom scores relative to Grazax (SMD – 0.18, 95% CI –0.32 to –0.04).

Two systematic reviews reported pooled effect estimates for SCIT versus placebo (13, 20). Meadows and colleagues (20) reported a significant improvement in total combined symptom–medication score, medication score, and disease-specific quality of life among participants taking SCIT relative to those taking placebo. Both Dranitsaris and colleagues (13) and Meadows and colleagues (20) reported a significant improvement in symptom score among participants taking SCIT relative to those taking placebo. Dranitsaris and colleagues (13) reported significantly more discontinuations among participants taking SCIT than among those taking placebo (RR 3.16, 95% CI 1.40 to 7.10).

Two systematic reviews assessed the efficacy of SCIT versus SLIT, both using indirect treatment comparisons. Dranitsaris and colleagues (13) compared symptom scores among participants taking Oralair (SLIT) with those taking SCIT, and reported a significant improvement among participants

taking Oralair. In contrast, Meadows and colleagues (20) reported a significant improvement in symptom scores among participants taking SCIT relative to those taking SLIT. Meadows and colleagues also reported significant improvements in medication scores in favour of SCIT, with no significant difference in disease-specific quality of life between SCIT and placebo.

Exhibit 5: Efficacy of subcutaneous and sublingual immunotherapy among participants with allergic rhinitis

Author, year	Population	Allergens	Comparison	Unadjusted SMD (95% CI); I^2 ; k							Search date
				TCS	Symptom score	Medication score	Disease-specific QoL	Adherence*	AMSTAR		
SLIT v. placebo											
Devillier 2014	Allergic RC	Grass, tree or ragweed pollen	SLIT v. placebo	Hedges' g: -0.31 (-0.39, -0.22); NR; 11	—	—	—	—	5	2013; month NR	
Dranitsaris 2014	AR	Grass pollen	Oralair (SLIT) v. placebo	—	—	—	—	RR 4.88 (2.41, 9.79); 6 trial arms	3	December 2012	
Dranitsaris 2014	AR	Grass pollen	Grazax (SLIT) v. placebo	—	—	—	—	RR 1.90 (1.21, 3.00); 8 trial arms	3	December 2012	
Meadows 2013	AR with or without AA	Grass, tree or ragweed pollen, <i>Alternaria</i> , <i>Parietaria</i>	SLIT v. placebo	-0.40 (-0.55, -0.25); 39%; 6	-0.33 (-0.42, -0.25); 42%; 42	-0.27 (-0.37, -0.17); 49%; 35	-0.37 (-0.52, -0.22); 59%; 7	—	10	April 2011	
Radulovic 2010	AR	<i>Parietaria</i> , tree or ragweed pollen, HDM, cat	SLIT v. placebo	—	-0.49 (-0.64, -0.34); 81%; 49	-0.32 (-0.43, -0.21); 50%; 38	—	—	10	August 2009	
SLIT v. SLIT											
Dranitsaris 2014	AR	Grass pollen	Oralair v. Grazax (SLIT v. SLIT; indirect)	—	-0.18 (-0.32, -0.04); 7 trial arms	—	—	—	3	December 2012	
SCIT v. placebo											
Dranitsaris 2014	AR	Grass pollen	SCIT v. placebo (indirect)	—	-0.30 (-0.39, -0.20); 7 trial arms	—	—	RR 3.16 (1.40, 7.10); 7 trial arms	3	December 2012	
Meadows 2013	AR with or without AA	Grass, tree or ragweed pollen, <i>Alternaria</i> , <i>Parietaria</i>	SCIT v. placebo	-0.48 (-0.67, -0.29); 22%; 8	-0.65 (-0.85, -0.45); 57%; 17	-0.55 (-0.75, -0.34); 57%; 16	MD: -0.74 (-0.92, -0.56); 0%; 8	—	10	April 2011	

Unadjusted SMD (95% CI); I^2 ; k										
Author, year	Population	Allergens	Comparison	TCS	Symptom score	Medication score	Disease-specific QoL	Adherence*	AMSTAR	Search date
SCIT v. SLIT										
Dranitsaris 2014	AR	Grass pollen	Oralair v. SCIT (indirect)	—	-0.21 (-0.36, -0.07); 7 trial arms; favours Oralair	—	—	—	3	December 2012
Meadows 2013	AR with or without AA	Grass, tree or ragweed pollen, <i>Alternaria</i> , <i>Parietaria</i>	SCIT v. SLIT (indirect)	—	SSD: 0.35 (0.13, 0.59) favours SCIT; SCIT: 17 trials, SLIT 42 trials	SSD: 0.27 (0.03, 0.53) favours SCIT; SCIT: 16 trials, SLIT 35 trials	SSD: -0.52 (-0.07, 1.04) SCIT: 8 trials, SLIT 4 trials	—	10	April 2011
Note: AA = allergic asthma, AR = allergic rhinitis, QoL = quality of life, k = number of systematic reviews, RC = rhinoconjunctivitis, RR = relative risk, SCIT = subcutaneous immunotherapy, SLIT = sublingual immunotherapy, SSD = standardized score difference, TCS = total combined symptom–medication score. *Treatment discontinuation, not discontinuation due to adverse events.										

Safety

Data were collected for each outcome defined in the PICO statement (Exhibit 1); however, data were limited for local and systemic reactions. Data for anaphylaxis and death are summarized below.

Allergic asthma

SCIT

Of the three systematic reviews that involved SCIT, anaphylaxis or the use of epinephrine was assessed in two reviews (6, 10) (Exhibit 6). Abramson and colleagues estimated the incidence of near-fatal reactions (anaphylaxis) to be 1 per 1 million injections, with a relative risk of a systemic reaction (includes anaphylaxis, asthma, rhinitis or urticaria) of 2.45 (95% CI 1.91 to 3.13) in the SCIT group. Calderon and colleagues (10) reported the occurrence of three reactions that required the use of epinephrine in the SCIT group.

Abramson and colleagues (6) estimated the incidence of fatal reactions to be 1 per 2.5 million injections; however, data were not provided to support this estimate.

SLIT

Of the two systematic reviews that assessed the safety of SLIT, neither reported the occurrence of anaphylaxis. Calderon and colleagues (10) reported that one patient in the placebo group experience an exacerbation of asthma, while Tao and colleagues (24) reported that three patients from one trial experienced severe asthma. Death was not assessed in the systematic review by Tao and colleagues (24), and no deaths were reported in the systematic review by Calderon and colleagues (10).

Exhibit 6: Anaphylaxis and death reported in mixed populations (adults and children/adolescents) with allergic asthma

Study, year	Intervention	Anaphylaxis	Anaphylaxis or epinephrine reported?	Death	Death reported?
SCIT					
Calderon 2013	SCIT v. placebo	“Several serious TEAEs (some of which required epinephrine) were reported. Pichler et al ⁵⁶ mentioned use but did not state whether this concerned an active treatment or placebo group participant. The 4 incidents reported by Bousquet et al ²⁵ (3 of which required epinephrine) all concerned the active treatment group during the rush up dosing phase”	Yes	Not reported	Not assessed
Lu 2015	SCIT v. placebo	Not reported	Not assessed	Not reported	Not assessed

Abramson 2010	SCIT v. placebo	"Systemic adverse reactions were reported by 32 studies. Systemic reactions were defined as any of anaphylaxis, asthma, rhinitis or urticaria, or any combination of these. The pooled relative risk was 2.45 (95% CI 1.91 to 3.13) in the 26 reporting reactions per patient and this was relatively homogeneous ($I^2 = 27\%$)." Incidence of near-fatal reactions estimated to be 1 per 1 million reactions	Yes	Incidence of fatal reactions estimated to be 1 per 2.5 million	No
SLIT					
Calderon 2013	SLIT v. placebo	"The only serious adverse event (AE) reported was a severe exacerbation of asthma in 1 patient in the placebo group in the study by Pham-Thi et al. ⁵⁵ "	No	"The only serious adverse event (AE) reported was a severe exacerbation of asthma in 1 patient in the placebo group in the study by Pham-Thi et al. ⁵⁵ "	No
Tao 2014	SLIT v. placebo	"The main adverse reactions in our analysis were mild local reactions, such as mouth and/or throat itchiness, redness and swelling. The risk of adverse effects found in our meta-analysis was RR 2.23 (95% CI, 1.17 to 4.24; P = 0.01) (Fig. 9). However, Tari et al. reported that severe asthma occurred in three patients attributing to the side effects of SLIT (22)."	No	Not reported	Not assessed
Note: CI = confidence interval, RR = relative risk, SCIT = subcutaneous immunotherapy, SLIT = sublingual immunotherapy, TEAE = treatment-emergent adverse event.					

Allergic rhinitis

SCIT

Five systematic reviews that assessed SCIT reported either anaphylaxis or death among participants with allergic rhinitis (9, 10, 17, 20, 21) (Exhibit 7). Of these, anaphylaxis or epinephrine use was reported in the SCIT group in all five systemic reviews; only one systematic review reported anaphylaxis in a participant receiving placebo (20).

Death was assessed in one systematic review, with no deaths reported (17). One systematic review reported that reactions were rare but associated with significant morbidity/mortality; however, no data were provided to support this statement (21).

SLIT

Seven systematic reviews that assessed SLIT reported either anaphylaxis or death among participants with allergic rhinitis (8-10, 12, 17, 19, 20, 22). One systematic review reported the safety of SLIT drops and tablets separately (9).

Anaphylaxis was assessed in seven systematic reviews (8-10, 17, 19, 20, 22). Of these, no anaphylactic reactions were reported in four reviews (9, 10, 17, 22). Two reviews reported the occurrence of anaphylaxis (19, 20). Meadows and colleagues (20) reported that anaphylaxis had occurred in four patients in the SLIT group of two trials, with no events in the placebo group. Manzotti and colleagues (19) reported that anaphylactic reactions had occurred in patients given a maintenance dose of Grazax as their first dose. One systematic review (8) reported that one patient in the placebo group and one patient receiving an allergen extract had received epinephrine following an adverse event.

Death was assessed in three systematic reviews (8, 9, 17). No deaths were reported in two systematic reviews (9, 17). CADTH reported that three deaths occurred in three trials, all in the SLIT group (8); however, the authors comment that none were considered by the manufacturer to be related to treatment.

The authors state that ““In study GT-08 (first year), a 31-year-old male participant in the PPAE treatment group was diagnosed with subarachnoid haematoma/ subarachnoid haemorrhage and later died. In study P05238, a 28-year-old male patient in the PPAE group suffered a multiple drug overdose. In study P08067, a 42-year-old male patient who had been treated with PPAE completed the study and had reported no adverse events during the study. He later died. He had been off the study drug for a month. The cause of death was reported as unknown.”

Exhibit 7: Anaphylaxis and death reported in mixed populations (adults and children/adolescents) with allergic rhinitis

Study, year	Intervention	Anaphylaxis	Anaphylaxis or epinephrine reported	Death	Death reported
SCIT					
Calderon 2010	SCIT v. placebo	"All studies reported a higher proportion of adverse events (AEs) in SIT groups than in placebo groups. Systemic AEs requiring administration of subcutaneous adrenaline were observed (17, 21)." (both were in SCIT group)	Yes	Not reported	Not assessed
Calderon 2013	SCIT v. placebo	"The 2 earliest publications ^{23,36} each featured 1 anaphylactic reaction caused by SCIT. More recent trials did not observe anaphylactic reactions."	Yes	Not reported	Not assessed
Meadows 2013	SCIT v. placebo	"Post-injection anaphylaxis was reported in only one small trial ¹⁵⁹ (total n=76) but was considerably more frequent following active treatment, occurring in approximately 10 of 39 patients (compared with 1 of 37 receiving placebo); 8 of the 10 patients were	Yes	Not reported	Not assessed

		treated with adrenaline"			
Lin 2013	SCIT v. placebo	"Thirteen anaphylactic reactions were reported in four trials" None reported in control group.	Yes	"No deaths were reported"	No
Purkey 2012	SCIT v. placebo	"1 episode of anaphylaxis consisting of asthma and pruritus of the ear canal and oropharynx that required administration of epinephrine and oral corticosteroids" "In the patient who experienced anaphylaxis, symptoms developed 1 minute after administration of the 61st dose of treatment. Administration of subcutaneous epinephrine, intravenous methylprednisone, and nebulized salbutamol resulted in rapid resolution of symptoms. SCIT was discontinued in this patient"	Yes	"Local and systemic reactions (rare but with significant morbidity/mortality if they occur)." [Data not provided to support this statement]	Unclear
SLIT					
Devillier 2014	SLIT v. placebo	Not reported	Not assessed	Not reported	Not assessed
CADTH 2014	SLIT v. placebo	"In studies P05238, P05239, and P08067, it was mentioned that no participants experienced anaphylactic shock, and in studies GT-02, GT-07, GT-08, GT-12, and GT-14, there was no specific mention of anaphylactic shock. No incidence of anaphylaxis was reported in GT-02, GT-07, GT-08, and GT-12. In study P05238, one participant in the PPAE group received epinephrine due to an adverse event that occurred following the first administration of the study drug, and one placebo-treated patient used epinephrine in response to an anxiety attack, which the manufacturer stated was not an indicated (or medically appropriate) use for this medication."	Yes	"There were no deaths reported in studies GT-07, GT-02, GT-14, GT-12, and P05239. In studies GT-08, P05238, and P08067, one death was reported in each study, as described below, but none were considered by the manufacturer to be treatment related."	Yes

Calderon 2013	SLIT v. placebo	"Bahceciler et al. ²² did not observe any AEs of note with a maintenance dose of 8 mg of "Der p" allergens in children and adolescents. In contrast, de Bot et al. ³¹ studied a maintenance dose of 2 mg of Der p 1 allergen and reported that 96% of both active and placebo group patients experienced TEAEs (including a high proportion of nonlocal AEs). Nevertheless, no immunotherapy-dependent serious AEs were reported in any of the active groups"	No	Not reported	Not assessed
Lin 2013	SLIT v. placebo	"...no life-threatening reactions, anaphylaxis, or deaths were reported in these trials."	No	"...no life-threatening reactions, anaphylaxis, or deaths were reported in these trials."	No
Meadows 2013	SLIT v. placebo	"Anaphylaxis was reported in two trials ^{192,195} and occurred in 4 of 427 patients receiving active treatment and in none of 282 patients receiving placebo."	Yes	Not reported	Not assessed
Manzotti 2013	SLIT (Grazax or Oralair) v. placebo	"However, it seems not advisable to use Grazax, that starts directly with the maintenance dose, in subjects with an history of systemic reactions to SCIT, because anaphylactic reactions at the first dose were reported in such subjects (21)"	Yes	Not reported	Not assessed
Radulovic 2010	SLIT v. placebo	" None of the studies reported anaphylaxis."	No	Not reported	Not assessed
Calderon 2010	SLIT drops v. placebo	"...no life-threatening AEs or fatalities were described."	No	"...no life-threatening AEs or fatalities were described."	No
Calderon 2010	SLIT tablets v. placebo	"All seven studies reported on safety in detail; the principal AEs were mild, local and transient and none required adrenaline administration. Treatment-related SAEs were not observed."	No	"All seven studies reported on safety in detail; the principal AEs were mild, local and transient and none required adrenaline administration. Treatment-related SAEs were not observed."	No
Note: CI = confidence interval, NA = not assessed, NR = not reported, SCIT = subcutaneous immunotherapy, SLIT = sublingual immunotherapy, TEAE = treatment-emergent adverse event.					

Subgroup analyses

Efficacy among adults with allergic asthma or allergic rhinitis

One systematic review (24) provided a pooled effect estimate of SLIT for the outcomes of interest among adults with allergic asthma (Exhibit 8). Tao and colleagues (24) reported a significant improvement in symptom scores among participants taking SLIT relative to those taking placebo.

There was no significant difference between groups for medication scores.

No data were available for the efficacy of SCIT among adults with allergic asthma.

Two systematic reviews assessed the efficacy of SLIT among adults with allergic rhinitis (20, 22). Meadows and colleagues (20) reported a significant improvement in total combined symptom–medication score, symptom score, medication score, and disease-specific quality of life among participants in the SLIT group relative to those in the placebo group. Radulovic and colleagues (22) reported a significant improvement in symptom scores among participants in the SLIT group relative to those in the placebo group.

One systematic review assessed the efficacy of SCIT among adults with allergic rhinitis. Meadows and colleagues (20) reported significantly better symptom and medication scores among participants in the SLIT group relative to those in the placebo group.

Exhibit 8: Efficacy of subcutaneous and sublingual immunotherapy among adults with allergic asthma or rhinitis

Author, year	Population	Allergens	Comparison	Unadjusted SMD (95% CI); \hat{P} ; k						Search date
				TCS	Symptom score	Medication score	Disease-specific QoL	Adherence*	AMSTAR	
Allergic asthma										
Tao 2014	AA, with or without AR and/or conjunctivitis	HDM, grass, birch	SLIT v. placebo	–	-0.40 (-0.76, -0.04); 0%; 2	0.00 (-0.36, 0.36); 0%; 2	–	–	6	March 2012
Allergic rhinitis										
Meadows 2013	AR with or without AA	Grass, tree or ragweed pollen, fungi, <i>Parietaria</i>	SLIT v. placebo	-0.44 (-0.62, -0.27); 41%; 5	-0.38 (-0.49, -0.27); 49%; 33	-0.35 (-0.47, -0.23); 45%; 27	-0.37 (-0.52, -0.22); NR; 6	–	10	April 2011
Radulovic 2010	AR	<i>Parietaria</i> , tree or ragweed pollen, HDM, cat	SLIT v. placebo	–	-0.44 (-0.56, -0.31); 58%; 34	–	–	–	10	August 2009
Meadows 2013	AR with or without AA	Grass, tree or ragweed pollen, fungi, <i>Parietaria</i>	SCIT v. placebo	–	-0.68 (-0.89, -0.47); 59%; 16	-0.53 (-0.75, -0.32); 58%; 15	–	–	10	April 2011
Note: AA = allergic asthma, AR = allergic rhinitis, HDM = house dust mite, k = number of systematic reviews, QoL = quality of life, SCIT = subcutaneous immunotherapy, SLIT = sublingual immunotherapy, SMD = standard mean difference, TCS = total combined symptom–medication score. *Treatment discontinuation, not discontinuation due to adverse events.										

Safety among adults with allergic asthma or allergic rhinitis

None of the included systematic reviews assessed anaphylaxis or death among adults with allergic asthma (Exhibit 9).

One study assessed anaphylaxis and death among adults with allergic rhinitis. In their 2014 report, the Canadian Agency for Drugs and Technologies in Health (CADTH) reported that five participants in the SLIT group experienced anaphylaxis, 3 of whom were treated with epinephrine (8). There were no anaphylactic reactions reported in the placebo group.

CADTH reported that three deaths occurred in the SLIT group of three trials involving adults with allergic rhinitis (8); however, none were considered by the manufacturer to be related to treatment.

No systematic reviews assessed anaphylaxis or death among adults with allergic rhinitis who received SCIT.

Exhibit 9: Anaphylaxis and death reported among adults with allergic asthma or rhinitis

Study, year	Intervention	Anaphylaxis	Anaphylaxis or epinephrine use?	Death	Death reported?
Allergic asthma					
No studies					
Allergic rhinitis					
CADTH 2014	SLIT v. placebo	"In study GT-14, five participants in the study drug group had anaphylactic reactions that were reported as probably being study drug related. One was considered of moderate severity and the remaining four were considered mild. Three participants were treated with epinephrine. All participants recovered from the event. No anaphylactic reaction was reported for the placebo group."	Yes	"In studies GT-08, P05238, and P08067, one death was reported in each study, as described below, but none were considered by the manufacturer to be treatment related."	Yes
Note: CI = confidence interval, NA = not assessed, NR = not reported, SCIT = subcutaneous immunotherapy, SLIT = sublingual immunotherapy, TEAE = treatment-emergent adverse event.					

Efficacy among children with allergic asthma or allergic rhinitis

One systematic review assessed the efficacy of SLIT among children with allergic asthma (24) (Exhibit 10). Tao and colleagues (24) reported significant improvements in symptom and medication scores among participants taking SLIT compared with those taking placebo. Total combined symptom–medication score, disease-specific quality of life, and adherence were not assessed.

Two reviews assessed the efficacy of SLIT among children with allergic rhinitis (20, 22). Meadows and colleagues (20) and Radulovic and colleagues (22) both reported a significant improvement in symptom scores among children taking SLIT compared with those taking placebo. Both reviews reported no significant difference between groups for medication scores. Meadows and colleagues (20) reported a significant improvement in disease-specific quality of life among children in the SLIT group compared with those in the placebo group.

None of the included systematic reviews assessed the efficacy of SCIT in children with allergic asthma or allergic rhinitis. Two systematic reviews provided narrative summaries of the use of SCIT in this population (10, 16).

Exhibit 10: Efficacy of subcutaneous and sublingual immunotherapy among children with allergic asthma or rhinitis

Author, year	Population	Allergens	Comparison	Unadjusted SMD (95% CI); I^2 ; k						Search date
				TCS	Symptom score	Medication score	Disease-specific QoL	Adherence*	AMSTAR	
Allergic asthma										
Tao 2014	AA, with or without AR and/or conjunctivitis	HDM, grass, birch	SLIT v. placebo	–	-0.87 (-1.54, -0.21); 92%; 12	-1.10 (-2.06, -0.14); 94%; 8	–	–	6	March 2012
Allergic rhinitis										
Meadows 2013	AR with or without AA	Grass, tree or ragweed pollen, <i>Alternaria</i> and <i>Parietaria</i> species	SLIT v. placebo	–	-0.24 (-0.35, -0.13); 0%; 9	-0.08 (-0.25, 0.08); 43%; 8	-0.31 (-0.57, -0.04); NA; 1	–	10	April 2011
Radulovic 2010	AR	<i>Parietaria</i> , tree or ragweed pollen, HDM, cat	SLIT v. placebo	–	-0.52 (-0.94, -0.10); 92%; 15	-0.16 (-0.32, 0.00); 36%; 12	–	–	10	August 2009
Note: AA = allergic asthma, AR = allergic rhinitis, HDM = house dust mite, SCIT = subcutaneous immunotherapy, SLIT = sublingual immunotherapy, NR = not reported, SMD = standard mean difference, *Treatment discontinuation, not discontinuation due to adverse events.										

Safety

None of the included systematic reviews assessed anaphylaxis or death among children with allergic asthma (Exhibit 11).

Four systematic reviews assessed the safety of SLIT among children with allergic rhinitis (8, 16, 17, 20). Of these, two reviews reported that no anaphylaxis occurred among the included trials (16, 17), while three reviews reported that epinephrine had been administered to a participant (8, 16, 20). Most participants who required epinephrine were in the SLIT group.

Two systematic reviews assessed deaths among children with allergic rhinitis treated with SLIT (8, 17). No deaths were reported.

One systematic review assessed the safety of SCIT among children with allergic rhinitis (17). There were no reported cases of anaphylaxis or death among children taking SCIT.

Exhibit 11: Anaphylaxis and death reported among children with allergic asthma or rhinitis

Study, year	Intervention	Anaphylaxis	Anaphylaxis or epinephrine use?	Death	Death reported?
Allergic asthma					
No systematic reviews					
Allergic rhinitis					
CADTH 2014	SLIT v. placebo	"In study P05239, three participants received epinephrine. In one participant, it was given for an allergic reaction following the first administration of the PPAE under the supervision of the investigator. In the other two cases, one participant in the PPAE group had viral pharyngitis and one participant in the placebo group had asthma exacerbation"	Yes	"There were no deaths reported in studies GT-07, GT-02, GT-14, <u>GT-12</u> , and <u>P05239</u> ." [GT-12 and P05239 involve children]	No
Lin 2013 ID268	SLIT v. placebo	"No life threatening systemic reactions or anaphylaxis were reported in these trials"	No	"No deaths were reported"	No
Larenas-Linneman 2011	SLIT v. placebo	"No anaphylaxis was found among 2469 treated children" "...epinephrine was administered to 3 children (2 in the active group and 1 in the placebo group), with only one administration due to a reaction to the tablet: this patient experienced lip angioedema, slight dysphagia, and intermittent cough with no other symptoms immediately after the first dose; epinephrine administration resolved this moderate local reaction (as judged by the investigator) and the patient discontinued participation in the trial."	Yes	Not reported	Not assessed
Meadows 2013	SLIT v. placebo	Only two trials ^{189,192} (total n=782) reported on adrenaline use. In each study, one instance of an AE in response to SLIT administration was treated with adrenaline. In both cases, the patients were receiving active treatment. [Reference 189 involves children only]	Yes	Not reported	Not assessed
Lin 2013	SCIT v. placebo	"There were no reports of anaphylaxis"	No	"There were no reports of... deaths"	No
Lin 2013	SCIT v. SLIT (direct comparison)	"Among these three studies with a total of 135 patients... . No systemic reactions were reported in patients receiving sublingual immunotherapy. Among patients receiving subcutaneous immunotherapy, four experienced systemic reactions, including 1 anaphylaxis event and 3 patients with moderate – severe respiratory symptoms."	Yes	Not reported	Not assessed
Note: CI = confidence interval, SCIT = subcutaneous immunotherapy, SLIT = sublingual immunotherapy, TEAE = treatment-emergent adverse event.					

Key messages

Children and adults

Allergic asthma (k= 3 SRs)

- SCIT is more effective than placebo for reducing asthma symptom scores (based on 2 SRs).
- SLIT is more effective than placebo for reducing symptom and medication scores (based on 1 RCT).
- Anaphylaxis was reported for SCIT but not SLIT.
- No deaths were reported.

Allergic rhinitis (k = 16 SRs)

- SCIT is more effective than placebo at reducing allergic rhinitis symptom scores (2 SRs), total combined symptom–medication score, and medication scores and at improving disease specific quality of life (1 SR).
- SCIT is associated with more discontinuations than placebo (1 SR).
- SLIT is more effective than placebo at reducing t total combined symptom–medication score, symptom scores, and medication scores (2 SRs) and at improving disease-specific quality of life (1 SR).
- SLIT is associated with more discontinuations than placebo (1 SR).
- Oralair is better than Grazax at reducing symptom scores (1 SR).
- SCIT is more effective than SLIT at improving medication scores (1 SR) and may be better than SLIT at improving symptom scores (1 of 2 SRs). There was no significant difference in disease-specific quality of life (1 SR).
- Anaphylaxis was reported for SCIT by all SRs (k= 6); no deaths were reported. Anaphylaxis was reported in 3 of 9 SRs that assessed SLIT; three deaths were reported in 1 SR in the SLIT group.

Exhibit 12: Summary of efficacy and safety of subcutaneous and sublingual immunotherapy among children and adults

Comparison*	Author, year	Efficacy	Anaphylaxis reported?	AMSTAR score	Search date
Allergic asthma					
SCIT v. placebo	Lu 2015	○●○○○○	Not assessed	7	February 2013
	Abramson 2010	○●○○○○	Yes	7	August 2005
SLIT v. placebo	Tao 2013	○●●○○○	No	6	March 2012
Allergic rhinitis					
SCIT v. placebo	Dranitsaris 2014	○●○○○●	Not assessed	3	December 2012
	Meadows 2013	●●●●○○	Yes	10	April 2011
SLIT v. placebo	Devillier 2014	●○○○○○	Not assessed	5	2013; month NR
	Dranitsaris 2014	○○○○○●	Not assessed	3	December 2012
	Meadows 2013	●●●●○○	Yes	10	April 2011
	Radulovic 2010	○●●○○○	No	10	August 2009
Oralair v. Grazax (SLIT v. SLIT)	Dranitsaris 2014	○●○○○○	Not assessed	3	December 2012
SCIT v. SLIT	Meadows 2013	○●●●●○	Yes	10	April 2011
	Dranitsaris 2014	○●○○○○	Not assessed	3	December 2012
<p>From LEFT to RIGHT, circles represent: total combined symptom–medication score, symptom score, medication score, disease-specific quality of life, adherence/discontinuation</p> <ul style="list-style-type: none"> • A green circle indicates that immunotherapy is significantly better than placebo • A red circle indicates that immunotherapy is significantly worse than placebo • A grey circle indicates that there is no significant difference between the immunotherapy and placebo • A white circle indicates that the outcome was not available for analysis <p>*In cases of immunotherapy v. immunotherapy, significance is reported relative to the first agent listed in the heading.</p>					

Adults**Allergic asthma**

- No systematic reviews were identified that assessed the efficacy or safety of SCIT or SLIT in adults with allergic asthma

Allergic rhinitis (K = 3 SRs)

- SLIT is more effective than placebo at reducing total combined symptom–medication score (1 SR), symptom scores (2 SRs), medication scores (1 SR) and improving disease-specific quality of life (1 SR)
- Five anaphylactic reactions were reported in the SLIT group of one trial (1 SR)
- Three deaths were reported in the SLIT group (1 SR)

Exhibit 13: Summary of efficacy and safety of subcutaneous and sublingual immunotherapy among adults

Comparison	Author, year	Efficacy	Anaphylaxis reported?	AMSTAR score	Search date
Allergic asthma					
SCIT v. placebo	No reviews				
Allergic rhinitis					
SLIT v. placebo	Meadows 2013	●●●●○	Not assessed	10	April 2011
	Radulovic 2010	○●○○○○	Not assessed	10	August 2009
	CADTH 2014	Not reported	Yes	7	June 2014
SCIT v. placebo	Meadows 2013	○●●○○	Not assessed	10	April 2011
<p>From LEFT to RIGHT, circles represent: total combined symptom–medication score, symptom score, medication score, disease-specific quality of life, adherence/discontinuation</p> <ul style="list-style-type: none"> • A green circle indicates that immunotherapy is significantly better than placebo • A red circle indicates that immunotherapy is significantly worse than placebo • A grey circle indicates that there is no significant difference between the immunotherapy and placebo • A white circle indicates that the outcome was not available for analysis <p>In cases of immunotherapy v. immunotherapy, significance is reported relative to the first agent listed in the heading.</p>					

Children

Allergic asthma (k = 1 SR)

- SLIT was more effective than placebo at improving symptom and medication scores
- Anaphylaxis and death were not assessed among children with allergic asthma using SLIT
- No data were available for SCIT among this population.

Allergic rhinitis (k = 5 SRs)

- SLIT was more effective than placebo at improving symptom scores, and there were no significant differences for medication scores (2 SRS).
- Anaphylaxis was reported by 2 systematic reviews in the SLIT group; epinephrine use was reported in one additional systematic review.
- There were no deaths among children in the SLIT group (2 SRs).
- There were no reports of anaphylaxis or death among children receiving SCIT (1 SR).

Exhibit 14: Summary of efficacy and safety of subcutaneous and sublingual immunotherapy among children and adults

Comparison	Author, year	Efficacy	Anaphylaxis reported?	AMSTAR score	Search date
Allergic asthma					
SCIT v. placebo	No reviews				
SLIT v. placebo	Tao 2014	○●●○○	Not assessed	6	March 2012
Allergic rhinitis					
SLIT v. placebo	Meadows 2013	○●●○○	Not assessed	10	April 2011
	Radulovic 2010	○●●○○	Not assessed	10	August 2009
	CADTH 2014	Not reported	Yes	7	June 2014
	Lin 2013	Not reported	No	11	May 2012
	Larenas-Linnemann 2011	Not reported	Yes	5	April 2011
SCIT v. placebo	Lin 2013	Not reported	No	11	May 2012
SCIT v. SLIT	Lin 2013	Not reported	Yes (SCIT)	11	May 2012
<p>From LEFT to RIGHT, circles represent: total combined symptom–medication score, symptom score, medication score, disease-specific quality of life, adherence/discontinuation</p> <ul style="list-style-type: none"> • A green circle indicates that immunotherapy is significantly better than placebo • A red circle indicates that immunotherapy is significantly worse than placebo • A grey circle indicates that there is no significant difference between the immunotherapy and placebo • A white circle indicates that the outcome was not available for analysis <p>In cases of immunotherapy v. immunotherapy, significance is reported relative to the first agent listed in the heading.</p>					

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Appendix 1: Search strategy

Allergens – Immunotherapy - Allergic Rhinitis

Final Strategies

2015 May 31

OVID Multifile

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2015 Week 22>

Search Strategy:

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1  exp Rhinitis, Allergic/ (48188)
2  (allerg* adj1 (rhinitis or rhinoconjunctivitis or rhino-conjunctivitis or rhinitides)).tw,kw. (34378)
3  ((seasonal* or nonseasonal* or non-seasonal* or perennial*) adj1 (rhinitis or rhinoconjunctivitis or rhino-conjunctivitis or rhinitides)).tw,kw. (1925)
4  ("seasonal AR" or "nonseasonal AR" or "non-seasonal AR" or "perennial AR").tw,kw. (391)
5  (allerg* adj1 asthma*).tw,kw. (22947)
6  ((seasonal* or nonseasonal* or non-seasonal* or perennial*) adj1 asthma*).tw,kw. (662)
7  (hay fever* or hayfever* or hay asthma*).tw,kw. (6856)
8  (pollen* adj2 allerg*).tw,kw. (9641)
9  (pollen* adj2 (rhinitis or rhinoconjunctivitis or rhino-conjunctivitis or rhinitides)).tw,kw. (698)
10 pollinos#.tw,kw. (3923)
11 summer bronchit#.tw,kw. (1)
12 ((animal$1 or dander or cat$1 or dog$1 or pet$1) adj3 (allerg* or hypersensitiv*).tw,kw. (7315)
13 ((dust$1 or fungus or fungi or mite$1 or mold* or mould* or insect or insects) adj3 (allerg* or hypersensitiv*).tw,kw. (14490)
14 ((ambrosia or grass$2 or plant$1 or weed$1 or ragweed$1 or tree or trees) adj3 (allerg* or hypersensitiv*).tw,kw. (8497)
15 (dander/ or cats/ or dogs/ or pets/ or exp Dust/ or exp Mites/ or exp Fungi/ or exp Poaceae/ or Plant Weeds/ or Trees/ or Ambrosia/ or "Insect Bites and Stings"/) and exp Hypersensitivity/ (52636)
16 or/1-15 (135804)
17 exp Desensitization, Immunologic/ (25434)
18 desensiti#ation*.tw,kw. (44862)
19 (allergen* adj2 (desensiti* or immunotherap* or immuno-therap* or immune therap* or (immunolog* adj therap*))).tw,kw. (5432)
20 (hyposensiti#ation* adj2 therap*).tw,kw. (352)
21 ((sublingual* or sub-lingual* or subcutaneous* or sub-cutaneous*) adj2 (desensiti* or immunotherap* or immuno-therap* or immune therap* or (immunolog* adj therap*))).tw,kw. (2948)
22 (SLIT or SCIT).tw,kw. (28744)
23 Oralair.tw,kw. (93)
24 (pollen$1 adj2 extract$1).tw,kw. (3487)
25 exp Plant Extracts/ and exp Pollen/ (1941)
26 (pollen* adj2 (desensiti* or immunotherap* or immuno-therap* or immune therap* or (immunolog* adj therap*))).tw,kw. (757)
27 (Grastek or Grazax).tw,kw. (269)
28 (grass* adj2 (desensiti* or immunotherap* or immuno-therap* or immune therap* or (immunolog* adj therap*) or vaccin*).tw,kw. (671)
29 Ragwitek.tw,kw. (5)
30 (pollinex or parietaria judaica pollen*).tw,kw. (332)
31 (allergen* adj2 (extract$1 or serum$1)).tw,kw. (5476)
32 or/17-31 (97598)
33 Allergens/ (75318)
34 allergen*.tw,kw. (104332)
35 33 or 34 (126289)
36 exp Immunotherapy/ (350999)
37 (immunotherap* or immuno-therap* or immune therap* or (immunolog* adj therap*)).tw,kw. (126854)
38 36 or 37 (398154)
39 administration, sublingual/ (6517)
40 exp Injections, Subcutaneous/ (119776)
41 (sublingual* or sub-lingual* or subcutaneous* or sub-cutaneous*).tw,kw. (21657)
42 or/39-41 (143330)
43 35 and 38 and 42 (3106)
44 32 or 43 (97811)
45 16 and 44 (15146)
46 limit 45 to systematic reviews [Limit not valid in Embase; records were retained] (8924)
47 meta analysis.pt. (56061)

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48 exp meta-analysis as topic/ (34057)
 49 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative
 overview* or research integration or research overview* or collaborative review*).kw,tw. (182897)
 50 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence
 adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology
 assessment* or HTA or HTAs).kw,tw. (217293)
 51 exp Technology assessment, biomedical/ (21003)
 52 ((network* or network-based) adj (MA or MAs)).kw,tw. (10)
 53 (NMA or NMAs or MTC or MTCs or MAIC or MAICs).kw,tw. (10577)
 54 ((indirect* or mixed) adj2 compar*).kw,tw. (7249)
 55 (multi* adj treatment* adj2 compar*).kw,tw. (315)
 56 (cochrane or health technology assessment or evidence report).jw. (26825)
 57 or/47-56 (418429)
 58 45 and 57 (426)
 59 46 or 58 (8993)
 60 exp Animals/ not (exp Animals/ and Humans/) (8148068)
 61 59 not 60 (8217)
 62 (comment or editorial or interview or news).pt. (1543141)
 63 (letter not (letter and randomized controlled trial)).pt. (1758791)
 64 61 not (62 or 63) (8026)
 65 limit 64 to yr="2010-current" (3249)
 66 65 use prmz (136) [MEDLINE RECORDS]
 67 exp allergic rhinitis/ (48188)
 68 (allerg* adj1 (rhinitis or rhinoconjunctivitis or rhino-conjunctivitis or rhinitides)).tw,kw. (34378)
 69 ((seasonal* or nonseasonal* or non-seasonal* or perennial*) adj1 (rhinitis or rhinoconjunctivitis or rhino-conjunctivitis
 or rhinitides)).tw,kw. (1925)
 70 ("seasonal AR" or "nonseasonal AR" or "non-seasonal AR" or "perennial AR").tw,kw. (391)
 71 (allerg* adj1 asthma*).tw,kw. (22947)
 72 ((seasonal* or nonseasonal* or non-seasonal* or perennial*) adj1 asthma*).tw,kw. (662)
 73 (hay fever* or hayfever* or hay asthma*).tw,kw. (6856)
 74 pollen allergy/ (17944)
 75 (pollen* adj2 allerg*).tw,kw. (9641)
 76 (pollen* adj2 (rhinitis or rhinoconjunctivitis or rhino-conjunctivitis or rhinitides)).tw,kw. (698)
 77 pollinos#s.tw,kw. (3923)
 78 summer bronchit#s.tw,kw. (1)
 79 house dust allergy/ (1740)
 80 ((animal\$1 or dander or cat\$1 or dog\$1 or pet\$1) adj3 (allerg* or hypersensitiv*)).tw,kw. (7315)
 81 ((dust\$1 or fungus or fungi or mite\$1 or mold* or mould* or insect\$1) adj3 (allerg* or hypersensitiv*)).tw,kw. (14490)
 82 ((ambrosia or grass\$2 or plant\$1 or weed\$1 or ragweed\$1 or tree or trees) adj3 (allerg* or hypersensitiv*)).tw,kw.
 (8497)
 83 (dander/ or exp cat/ or exp dog/ or pet animal/ or house dust/ or mould/ or exp Poaceae/ or tree/ or weed/ or exp
 ragweed/ or exp insect sting/ and allergy/ (8048)
 84 or/67-83 (109102)
 85 desensitization/ (16638)
 86 desensiti#ation*.tw,kw. (44862)
 87 (allergen* adj2 (desensiti* or immunotherap* or immuno-therap* or immune therap* or (immunologic* adj
 therap*))).tw,kw. (5432)
 88 (hyposensiti#ation* adj2 therap*).tw,kw. (352)
 89 ((sublingual* or sub-lingual* or subcutaneous* or sub-cutaneous*) adj2 (desensiti* or immunotherap* or immuno-
 therap* or immune therap* or (immunologic* adj therap*))).tw,kw. (2948)
 90 (SLIT or SCIT).tw,kw. (28744)
 91 Oralair.tw,kw. (93)
 92 pollen extract/ (1246)
 93 (pollen\$1 adj2 extract\$1).tw,kw. (3487)
 94 exp plant extract/ (155647)
 95 (pollen* adj2 (desensiti* or immunotherap* or immuno-therap* or immune therap* or (immunologic* adj
 therap*))).tw,kw. (757)
 96 (Grastek or Grazax).tw,kw. (269)
 97 grass pollen vaccine/ (213)
 98 (grass* adj2 (desensiti* or immunotherap* or immuno-therap* or immune therap* or (immunologic* adj therap*) or
 vaccin*).tw,kw. (671)
 99 Ragwitek.tw,kw. (5)
 100 ragweed pollen extract/ (19)
 101 (pollinex or parietaria judaica pollen*).tw,kw. (332)
 102 (allergen* adj2 (extract\$1 or serum\$1)).tw,kw. (5476)
 103 or/85-102 (246356)
 104 exp allergen/ (52507)
 105 allergen*.tw,kw. (104332)

106 104 or 105 (117955)
 107 exp immunotherapy/ (350999)
 108 (immunotherap* or immuno-therap* or immune therap* or (immunologic* adj therap*)),tw,kw. (126811)
 109 107 or 108 (398115)
 110 sublingual drug administration/ (6517)
 111 subcutaneous drug administration/ (84279)
 112 (sc or li).fs. (247653)
 113 (sublingual* or sub-lingual* or subcutaneous * or sub-cutaneous*).tw,kw. (21657)
 114 or/110-113 (353044)
 115 106 and 109 and 114 (3578)
 116 103 or 115 (246879)
 117 84 and 116 (13135)
 118 meta-analysis/ (149714)
 119 "systematic review"/ (89739)
 120 "meta analysis (topic)"/ (19797)
 121 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).kw,tw. (182897)
 122 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).kw,tw. (217293)
 123 biomedical technology assessment/ (19899)
 124 ((network* or network-based) adj (MA or MAs)).kw,tw. (10)
 125 (NMA or NMAs or MTC or MTCs or MAIC or MAICs).kw,tw. (10577)
 126 ((indirect* or mixed) adj2 compar*).kw,tw. (7249)
 127 (multi* adj treatment* adj2 compar*).kw,tw. (315)
 128 (cochrane or health technology assessment or evidence report).jw. (26825)
 129 or/118-128 (453477)
 130 117 and 129 (486)
 131 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (38332640)
 132 exp humans/ or exp human experimentation/ or exp human experiment/ (29815388)
 133 131 not 132 (8518838)
 134 130 not 133 (485)
 135 editorial.pt. (853366)
 136 letter.pt. not (letter.pt. and randomized controlled trial/) (1754392)
 137 134 not (135 or 136) (475)
 138 limit 137 to yr="2010-current" (300)
 139 138 use emez (204) [EMBASE RECORDS]
 140 66 or 139 (340)
 141 remove duplicates from 140 (244) [UNIQUE RECORDS – BOTH DATABASES]
 142 141 use prmz (126) [UNIQUE RECORDS – MEDLINE]
 143 141 use emez (118) [UNIQUE RECORDS – EMBASE]

Search Name: Allergens Immunotherapy
 Date Run: 31/05/15 10:57:37.135
 Description: Ottawa Heart Institute - 2015 May 31

ID	Search	Hits
#1	[mh "Rhinitis, Allergic"]	2179
#2	(allerg* near/2 (rhinitis or rhinoconjunctivitis or "rhino-conjunctivitis" or rhinitides)):ti,ab,kw	5643
#3	((seasonal* or nonseasonal* or (non next seasonal*) or perennial*) near/2 (rhinitis or rhinoconjunctivitis or "rhino-conjunctivitis" or rhinitides)):ti,ab,kw	4052
#4	("seasonal AR" or "nonseasonal AR" or "non-seasonal AR" or "perennial AR"):ti,ab,kw	73
#5	(allerg* near/2 asthma*):ti,ab,kw	2578
#6	((seasonal* or nonseasonal* or (non next seasonal*) or perennial*) near/2 asthma*):ti,ab,kw	207
#7	((hay next fever*) or hayfever* or (hay next asthma*)):ti,ab,kw	620
#8	(pollen* near/3 allerg*):ti,ab,kw	1131
#9	(pollen* near/3 (rhinitis or rhinoconjunctivitis or "rhino-conjunctivitis" or rhinitides)):ti,ab,kw	765
#10	pollinos*:ti,ab,kw	240
#11	(summer next bronchit*):ti,ab,kw	0
#12	((animal* or dander or cat or cats or dog or dogs or pet or pets) near/4 (allerg* or hypersensitiv*)):ti,ab,kw	486
#13	((dust* or fungus or fungi or mite or mites or mold* or mould* or insect or insects) near/4 (allerg* or hypersensitiv*)):ti,ab,kw	827
#14	((ambrosia or grass* or plant or plants or weed or weeds or ragweed* or tree or trees) near/4 (allerg* or hypersensitiv*)):ti,ab,kw	1054

#15 ([mh "Insect Bites and Stings"] or [mh dander] or [mh cats] or [mh dogs] or [mh pets] or [mh Dust] or [mh Mites] or [mh Fungi] or [mh Poaceae] or [mh "plant weeds"] or [mh trees] or [mh Ambrosia]) and [mh Hypersensitivity] 1045

#16 {or #1-#15} 9388

#17 [mh "Desensitization, Immunologic"] 766

#18 (desensitization* or desensitisation*):ti,ab,kw 2062

#19 (allergen* near/3 (desensiti* or immunotherap* or immuno-therap* or (immune next therap*) or (immunologic* next therap*)):ti,ab,kw 472

#20 (hyposensiti*ation* near/3 therap*):ti,ab,kw 21

#21 ((sublingual* or (sub next lingual*) or subcutaneous* or (sub next cutaneous*)) near/3 (desensiti* or immunotherap* or (immuno next therap*) or (immune next therap*) or (immunologic* next therap*)):ti,ab,kw 870

#22 (SLIT or SCIT):ti,ab,kw 1164

#23 Oralair:ti,ab,kw 7

#24 ((pollen or pollens) near/3 (extract or extracts)):ti,ab,kw 349

#25 [mh "Plant Extracts"] and [mh Pollen] 126

#26 (pollen* near/3 (desensiti* or immunotherap* or (immuno next therap*) or (immune next therap*) or (immunologic* next therap*)):ti,ab,kw 316

#27 (Grastek or Grazax):ti,ab,kw 61

#28 (grass* near/3 (desensiti* or immunotherap* or (immuno next therap*) or (immune next therap*) or (immunologic* next therap*) or vaccin*):ti,ab,kw 284

#29 Ragwitek:ti,ab,kw 0

#30 (pollinex or ("parietaria judaica" next pollen*)):ti,ab,kw 29

#31 (allergen* near/3 (extract* or serum*)):ti,ab,kw 358

#32 {or #17-#31} 4103

#33 [mh Allergens] 1553

#34 allergen*:ti,ab,kw 4223

#35 #33 or #34 4223

#36 [mh Immunotherapy] 6968

#37 (immunotherap* or (immuno next therap*) or (immune next therap*) or (immunologic* next therap*)):ti,ab,kw 4921

#38 #36 or #37 10047

#39 [mh "administration, sublingual"] 765

#40 [mh "Injections, Subcutaneous"] 3548

#41 (sublingual* or (sub next lingual*) or subcutaneous* or (sub next cutaneous*)):ti,ab,kw 14045

#42 {or #39-#41} 14598

#43 #35 and #38 and #42 552

#44 #32 or #43 4114

#45 #16 and #44 Publication Year from 2010 to 2015 619

DSR – 5
DARE – 18
HTA - 6

Appendix 2: Excluded records

1. DeYoung K, Wentzel JL, Schlosser RJ, et al. Systematic review of immunotherapy for chronic rhinosinusitis. *Am J Rhinol Allergy*. 2014; 28:145.
2. Mosges R, Ritter B, Kayoko G, et al. Carbamylated monomeric allergoids as a therapeutic option for sublingual immunotherapy of dust mite- and grass pollen-induced allergic rhinoconjunctivitis: a systematic review of published trials with a meta-analysis of treatment using Lais tablets. *Acta Dermatovenerol Alp Pannonica Adriat*. 2010;19:3.
3. Tsubouri S, Tseretopoulou X, Priftis K, et al., Omalizumab for the treatment of inadequately controlled allergic rhinitis: a systematic review and meta-analysis of randomized clinical trials. *J Allergy Clin Immunol Pract*. 2014;2:332.
4. Aboshady OA, Elghanam KM. Sublingual immunotherapy in allergic rhinitis: efficacy, safety, adherence and guidelines. *Clin Exp Otorhinolaryngol*. 2014;7:241.
5. Alzakar RH, Alsamarai AM. Efficacy of immunotherapy for treatment of allergic asthma in children. *Allergy Asthma Proc*. 2010; 31:324.
6. Ameille J, Didier A, Serrano E, et al. Recommendations for the prevention and management of occupational allergic rhinitis. Societe francaise de medecine du travail. Societe de pneumologie de langue francaise. Societe francaise d'allergologie. Societe francaise d'oto-rhino-laryngologie et de chirurgie de la face et du cou. *Rev Mal Respir*. 2011; 28:940.
7. Baena-Cagnani CE, Larenas-Linnemann D, Teijeiro A, et al. Will sublingual immunotherapy offer benefit for asthma?. *Curr Allergy Asthma Rep*. 2013; 13:571.
8. Bahceciler NN, Cobanoglu N. Subcutaneous versus sublingual immunotherapy for allergic rhinitis and/or asthma. *Immunotherapy*. 2011; 3:747.
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10. Bahceciler NNH. A milestone in house dust-mite-allergen immunotherapy: The new sublingual tablet S-524101 (actair). *Expert Rev Vaccines*. 2014; 13:1427.
11. Barr JG, Al-Reefy H, Fox AT, et al. Allergic rhinitis in children. *BMJ*. 2014; 349:g4153.
12. Biagtan M, Viswanathan R, Bush RK. Immunotherapy for house dust mite sensitivity: where are the knowledge gaps?. *Curr Allergy Asthma Rep*. 2014; 14:482.
13. Bilo MB, Antonicelli L, Bonifazi F. Honeybee venom immunotherapy: certainties and pitfalls. *Immunotherapy*. 2012; 4:1153.
14. Boyle RJ, Elremeli M, Hockenhull J, et al. Venom immunotherapy for preventing allergic reactions to insect stings. *Cochrane Database Syst Rev*. 2012; 10:CD008838.
15. Brehler R, Klimek L, Kopp MV, et al. Specific immunotherapy-indications and mode of action. *Dtsch Arztebl Int*. 2013; 110:148.
16. Brown TC, Tankersley MS. The sting of the honeybee: an allergic perspective. *Ann Allergy Asthma Immunol*. 2011; 107:463.
17. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010; 126:466.
18. Burks AW, Calderon MA, Casale T, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. *J Allergy Clin Immunol*. 2013; 131:1288.
19. Burton MJ, Krouse JH, Rosenfeld RM. Extracts from The Cochrane Library: Sublingual immunotherapy for Allergic Rhinitis. *Otolaryngol Head Neck Surg*. 2011; 144:149.
20. Calderon MA, Bernstein DI, Blaiss M, et al. A comparative analysis of symptom and medication scoring methods used in clinical trials of sublingual immunotherapy for seasonal allergic rhinitis. *Clin Exp Allergy*. 2014; 44:1228.

21. Calderon MA, Boyle RF, Penagos M, et al. Immunotherapy: The meta-analyses. What have we Learned? *Immunol Allergy Clin North Am*. 2011; 31:159.
22. Calderon MA, Casale TB, Togias A, et al. Allergen-specific immunotherapy for respiratory allergies: from meta-analysis to registration and beyond. *J Allergy Clin Immunol*. 2011; 127:30.
23. Calderon MA, Eichel A, Makatsori M, et al. Comparability of subcutaneous and sublingual immunotherapy outcomes in allergic rhinitis clinical trials. *Current Opinion in Allergy and Clinical Immunology*. 2012; 12:249.
24. Calderon MA, Penagos M, Sheikh A, et al. Sublingual immunotherapy for allergic conjunctivitis: Cochrane systematic review and meta-analysis. *Clin Exp Allergy*. 2011; 41:1263.
25. Calderon MA, Rodriguez Del Rio P, Vidal C, et al. An EAACI "European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI)": the methodology. *Clin Transl Allergy*. 2014; 4(22):1.
26. Calderon MA, Van Wijk GR, Eichler I, et al. Perspectives on allergen-specific immunotherapy in childhood: An EAACI position statement. *Pediatr Allergy Immunol*. 2012; 23:300.
27. Calderon MA. Sublingual allergen immunotherapy in children: An evidence-based overview. *Rev Fr Allergol*. 2012; 52:20.
28. Caminati M, Dama A, Schiappoli M, et al. Balancing efficacy against safety in sublingual immunotherapy with inhalant allergens: what is the best approach?. *Expert Rev Clin Immunol*. 2013; 9:937.
29. Canonica GW. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J*. 2014; 7:6.
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34. Compalati E, Braido F, Canonica GW. Sublingual immunotherapy: recent advances. *Allergol Int*. 2013; 62:415.
35. Cox L, Calderon M, Pfaar O. Subcutaneous allergen immunotherapy for allergic disease: examining efficacy, safety and cost-effectiveness of current and novel formulations. *Immunotherapy*. 2012; 4:601.
36. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011; 127:S1.
37. Cox L. Allergy immunotherapy in reducing healthcare cost. *Curr Opin Otolaryngol Head Neck Surg*. 2015;23:247.
38. Cox L. Sublingual immunotherapy for aeroallergens: status in the United States. *Allergy Asthma Proc*. 2014; 35:34.
39. Davila I, Navarro A, Dominguez-Ortega J, et al. SLIT: indications, follow-up, and management. *J Investig Allergol Clin Immunol*. 2014; 24:S1.
40. De Bot CM, Moed H, Berger MY, et al. Sublingual immunotherapy in children with allergic rhinitis: quality of systematic reviews. *Pediatr Allergy Immunol*. 2011; 22:548.
41. Demoly P, Jeanniard GB. Cross-reactivity and allergic rhinoconjunctivitis: Practical implications for immunotherapy with a timothy grass pollen tablet. *Rev Fr Allergol*. 2012; 52:388.
42. Di Bona D, Leto-Barone MS, La Piana S, et al. Sublingual immunotherapy with natural grass pollen extracts: An appraisal of the evidence. *Therapy*. 2011; 8:443.
43. Di Bona D, Plaia A, Leto-Barone MS, et al. Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a meta-analysis-based comparison. *J Allergy Clin Immunol*. 2012; 130:1097.

44. Di Bona D, Plaia A, Scafidi V, et al. Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a systematic review and meta-analysis. *J Allergy Clin Immunol.* 2010; 126:558.
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46. Eifan AO, Calderon MA, Durham SR. Allergen immunotherapy for house dust mite: clinical efficacy and immunological mechanisms in allergic rhinitis and asthma. *Expert Opin Biol Ther.* 2013; 13:1543.
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49. Frati F, Incorvaia C, David M, et al. Requirements for acquiring a high-quality house dust mite extract for allergen immunotherapy. *Drug Des Devel Ther.* 2012; 6:117.
50. Frati F, Incorvaia C, Lombardi C, et al. Allergen immunotherapy: 100 years, but it does not look like. *Eur Ann Allergy Clin Immunol.* 2012; 44:99.
51. Fujimura T, Okamoto Y, Taniguchi M. Therapeutic effects and biomarkers in sublingual immunotherapy: a review. *J Allergy (Cairo).* 2012; 2012:1.
52. Garbo G, Tessema B, Brown SM. Complementary and Integrative Treatments: Allergy. *Otolaryngol Clin North Am.* 2013; 46:295.
53. Gentile D, Bartholow A, Valovirta E, et al. Current and Future Directions in Pediatric Allergic Rhinitis. *J Allergy Clin Immunol Pract.* 2013; 1:214.
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57. Hankin CS, Cox L. Allergy immunotherapy: what is the evidence for cost saving?. *Curr Opin Allergy Clin Immunol.* 2014; 14:363.
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59. Incorvaia C, Di Rienzo A, Celani C, et al. Treating allergic rhinitis by sublingual immunotherapy: a review. *Ann Ist Super Sanita.* 2012; 48:172.
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Appendix 4: Irretrievable records

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Appendix 5: AMSTAR rating for each included systematic review

Author, date	A priori design	Duplicate selection/ extraction	Literature search	Publication status	List of studies	Study characteristics	Quality assessed	Quality appropriately used	Methods appropriate	Publication bias assessed	Conflicts stated	AMSTAR rating
Lu 2015	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	7
Devillier 2014	No	Can't answer	Yes	No	Yes	Yes	No	No	Yes	Yes	No	5
Dranitsaris 2014	No	Can't answer	No	No	NO	Yes	No	No	Yes	Yes	No	3
Feng 2014	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	8
Tao 2013	No	yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No	6
Calderon 2013	No	Can't answer	No	No	Yes	Yes	No	No	NA	No	No	3
Purkey 2013	No	Yes	No	No	No	Yes	Yes	No	No	No	No	3
Meadows 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Manzotti 2013	No	Can't answer	No	No	No	Yes	No	No	No	No	No	1
Larenas-Linneman 2013	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	6
Larenas-Linneman 2011	No	No	Yes	No	No	Yes	Yes	Yes	No	Yes	No	5
Calderon 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Seidman 2015	No	No	No	No	No	No	No	No	No	No	No	0
Radulovic 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Abramson 2010	Yes	No	Yes	Yes	Yes	Yes	Yes	NO	Yes	No	No	7

Calderon 2010	No	No	No	No	No	Yes	No	No	Can't answer	No	No	1
Lin 2013	Yes	Yes	Yes	11								
CADTH 2014	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	7
Bousquet 2011	No	No	Yes	No	No	Yes	No	No	NA	No	No	2
