Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Sublingual and Injectable Customized Allergy Immunotherapy: Clinical and Cost-Effectiveness and Guidelines

DATE: 31 May 2016

CONTEXT AND POLICY ISSUES

Respiratory allergic diseases (also known as allergies), such as rhinitis, asthma, and conjunctivitis, affect more than 400 million people globally[1] and are on the rise in industrialized countries.[2] Allergies result from hypersensitivity to various allergens, such as airborne particles, food, and venom. Respiratory allergens, which are the most common type of allergens, are airborne and include house dust mites (HDMs) (*Dermatophagoides pteronyssinus [D.pteronyssinus]*, *Dermatophagoides farinae [D.farinae]*); grass and tree pollen (for example, *Phlerum.pratense [P.pratense], Artemisia*, ragweed, *Parietaria*, birch, olive); mold or fungi (*Alternaria*, *Cladosporium*); and dog or cat epithelia (dander).[3] Allergies may be seasonal or perennial. Symptoms may be mild, moderate, severe, or sometimes fatal. Mild forms of allergies can be treated with pharmacotherapy (in the form of antihistamines or corticosteroids), but moderate-to-severe allergic reactions require specific allergen immunotherapy (SIT).[1]

SIT involves administering gradually increasing doses of extracts of the causative allergen to which a patient is hypersensitive.[4] The aim of treatment is to reduce the clinical reactions of allergic patients.[1,5] The outcomes of SIT include reduction in allergic symptoms or medication use, improvement in health-related quality of life (HRQoL) and changes to immunologic parameters.[6] Subcutaneous (or injectable) immunotherapy (SCIT) has been the primary method for treating patients with allergies; however, this mode of treatment is associated with severe adverse effects. For example, patients with asthma have been known to experience local (at the site of treatment) or systemic (at a location distant from the site of treatment) adverse effects (like anaphylaxis) requiring life-saving adrenaline injections.[5] Besides adverse effects, multiple injections make SCIT challenging, particularly when children are involved.[3]

Alternative forms of SIT for respiratory allergies include intralymphatic immunotherapy (ILIT), oral immunotherapy (OIT), local nasal immunotherapy (LNIT), and sublingual immunotherapy (SLIT).[3,5] Intralymphatic immunotherapy is relatively new and is still under early investigation. OIT has proven ineffective against grass pollen in patients with rhinitis although, at high doses, there is some evidence of safety and efficacy of *D.pteronyssinus* and *Artemisia* extracts.[3] LNIT,

though effective, has not been well-tolerated suggesting potential challenges with patient compliance.[5,7] Since becoming available in the mid-1980s, SLIT has been used as an alternative to SCIT for adults and children with rhinitis with or without asthma, albeit with attendant adverse effects.[5] SLIT involves applying an allergen extract in solution (drop) or tablet form under the tongue for at least a minute to enable incorporation into the oral Langerhans cells.[3] Adverse effects of SLIT include reactions in the oropharynx and gastrointestinal tract, and less often, asthma, rhinitis, and urticaria (hives).[5]

Despite the growing evidence of efficacy of both SCIT and SLIT, questions remain about dosing, consistency of outcomes, the effect of combining pharmacotherapy and immunotherapy, and the impact on multi-allergic persistent asthma.[8] Differences beyond delivery mode (subcutaneous versus sublingual) of SCIT and SLIT make it a challenge to perform head-to-head trials; dosing (length of induction and maintenance phases), calculation of outcome measures, and trial designs are not adequately standardized.[6]

A 2012 CADTH Rapid Response review of SCIT included three randomized controlled trials (RCTs) with direct comparisons of SCIT and SLIT.[9] The report found inconsistent comparative evidence of efficacy between SCIT and SLIT.

The purpose of this Rapid Response report is to review the evidence of comparative clinical effectiveness and cost-effectiveness of SCIT, SLIT, and oral antihistamines in patients with allergies, and to identify published, evidence-based guidelines on the use of SCIT or SLIT for allergies.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of sublingual versus injectable forms of customized allergy immunotherapy in patients with allergies?

2. What is the comparative clinical effectiveness of either the sublingual or injectable forms of customized allergy immunotherapy versus oral antihistamines in patients with allergies?

3. What is the comparative cost-effectiveness of either the sublingual or injectable forms of customized allergy immunotherapy versus oral antihistamines in patients with allergies?

4. What are the evidence-based guidelines associated with the use of either the sublingual or injectable forms of customized allergy immunotherapy in patients with allergies?

KEY FINDINGS

Four systematic reviews, six RCTs, one cost-effectivess analysis (CEA) , and one evidence-based guideline were identified that provided evidence comparing SLIT to SCIT or oral antihistamines. Overall, the majority of evidence (of low to moderate quality) favoured SCIT over SLIT in reducing asthma or rhinitis symptoms or medication use. In one RCT involving oral antihistamine, the results favoured SLIT. While local and systemic adverse effects were reported, no deaths occurred during the included studies. A CEA done in Germany found the SLIT tablet Oralair® to be more cost-effective than antihistamine (loratadine) and steroid (budesonide) treatment. An evidence-based guideline recommended the use of immunotherapy

after a patient has not responded to pharmacotherapy, and the patient has received counseling about avoiding allergens and about the adverse effects of immunotherapy.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. To address questions one, two and three, no filters were applied to limit the retrieval by study type. To address question four, methodological filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and May 3, 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1. SRs with placebo-controlled clinical trials were included if embedded meta-analyses reported on head-to-head comparisons of SCIT and SLIT.[10]

Table 1: Selection Criteria

Population	Adult and pediatric patients with allergies
Intervention	Q1: Sublingual form of customized allergy immunotherapy only Qs2-4: Sublingual form of customized allergy immunotherapy (SLIT) orInjectable form of customized allergy immunotherapy (SCIT)
Comparator	Q1: Injectable form of customized allergy immunotherapy Qs2 and 3: Oral antihistamines Q4: No comparator
Outcomes	Qs1and 2: Comparative clinical effectiveness (including safety, patient benefits and harms) Q3: Cost-effectiveness Q4: Guidelines
Study Designs	Health technology assessments/systematic reviews/meta-analyses, RCTs, economic evaluations, evidence-based clinical practice guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011.

Critical Appraisal of Individual Studies

The included systematic reviews (SRs) were critically appraised using A Measurement Tool to Assess Systematic Reviews (AMSTAR),[11] RCTs were critically appraised using the Downs and Black checklist,[12] economic studies were assessed using the Drummond checklist,[13] and evidence-based guidelines were assessed with the AGREE II instrument.[14] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 308 citations were identified in the literature search. Following screening of titles and abstracts, 244 citations were excluded and 64 potentially relevant reports from the electronic search were retrieved for full-text review. Six potentially relevant publications were retrieved from the grey literature search. Of the 70 potentially relevant articles, 58 publications were excluded for various reasons, while 12 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest that did not meet the selection criteria are provided in Appendix 5 – Additional References of Potential Interest.

Summary of Study Characteristics

Additional details of study characteristics are provided in Appendix 2, Tables A1 to A5.

Study Design

Four SRs,[15-18] six RCTs,[1,2,19-22] one CEA,[23] and one evidence-based guideline[24] met the inclusion criteria for this review. Two SRs included network meta-analyses (NMAs) of placebo-controlled RCTs.[15,18]

Three of the SRs were published in 2013[16-18] and one in 2015.[15] The RCTs were published between 2011 and 2015, and the CEA and guidelines were published in 2015. Five of the RCTs compared SCIT with SLIT,[1,19-22] and one compared SLIT with an oral antihistamine.[2] One study[20] was a continuation of another study.[21] Follow-up ranged from three months[1] to three years,[2,19] and patients were randomized by computer-generated code in several studies.[1,20-22] Two studies did not provide details of the randomization process used.[2,19]

Country of Origin

Two of the SRs were published by authors in the United Kingdom,[15,18] and two were published in the United States.[16,17] The RCTs took place in Turkey,[19-21] Italy,[2,22] and Denmark.[1] The CEA was done in Germany,[23] and the guideline document was authored in the United States.[24]

Patient Population

The SRs included adult and pediatric patients with allergies related to dust mites, grass pollen, and tree pollen. Patients suffered from rhinitis, conjunctivitis, or asthma alone or in combination. The RCTs enrolled adults[1,22] or children[2,19-21] who were allergic to dust mites,[2,19-21] grass pollen,[1] or had birch-apple syndrome.[22] Allergic symptoms were reported as rhinitis[1], persistent asthma

with or without, rhinitis[19], perennial rhinitis with[20,21] or without[2] mild asthma, and seasonal rhinitis.[22] Half of the patients enrolled in one study lived in an environment where they were exposed to passive smoking.[2]

Interventions and Comparators
One SR compared SLIT tablets with SCIT and SLIT drops,[15] while the others did not specify the form in which SLIT was administered.[16-18] Patients took rescue medication as needed. Two of the SRs based their comparisons on placebo-controlled RCTs,[15,18] while two limited their comparisons to RCTs with active controls.[16,17] The CEA incorporated studies comparing SLIT with SCIT or placebo.[23] The evidence-based guideline reported on all treatment options relevant to allergic rhinitis.[24]

The RCTs compared SLIT with oral antihistamines in adult patients[2] or with SCIT in adult[1,23] or pediatric patients.[19-21] One RCT included an additional pharmacotherapy arm,[19] one included a control arm in which 10 patients received placebo injections and placebo sublingual drops,[21] and one included an untreated arm.[1] Outcomes relevant to the active treatments as listed in Table 1 were included in this report, but the findings for the additional pharmacotherapy arm were not included as details of treatment were not disclosed.[19]

Administration of SLIT:
Patients allergic to dust mites were treated with extracts of mixtures of *D.farinae* and *D.pteronyssinus*[2,19] *or D.pratense,*[20,21] in drop format. Induction periods varied from one month[19] to approximately three months.[20,21] Patients received placebo injections in two RCTs,[20,21] and were allowed to take rescue medication, inhaled or intranasal corticosteroids, antihistamines, and oral corticosteroids as needed.[19] For grass pollen allergies, SLIT was administered in the form of an ALK Grazax tablet placed under the tongue.[1] For birch-apple syndrome, patients received birch, alder, and hazelnut tree pollen extracts.[22]

Administration of SCIT:
Patients allergic to dust mites were injected with extracts of mixtures of *D.farinae* and *D.pteronyssinus*[2,19] *or D.pratense.*[20,21] Induction periods spanned 12[20-22] to 16 weeks.[19] Patients received placebo sublingual drops in two RCTs,[20,21] and were allowed to take rescue medication, inhaled/intranasal corticosteroids, antihistamines, and oral corticosteroids as needed in one study.[19] For grass pollen allergies, patients received ALK (Alutard 225 *P.pratense*) injections.[1] Patients with birch-apple syndrome received injections of birch, alder, and hazelnut tree pollen extracts.[22]

Administration of Oral Antihistamine:
In one RCT, patients allergic to dust mites received cetirizine in the oral antihistamine arm.[2] Patients were allowed to take salbutamol by inhalation and nasal corticosteroids as needed.

Outcomes
Clinical effectiveness outcomes of interest were symptom scores,[15-21] medication use scores,[15-20] combined symptom–medication score,[16-18] disease-specific quality of life (QoL) or visual analog scale (VAS) scores,[18,19] and response to provocation tests, such as skin reactivity or nasal challenge.[1,19-22] Adverse effects included, but were not limited to, injection site reactions, oral cavity reactions, respiratory, gastrointestinal, cardiovascular, anaphylaxis, and death.[16,17,19,21,22] Symptom scores were derived from qualitative assessments of severity of symptoms.[19] No symptoms, as well as mild, moderate, and severe intensity of individual symptoms were scored as 0, 1, 2, and 3, respectively. Rhinitis symptoms were rhinorrhea,

sneezing, itching, and nasal blockage.[19] Asthma symptoms were wheezing, breathlessness, cough, and chest tightness.[19] Other clinical effectiveness outcomes that were frequently reported but out of scope for this report were immunologic measures, such as serum immunoglobulin E (IgE) and immunoglobulin G (IgG) (total and specific).[1]

The cost-effectiveness outcome of interest was the incremental cost effectiveness ratio (ICER).[23]

Summary of Critical Appraisal

A detailed summary of the strengths and limitations of SRs, RCTs, the economic study, and guideline is provided in Appendix 3, Tables A6 to A9.

Systematic Reviews

The SRs had more strengths than limitations and were considered to be of moderate to high quality.[15-18] All SRs conducted a comprehensive literature search usng multiple databases, had two independent reviewers perform the study selection and data extraction, and assessed the quality of included studies. The limitations were as follows: a protocol was not mentioned,[15] a consensus procedure for study selection was not described,[15] a list of excluded studies was not provided,[15,16] the publication status was not used as an inclusion criterion,[16,18] and a quantitative assessment of the evidence[16,17] nor the potential publication bias were reported.[17]

Randomized Controlled Trials

The RCTs also had more strengths than limitations although there was variation across the studies.[1,2,19-22]

All studies explicitly stated the objectives in the introduction, described interventions, outcomes, and characteristics of included patients, and reported the probability values for the main outcomes. There were no unplanned analyses, follow-up times were consistent, appropriate statistical tests were used to assess the main outcomes, and there was reliable compliance with the intervention in all RCTs. Two studies stated estimates of random variability for the main outcomes.[19,22] Invited and included participants were representative of the target population in each study. As well, SCIT was administered in a clinic, and SLIT was administered in a home environment.[19-21] In one study, half of the participants were exposed to passive smoking.[2] The representativeness of a 50% exposure rate was not discussed. The outcome assessors were blinded in four RCTs.[1,19-21] All studies recruited patients from similar populations and accounted for follow-up losses. Randomization was performed by computer software in four studies,[1,20-22] but not described in two.[2,19] With respect to limitations, none of the studies provided a means of verifying that the main outcomes measured were accurate nor did they assess statistical power. Authors declared conflicts of interest in one RCT[1] and made no statement in two.[20,21] The remaining studies declared that the authors had no conflicts of interest.[2,19,21,22]

Economic Evaluation

The cost-effectiveness study was of high quality.[23] Its main limitation was the lack of generalizability to the Canadian healthcare context. The authors explicitly reported model design and inputs, conducted sensitivity analyses, set up discounted costs and benefits t a 3% rate, defined the outcome of interest (i.e., ICER), reported resources, unit costs, and disaggregated results, provided details about the intervention and comparator (for example, components of the SLIT tablet), specified a nine-year time horizon, and used a literature review and a meta-analysis as data sources on efficacy. The authors specified that costs were based

on the literature, consumer payments, and assumptions on treatment duration. The payer perspective was taken.

Evidence-based Guideline
The evidence-based guideline was of high quality.[24]

The guideline described its overall objectives, the health question, and the population of interest. In terms of strengths, the guideline included a panel of experts from various disciplines relevant to the topic. While the views and opinions of children, which was the target population, were not sought specifically, a consumer advocacy group was represented on the panel. The authors systematically searched for evidence and explicitly outlined the criteria used for study selection. The strengths and limitations of the evidence and the methods used to develop the recommendations were described. The health benefits, side effects, and risks were considered in formulating the recommendations. There was an explicit link between the recommendations and the supporting evidence. Also, external experts had the opportunity to review the final draft of the recommendations prior to publication. The recommendations were specific and unambiguous. The different options for management of allergic rhinitis in children were presented, and the key recommendations were easily identifiable. The guideline described the facilitators to its application, provided advice or tools on how the recommendations can be put into practice, and presented the monitoring or auditing criteria. The authors provided a list of future research needed to update the guidelines. Efforts were made to ensure that the views of the funding body did not influence the content of the guidelines, and all members of the panel had an opportunity to declare conflicts of interest. Panelists with conflicts of interest were charged to remind the panel of potential conflicts before any related discussion, recuse themselves from a related discussion if asked by the panel, and were not to discuss any aspect of the guideline with industry before publication. One limitation was that the potential resource implications of applying the recommendations were not discussed. The authors stated that the guideline was not intended to be comprehensive. Another limitation of the guideline is that it focused on allergic rhinitis and not SIT.

Summary of Findings

Additional details are provided in Appendix 4, tables A10 to A13.

1. *What is the comparative clinical effectiveness of sublingual versus injectable forms of customized allergy immunotherapy in patients with allergies?*

Symptom Scores
Based on the evidence from a set of four RCTs, two SRs reported that, in adults and children allergic to dust mites, there was low strength/grade evidence favouring SCIT over SLIT in reducing asthma symptoms.[16,17] Low strength/grade indicates that there is low confidence that the evidence reflects the true effect. Further research is likely to change the authors' confidence in the estimate of the effect and is likely to change the estimate.[16,17] In one RCT,[19] both SCIT and SLIT caused a decrease in the total asthma symptom scores in children. The statistical significance of the difference between the two treatments was not reported. In comparison with SLIT, SCIT was associated with a significantly larger decrease in both rhinitis and asthma symptom scores relative to baseline measurements.[20,21] The difference was reported as statistically significant following two years of treatment.[20]

In patients with rhinitis with or without conjunctivitis or asthma related to dust mites or birch tree pollen, there was moderate strength/grade evidence favouring SCIT over SLIT in reducing allergic nasal or eye symptoms.[16,17] Moderate strength/grade indicates that there is moderate confidence that the evidence reflects the true effect, and further research may change the authors' confidence in the estimate of the effect and may change the estimate.[16,17]

In adults and children with temperate grass pollen-induced seasonal allergic rhinitis or asthma, one NMA of 37 placebo-controlled RCTs found no statistically significant difference between SLIT drops and SCIT or SLIT tablets and SCIT.[15] In a subgroup analysis involving adults only, the conclusion remained the same for SCIT versus SLIT drops or tablets. A subgroup analysis was not possible for children due to the lack of comparisons involving SCIT. The authors reported some visual indications of asymmetry in funnel plots, but there was no quantitative evidence of publication bias in the evidence on SCIT, SLIT drops, or SLIT tablets. Another NMA of 59 placebo-controlled RCTs involving adults and children with tree or grass pollen allergies reported results favouring SCIT over SLIT.[18] The results were associated with substantial residual heterogeneity. Based on data from one 3-arm RCT, the same authors reported that there was no statistically significant difference between SLIT and SCIT in adults treated with birch pollen extract.[18] A study by the same group of authors[25] reported identical findings but was not included in this report as it duplicated the results.

Medication Use Scores

Both SCIT and SLIT lowered total (rhinitis and asthma) medication use scores relative to baseline measurements in children allergic to dust mites.[19] The statistical significance of the difference between the two treatments was not reported. In another study involving children who were allergic to dust mites, SCIT led to statistically significantly better reduction in asthma medication use score from baseline but not in rhinitis medication use score.[20]

Though a RCT of patients allergic to birch tree pollen favoured SLIT over SCIT, equivocal results across four RCTs involving patients who were allergic to dust mites led authors of two SRs to conclude that there was low strength/grade evidence of equivalence between SCIT and SLIT in reducing the use of antihistamines, corticosteroids, or agonists by patients with rhinitis or asthma.[16,17] One NMA found that, in patients with grass pollen-induced seasonal allergic rhinitis or asthma, there was no statistically significant difference between SLIT drops and SCIT or SLIT tablets and SCIT.[15] The authors observed some visual indications of asymmetry in funnel plots, but quantitative evidence of publication bias was not identified in the evidence on SLIT tablets. The NMA of data from studies involving patients allergic to tree or grass pollen marginally favoured SCIT over SLIT across multiple tree and grass allergens.[18] Based on data from one 3-arm RCT, the same authors reported that in adults treated with birch pollen extract, there was no statistically significant difference between SLIT and SCIT.[18]

Combined Symptom-medication Score

Both SRs reported low strength evidence favouring SCIT in the reduction of allergic rhinitis symptom-medication scores in patients with hypersensitivity to dust mites or birch tree pollen based on data from two RCTs involving 65 patients.[16,17] The NMA of data from studies involving patients allergic to tree or grass pollen found no statistically significant difference between SCIT and SLIT with a large degree of uncertainty.[18] In patients with birch-apple syndrome, the combined symptom-medication score was higher with SCIT but the difference was not statistically significant.[22]

Visual Analog Scale Score
In one RCT involving children allergic to dust mites, both SCIT and SLIT decreased visual analog scores relative to baseline measurements.[19] The statistical significance of the difference between the two treatments was not reported.

Quality of Life
The evidence on QoL from one RCT involving patients allergic to dust mites or birch tree pollen was limited to the point that it could not be graded.[17] In another RCT, both SCIT and SLIT significantly reduced VAS scores relative to baseline measurements.[19] The NMA of data from studies involving patients allergic to tree or grass pollen reported that, with a large degree of uncertainty across multiple studies, there was no statistically significant difference between SCIT and SLIT.[18]

Response to Provocation
Based on an assessment of changes to nasal symptoms in four RCTs, one SR[17] reported that there was evidence that both SCIT and SLIT led to an increase in tolerance to dust mite allergen (relative to baseline measurements) in children with rhinitis or conjunctivitis. Both SCIT and SLIT also resulted in less skin reactivity to *D.pteronyssinus* and *D.farinae.*[19] The decreases were statistically significant for both treatments reacting to *D.pteronyssinus* but only in SCIT reacting to *D.farinae.* Both forms of SIT significantly lowered the wheal diameter from a skin-prick test (*D.pratense, D.farinae*) and raised the tolerance to nasal provocation and HDM-specific bronchial provocation.[20,21] SCIT significantly increased the tolerance to HDM-specific bronchial provocation while SLIT did not.[21] Similarly, there were significant changes in allergen dose in the SCIT group in an assessment of changes to bronchial symptoms.[19] In patients allergic to grass pollen, SCIT significantly reduced nasal challenge symptoms relative to baseline after three or 15 months while SLIT did not result in a reduction.[1] Out of eight patients treated with SCIT for a year, five experienced an increase in tolerance to apple, of which two achieved complete tolerance.[22] Out of seven patients treated with SLIT, three experienced an increase in tolerance, of which one achieved complete tolerance.

Adverse Events
Compared with baseline measurements, the frequency of local reactions increased by 6.7% to 56% in patients treated with SLIT versus 20% in patients treated for dust mite allergies with SCIT.[16,17] Systemic reactions were primarily limited to respiratory and gastrointestinal events.[16,17] Anaphylaxis was reported in one child treated with SCIT,[16,17] and no deaths were reported.[16,17] Systemic reactions occurred during build-up in 17% of patients treated with SCIT, compared with 0% in those treated with SLIT.[17,19] One study reported that there were no systemic reactions, but two local adverse events at the injection site in patients treated with SCIT and itching or mild edema of the mouth or throat in three patients treated with SLIT were reported.[21] Out of 19 patients on SCIT, 16 experienced systemic reactions while none were reported in the SLIT group.[22] Neither group had serious adverse effects. The statistical significance of the differences in adverse events between the two treatments was not reported.

2. *What is the comparative clinical effectiveness of either the sublingual or injectable forms of customized allergy immunotherapy versus oral antihistamines in patients with allergies?*

One study that compared SLIT to oral antihistamines in patients allergic to dust mites was identified.[2]

Symptom Score
There was no statistically significant difference in mean monthly symptom scores in patients treated with SLIT and those taking cetirizine.[2]

Medication Use Score
Irrespective of exposure to passive smoke, reduction in mean medication use was higher in patients treated with SLIT.[2] The statistical significance of the difference between the two treatments was not reported.

3. What is the comparative cost-effectiveness of either the sublingual or injectable forms of customized allergy immunotherapy versus oral antihistamines in patients with allergies?

One CEA that was done in Germany compared SLIT tablets (Oralair®, 5-Grass) to symptomatic treatment for allergic rhinitis with or without conjunctivitis due to grass pollen, from the payer's perspective.[23] Symptomatic treatment included both oral antihistamines (Loratadine) and steroids (Budesonide). The analysis built on a previous comparison of Oralair to Grazax® (SLIT mono-grass tablet), Alutard® (SCIT with native extracts), and symptomatic treatment. Using a time horizon of nine years, Oralair was deemed to be more cost-effective than symptomatic treatment. Sensitivity analyses accounted for lump sum payments, private service, societal perspective, changing utilities, and a shorter pollen season. The results of the sensitivity analyses did not lead to changes in the conclusions of the CEA.

4. What are the evidence-based guidelines associated with the use of either the sublingual or injectable forms of customized allergy immunotherapy in patients with allergies?

The guidelines from the American Academy of Otolaryngology recommended that clinicians should offer, or refer to a clinician who can offer, immunotherapy (sublingual or subcutaneous) for patients, who were at least 2 years old, with allergic rhinitis who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls.[24] The guideline statement was based on RCTs and SRs with a preponderance of benefit over harm. Thirteen other guideline statements relevant to management of patients with allergies were included.

Limitations

While covering a broad array of allergic symptoms and allergens, the body of evidence was limited in depth. Twelve studies reported on adults and children with varying levels and combinations of rhinitis, conjunctivitis, and asthma, and reported partially overlapping sets of outcomes. Two of the SRs extracted comparative data for SLIT and SCIT by performing NMA of placebo-controlled trials.[15,18] Two SRs of RCTs involving head-to-head comparisons did not provide quantitative comparisons between the treatments.[16,17]

There was heterogeneity across the studies in the allergens of interest, type of extract used for treatment, length of induction period, dose during induction, and maintenance dose. The sample size of six RCTs ranged from nine[19] to 34 patients.[2] Two RCTs imposed adequate blinding by administering placebo injections to patients in the SLIT arm and placebo drops to patients in the SCIT arm, as described in the studies.[20,21]

The primary goal of the CEA was to compare a specific SLIT medication with a mix of SCIT allergoids. The comparison between SLIT and symptomatic treatment was secondary. Furthermore, symptomatic treatment included the use of steroids (Budesonide) alongside the antihistamine (Loratadine). Both medications are approved and available for use in Canada.[26]

Finally, the evidence-based guideline document focused on patients with allergic rhinitis, and not immunotherapy.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The available evidence that compared SLIT to SCIT or oral antihistamines is sparse. In patients allergic to dust mites or birch tree pollen, the level of evidence that suggested clinical effectiveness in SCIT over SLIT in controlling asthma symptoms, combined symptom-medication scores, rhinitis medication use, and combined rhinitis symptom-medication scores was consistently of low grade while that for rhinitis or conjunctivitis symptoms was of moderate grade. There is insufficient evidence to make any firm conclusions about the impact of SLIT versus SCIT in patients allergic to tree or grass pollen or with birch-apple syndrome. There is also insufficient evidence to make any conclusions about on the impact of SLIT over antihistamines. Moreoever, the cost-effectiveness of SLIT over antihistamines may require validation within the Canadian healthcare context. Partly due to the variability in available evidence, the guidelines involving immunotherapy should be interpreted with caution.

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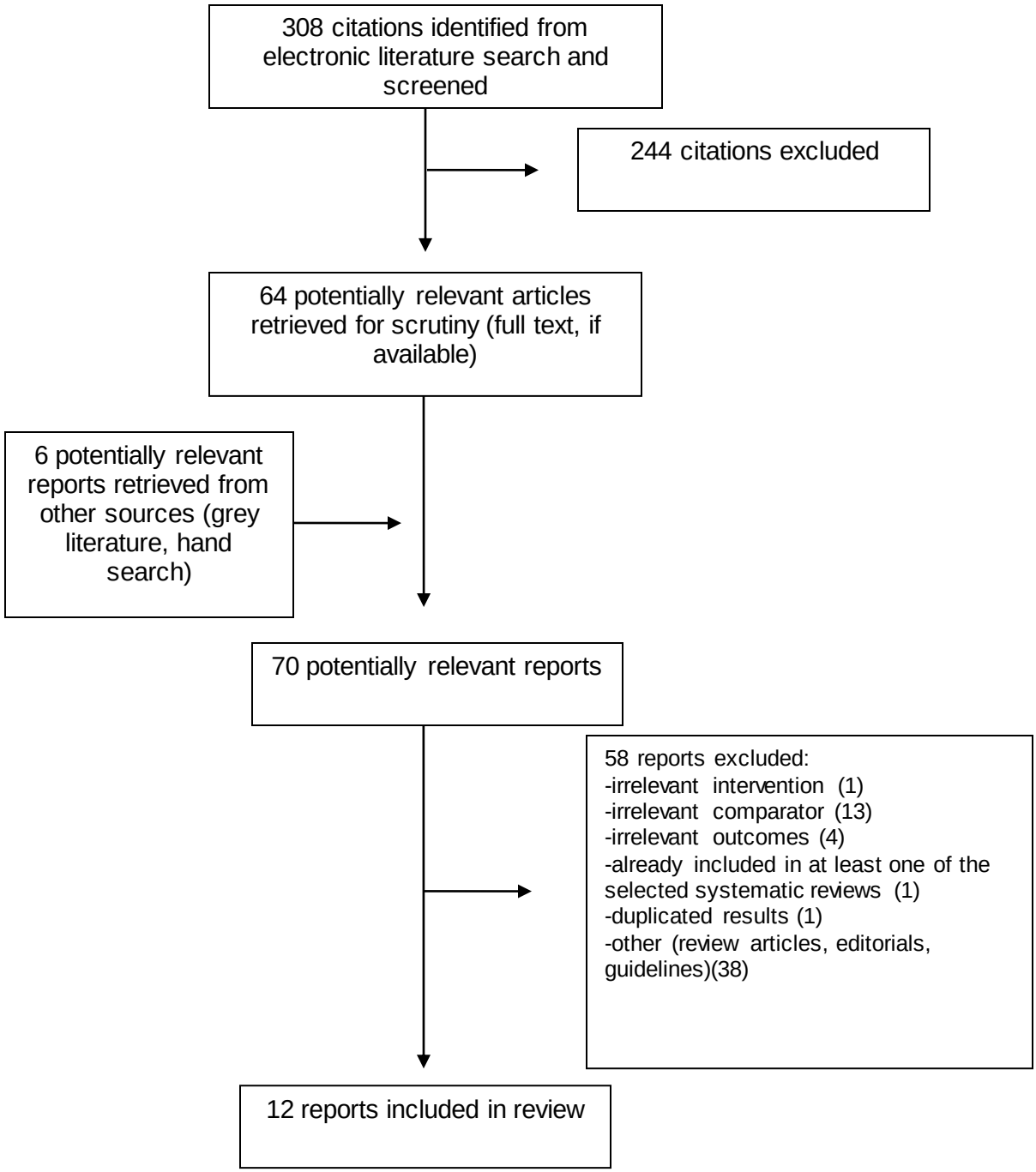
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Nelson, 2015,[15] United Kingdom	SR and NMA of 37 placebo-controlled RCTs	7,759 adults and children with rhinitis, conjunctivitis, and/or asthma related to grass pollen	SLIT tablets (14 RCTs)	SCIT (9 RCTs) SLIT drops (14 RCTs)	Symptom scores (37 RCTs), medication scores (33 RCTs) Follow-up: NR
Chelladurai, 2013,[16] United States	SR of 8 RCTs comparing SLIT with SCIT	413 patients with rhinoconjunctivitis, rhinitis, and/or asthma related to tree pollen (2 RCTs) or dust mite allergies (6 RCTs); mean age 6 to 40 years	SCIT alone or in combination with usual care (pharmacotherapy and environmental interventions as needed); n=189; 10 dropouts	SLIT alone or in combination with usual care (pharmacotherapy and environmental interventions as needed); n=196; 18 dropouts	Primary: symptoms scores, medication use scores, combined symptom-medication scores Secondary: frequency of adverse events (local reactions. anaphylaxis, death) Follow-up: 1 year (four RCTs)
Lin, 2013,[17] United States	CER of 142 RCTs, including 8 comparing SLIT with SCIT	413 patients with rhinoconjunctivitis or rhinitis with or without asthma related to tree pollen or dust mite allergies	SCIT with conventional or rescue medication as needed; n=189; 10 dropouts	SLIT with conventional or rescue medication as needed; n=196; 18 dropouts	Symptoms scores, medication use scores, combined symptom-medication scores; frequency of adverse events (local reactions. anaphylaxis, death) Follow-up: 1-3 years
Meadows, 2013,[18] United Kingdom	SR and NMA of 59 double-blind placebo-controlled RCTs and one 3-arm RCT	3,099 treatment-naive adults and children with a confirmed diagnosis and symptoms of seasonal allergic rhinitis (hay fever) with or without	SCIT (n=659) or SLIT (n=2440)	SCIT, SLIT with or without conventional rescue medication	Symptom severity score, medication use score, combined symptom-medication scores, QoL Follow-up: NR

Table A2: Characteristics of Included Systematic Reviews and Meta-Analyses					
First Author, Publication Year, Country	**Types and numbers of primary studies included**	**Population Characteristics**	**Intervention**	**Comparator(s)**	**Clinical Outcomes, Length of Follow-Up**
		seasonal asthma 3-arm RCT: 71 adults who had not been treated in 5 years			

NMA = Network meta-analysis; NR = Not reported; QoL = Quality of life; RCT = Randomized controlled trial; SCIT = Subcutaneous immunotherapy; SLIT = Sublingual immunotherapy; SR = Systematic review

Table A3: Characteristics of Included Randomized Controlled Trials					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Karakoc-Aydiner, 2015,[19] Turkey	3-arm RCT	40 children with mild to moderate persistent asthma and/or rhinitis, monosensitized to HDM, who had not responded to corticosteroid treatment in the outpatient clinic for ≥ 2 years 10 patients enrolled in the pharmacotherapy arm were not included in this report	SCIT (n=12): 1:1 mixture of *D. pteronyssinus* and *D. farinae* (SLIT, SLIT; ALK-ABELLO, S.A., Madrid, Spain) or adsorbed on aluminium hydroxide (SCIT, ALUTARD SQ; ALK-ABELLO, S.A.) administered over a 16-week induction period. Patients were allowed to take rescue medication, inhaled/intranasal corticosteroids, antihistamines, and oral corticosteroids as needed. Dropouts: noncompliance	SLIT (n=9): 1:1 mixture of *D. pteronyssinus* and *D. farinae* self-administered at five drops three times a week following one-month induction. The standardized extract came in the form of as a glycerinated solution (SLIT, SLIT; ALK-ABELLO, S.A., Madrid, Spain) or adsorbed on aluminium hydroxide (SCIT, ALUTARD SQ; ALK-ABELLO, S.A.). Patients were allowed to take rescue medication, inhaled/intranasal corticosteroids, antihistamines, and oral	Change in symptom and medication scores, lung function, response to nonspecific bronchial methacholine challenge; allergen-specific nasal provocation; and skin prick test, after 3 years of treatment Rhinitis symptoms (rhinorrhea, sneezing, itching, and nasal blockage) and asthma symptoms (cough, wheezing, breathlessness, and dyspnea) were recorded

Table A3: Characteristics of Included Randomized Controlled Trials					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
			with treatment (n=2)	corticosteroids as needed. Dropouts: noncompliance with diary completion (n=2), noncompliance with treatment (n=2), and failure to attend more than 3 visits (n=2).	on a 4-point scale (0, no symptoms; 1, mild; 2, moderate; 3, severe). The total scores comprising all 4 rhinitis and asthma symptoms were termed total rhinitis symptom score and total asthma symptom score, respectively. These scores were then combined to create the total symptom score. Patients scored their use of medications as follows: β-2 agonists, 1 point; inhaled/intranasal corticosteroids, 2 points; and 1 corticosteroid tablet, 3 points. The points were totalled to calculate the total medication score. Individual symptom and medication scores were recorded daily for the entire study period and mean monthly scores were recorded at every 3-monthly study visit. The severity of asthma and rhinitis symptoms was

Table A3: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
					evaluated using a VAS consisting of a 10-cm line ranging from no symptoms (0 cm) to the highest level of symptoms (10 cm).
Aasbjerg, 2014,[1] Denmark	3-arm RCT	40 adults with history of rhinitis with hayfever symptoms during the grass pollen season; allergy verified by skin-prick test (*P.pratense*, Merck Canada Inc.); eligible for immunotherapy; 10 untreated patients were excluded from this report	SCIT (n=15) with a start-up kit with four ampoules of ALK (Alutard 225 *P.pratense*), each containing 5 mL solution of increasing concentrations of grass pollen extract. The first injection contained 20 SQ-U. Gradual up-dosing occurred every week for 15 weeks up to a maintenance dose of 100,000 SQ-U every two months. All injections were given within 2 weeks of the optimal schedule.	SLIT (n=15) with an ALK Grazax 75,000 SQ-T tablet placed under the tongue	Nasal response symptom score (self-reported, non-blinded) in response to Aquagen 225 grass pollen extract at -2, 3, 10 and 15 months of treatment, using a VAS score
Yukselen, 2013,[20] Turkey	2-arm follow on, open-phase of placebo-controlled, double-blind, double-dummy trial with 1-year study run-in period	30 children with perennial rhinitis and mild asthma related to HDM allergy symptoms continuing a double-blind, double-dummy trial of SCIT and SLIT; monosensitized allergy verified by skin-prick test and	SCIT (n=15): 1:1 *D.pratense: D.farinae* (NovoHelisen Depot, Allergopharma); induction of 0.2 ml of 50 TU/ml to 0.8 ml of 5000 TU/ml in week 12; maintenance dose once every four weeks;plus placebo sublingual drops; administered in clinic; 5 patients had previously	SLIT (n=15):1:1 *D.pratense: D.farinae* (NovoHelisen Oral, Allergopharma) self-administered in drop form plus placebo subcutaneous injections; daily increases dose in multiples of 10 TU/ml every 28 days up to day 84 induction; maintenance dose of 28 drops of 1,000 TU/ml three	Change in monthly median symptom and medication scores filled out by parents between end of run-in period (baseline) and end of 2 years of treatment for 20 children and 1 year of treatment for 10 children (previously randomized to a placebo group);[21]

Table A3: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
		specific IgE; 10 children previously enrolled in placebo arm were randomized to SLIT or SCIT	been randomized to a placebo group	times a week; 5 patients had previously been randomized to a placebo group; 1 patient dropped out prior to treatment period	VAS score; clinical nasal challenge; allergen-specific bronchial provocation tests; and adverse events. Parents completed a self-assessment diary each day, scoring the symptoms of rhinitis (rhinorrhea, sneezing, nasal itching and blocked nose) and asthma (cough, wheezing, dyspnea and chest tightness) in the same way for the run-in and immunotherapy period. The symptoms were rated as: 0 = no symptoms, 1 = mild, 2 = moderate and 3 = severe. The combination of rhinitis and asthma symptoms was calculated as total symptom scores. Prophylactic and rescue drug intake was recorded daily on the same diary card. One point was given if a β_2-agonist

Table A3: Characteristics of Included Randomized Controlled Trials					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
					rescue drug was taken on that day, and 0 if not. Similarly, if antihistamines such as cetirizine or loratadine were used for rhinitis on that day, it was scored as 1 point. The daily dose of inhaled budesonide and intranasal mometasone was also scored. The combination of rhinitis and asthma medication scores was termed as total medication scores. Nasal provocation: Nasal provocation was performed according to the European Academy of Allergy and Clinical Immunology guidelines using a Rhinospir 165 rhinomanometer (Sibelmed, Barcelona, Spain). The response was evaluated by measuring nasal resistance at 150 pascals with active rhinomanometry and by scoring the clinical

Table A3: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
					symptoms. Total symptom scores represented the sum of the scores for: sneezing (0 points for 0–2 sneezes, 1 point for 3–5 sneezes, 2 points for > 5 sneezes), rhinorrhea (1 point = moderate, 2 points = severe), tears in eyes or itching of eyes or throat (1 point) and conjunctivitis, cough, urticaria and/or dyspnea (2 points). Positive clinical nasal challenge was defined as > 3 points. After spraying 0.2 ml of the diluent, increasing concentrations of allergen extract (50, 500, 5,000 BU/ml; Allergopharma) were sprayed into the same nostril every 15 min until symptoms appeared and resistances doubled those induced by the diluent.
Yukselen, 2012,[21] Turkey	3-arm double-blind, double-dummy with	32 children referred for treatment for perennial rhinitis with	SCIT (n=10): 1:1 *D.pratense: D.farinae* (NovoHelisen Depot,	SLIT (n=11):1:1 *D.pratense: D.farinae* (NovoHelisen Oral, Allergopharma) self-	Change in monthly median symptom and medication scores

Table A3: Characteristics of Included Randomized Controlled Trials					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
	1-year study run-in period	mild asthma related to HDM allergy symptoms and no history of immunotherapy; monosensitized allergy verified by skin-prick test and specific IgE Patients were encouraged to control asthma with inhalants, and to control rhinitis with nasal steroids, and antihistamines Patients in the placebo group (n-10) were excluded from this repot	Allergopharma); induction of 0.2 ml of 50 TU/ml to 0.8 ml of 5000 TU/ml in week 12; maintenance dose once every four weeks;plus placebo sublingual drops; administered in clinic	administered in drop form plus placebo subcutaneous injections; daily increases dose in multiples of 10 TU/ml every 28 days up to day 84 induction; maintenance dose of 28 drops of 1,000 TU/ml three times a week; 1 patient dropped out prior to treatment period	between end of run-in period (baseline) and end of 1 year of treatment; visual analog scale score; clinical nasal challenge; allergen-specific bronchial provocation tests; and adverse events.
Marogna, 2011,[2] Italy	Open-label 2-arm RCT	68 children with perennial rhinitis and intermittent asthma monosensitized to dust mites; with (n=34) or without (n=34) exposure to parental passive smoking	SLIT (n=34) with monomeric allergoid (Lais, Italy) in a 1:1 mixture of *D.pteronyssinus* and *D.farinae* was administered in incremental doses of 25-100-300-1000 allergy units (AU), starting with 25 AU three times weekly and dose increases according to the	Oral antihistamine (n=34): Continuous tx with cetirizine (antiH1) in the form of 1 mg/2.5 kg/day (age < 12 years old) or 10 mg/day (age > 12 years old). Patients were allowed to take salbutamol by inhalation (100mcg 1-2 puffs as needed) and nasal	Average monthly symptom score; consumption of salbutamol or nasal budesonide; follow-up of 3 years Each symptom (coughing; wheezing; dyspnoea; nasal

Table A3: Characteristics of Included Randomized Controlled Trials					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
			manufacturer's guidelines up to 1000 AU weekly for 3 years. Cumulative annual average dose was approximately 60,000 AU.	corticosteroids (budesonide 100 µg, one puff per nostril once or twice per day as needed).	obstruction; nasal pruritis; rhinorrhea; sneezing; conjunctival pruritis; conjunctival redness; and watery eyes) was evaluated in accordance with the following scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. The monthly values ranged between 0 and 900. An average monthly symptom score was also obtained during the observation period for statistical purposes. The consumption of symptomatic drugs was recorded separately (salbutamol: 1 puff = 1 point, nasal budesonide: 1 puff (100 µg per nostril = 1 point).
Mauro, 2011,[22] Italy	2-arm RCT	47 adults referred for outpatient treatment for seasonal rhinitis (February to April) with or without apple-induced oral allergy syndrome (pin-prick verified); age	SCIT (n=19) with birch, alder, and hazelnut tree pollen extracts at maintenance dose of 10 IR following a 12-week induction period	SLIT (n=15) with birch, alder, and hazelnut tree pollen extracts at maintenance dose of 100 IR following an 11-day induction period	Symptom-medication score in March before; response to oral apple challenge one year after treatment. All patients registered their symptoms and drug

Table A3: Characteristics of Included Randomized Controlled Trials					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
		between 18 and 60 years; positive IgE assay to birch allergen Bet v1.			consumption in diary cards during the month of March in the year before the start of treatment and in the same month after treatment. The oral challenge with fresh apples was performed openly, using a standardized technique: increasing amounts from 4 to 64 g of fresh apples were administered at 15-minute intervals. The challenge was stopped when symptoms appeared. The grade of reaction was classified as follows: grade 1, only oral mucosal symptoms (itching and burning); grade 2, oral mucosal and gastrointestinal symptoms (nausea, vomiting, abdominal pain and diarrhea); grade 3, oral mucosal and systemic symptoms (urticaria, rhinoconjunctivitis and asthma); grade 4, oral mucosal and

Table A3: Characteristics of Included Randomized Controlled Trials					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
					anaphylactic symptoms (laryngeal edema, shock). The challenge was performed before randomization and after 1 year of treatment.

ALK = Alutard 225 *P.pratense*; AU = Allergy units; *D.* = *Dermatophagoides;* HDM = House dust mites; IgE = Immunoglobulin E; IR = Index of reactivity; OAS = Oral allergy syndrome; QoL = quality of life; *P.= Phleum* ; RCT = Randomized controlled trial; SCIT = Subcutaneous immunotherapy; SLIT = Sublingual immunotherapy; SQ-T = Square unit tablet; SQ-U = Square unit; TU = Therapeutic unit; tx = Therapy; VAS = Visual analog scale

Table A4: Characteristics of Included Economic Analysis					
First author, Publication Year, Country	**Type of Analysis, Perspective**	**Intervention, Comparator**	**Study Population**	**Time Horizon**	**Main Assumptions**
Verheggen, 2015,[23] Germany	A CEA based on a Markov model	SLIT tablets (Oralair®, 5-Grass), symptomatic treatment, grass pollen allergoid SCIT group (Allergovit®, Depiquick®, Pollinex® Quattro, and Purethal®)	Patients with grass pollen AR and/or conjunctivitis with a positive grass allergen-specific skin prick test and/or elevated serum grass allergen-specific IgE; on enrollment patients did not have asthma	9 years	Drug effects during three seasons were independent; symptom score values remain constant during post-treatment period

CEA = Cost-effectiveness analysis; SCIT = Subcutaneous immunotherapy; SLIT = Sublingual immunotherapy; IgE = Immunoglobulin E

Table A5: Characteristics of Included Guideline						
Objectives			Methodology			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
Seidman, 2015[24] – American Academy of Otolaryngology						
Adults and children aged ≥ 2 years with allergic rhinitis	Evidence-based guidelines to address quality improvement opportunities for all clinicians, in any setting, who are likely to manage patients with allergic rhinitis, as well as to optimize patient care, promote effective diagnosis and therapy, and reduce harmful or unnecessary variations in care	Selected from full list of outcomes: • Expenditure reduction for ineffective environmental measures • Increased treatment optimization and reduced complications from comorbidities • Optimization of proven effective therapy • Avoidance of sedating antihistamine and promotion of direct therapy • Improved awareness of the different classes of medication for effective treatment of AR • Reduction in the use of a less	Evidence was collected from a literature search for clinical practice guidelines, systematic reviews, and RCTs	Followed the American Academy of Pediatrics classification scheme	Statements were listed as: Strong recommendation, recommendation, option, or no recommendation, based on strength and quantity of supporting evidence	Extensive external peer review of draft guidelines. Guideline development panel gave final approval. Where data were lacking, a combination of clinical experience and expert consensus was used.

Table A5: Characteristics of Included Guideline						
Objectives			Methodology			
Intended users/ Target population	Intervention and Practice Considered	Major Outcomes Considered	Evidence collection, Selection and Synthesis	Evidence Quality and Strength	Recommendations development and Evaluation	Guideline Validation
		effective first-line agent • Improved symptom control and reduction in care variation • Increased awareness and appropriate use of IT and reduction in care variation				

AR = Allergic rhinitis; IT = Immunotherapy; RCT = Randomized clinical trial

APPENDIX 3: Critical Appraisal of Included Publications

Table A6: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[11]

Strengths	Limitations
Nelson, 2015[15]	
• Conducted a comprehensive literature search on multiple databases and the Cochrane Library • Two independent reviewers performed study selection and data extraction • Data were requested from authors and study sponsors in cases in which data in published articles were not reported or were not suitable for inclusion in the meta-analysis • Provided list of included studies as well as study characteristics • Assessed scientific quality of primary studies using The National Institute of Clinical Excellence's Randomized Controlled Trials checklist • Assessed heterogeneity in studies used for pooled estimated and conducted subgroup analysis and a statistical heterogeneity test using the I^2 statistic • Used standardized means to combine findings of studies • Qualitatively assessed publication bias using a funnel plot and quantitatively using Egger's test • Authors disclosed potential conflicts of interest and affiliations	• Did not refer to a protocol, ethics approval, or pre-determined research objectives • Study selection was limited to commercialized products • Consensus procedure for study selection was not reported • Status of publications was not used as an inclusion criterion • Did not provide list of excluded studies
Chelladurai, 2013[16]	
• Created a protocol with input from the technical expert panel and representatives from the Agency for Healthcare Research and Quality • Conducted a comprehensive literature search on multiple databases and the Cochrane Library • Two independent reviewers performed study selection and data extraction. Disagreements were resolved through consensus • Provided list of included studies as well as study characteristics. Provided reasons for excluding studies • Qualitatively assessed publication bias using the Cochrane Collaboration Tool for Assessing Risk of Bias • Used GRADE to assess the quality of evidence • Authors disclosed potential conflicts of interest and affiliations	• Limited study selection to English language articles • Did not use status of publications as an inclusion criterion • Did not provide a list of excluded studies • Did not quantitatively assess the evidence
Lin, 2013[17]	
• Research objectives were pre-determined by a panel of experts following the development of a	• Did not provide a quantitative comparison • Did not assess publication bias

Table A6: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[11]

Strengths	Limitations
study protocol • Conducted a comprehensive literature search on multiple databases • Additional information was requested from manufacturers • Two independent reviewers performed study selection and data extraction. Disagreements were resolved through consensus • Provided list of included studies as well as study characteristics • Provided list of excluded studies as well as reasons for exclusion • Qualitatively assessed publication bias using the Cochrane Collaboration Tool for Assessing Risk of Bias • Used GRADE to assess the quality of evidence • Authors disclosed there were no conflicts of interest	
Meadows, 2013[18]	
• Research objectives were pre-determined by a panel of experts following the development of a study protocol • Conducted a comprehensive literature search on multiple databases • Placed no language restrictions on articles • One reviewer screened titles and abstracts. Two independent reviewers performed study selection and data extraction. Disagreements were resolved through consensus or referral to a third reviewer • Provided list of included studies as well as study characteristics • Provided list of excluded studies as well as reasons for exclusion • Qualitatively assessed publication bias using funnel plots and the Cochrane Collaboration Tool for Assessing Risk of Bias	• Status of publications was not used as an inclusion criterion • Conflict of interest statement was not included although funding was reported as being provided by an independent source

Table A7: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[12]

Strengths	Limitations
Karakoc-Aydiner, 2015[19]	
Reporting • Explicitly stated the objective(s) in the introduction • Explicitly described outcomes • Explicitly described the characteristics of included patients • Explicitly described the interventions of interest	*Internal Validity – Bias* • Patients were not blinded to treatment • Included a placebo control group • Accuracy of main outcome measures was not discussed *Internal Validity – Confounding* • Statistical significance of differences between

Table A7: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[12]

Strengths	Limitations
• Described distribution of potential confounders (age, sex, and duration of symptoms) but did not discuss • Described main findings • Stated estimates of random variability for main outcomes • There were no adverse events • Described characteristics of patients lost to follow-up • Reported probability values for main outcomes *External Validity* • Invited participants were representative of the population • Included participants were representative of the population • SLIT was self-administered at home and SCIT was administered in a clinic *Internal Validity – Bias* • Outcome assessors were blinded to treatment allocation • There were no unplanned analyses • Follow-up was set at 3 years • Reported statistical significance of main outcomes (relative to baseline measurements) • Non-compliant participants were excluded from the analysis *Internal Validity – Confounding* • All patients were recruited from the same population • Follow-up losses were taken into account *Conflict of Interest* • Authors declared that there were no competing conflicts of interest	SCIT and SLIT was not calculated for the majority of outcomes • The randomization process was not described • Potential influence of confounders was not assessed *Power* • Study power was not calculated
Aasberg, 2014[1]	
Reporting • Explicitly stated the objective(s) in the introduction • Explicitly described interventions, outcomes, and characteristics of included patients • Described main findings • There was a comprehensive attempt to report adverse events • Participants who did not complete the SCIT treatment and SLIT-tablet-treated participants with an adherence rate less than 75% were excluded from the final data analysis • Reported probability values for main outcomes *External Validity* • Invited participants were representative of the population	*Reporting* • Primarily focused on impact of SIT on immunologic response • Did not discuss confounders • Did not report estimates of random variability for main outcomes • Did not report probability values for all outcomes *External Validity* • Treatment environment was not described *Internal Validity – Bias* • Accuracy of outcomes of interest could not be determined *Internal Validity – Confounding* • Randomization was not concealed *Power*

Table A7: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[12]

Strengths	Limitations
• Included participants were representative of the population *Internal Validity – Bias* • Outcome assessor was partially blinded to treatment allocation • There were no unplanned analyses • All patients were followed for 15 months • Used appropriate statistical tests to assess main outcomes • There was reliable compliance with the intervention. Non-compliant patients were excluded *Internal Validity – Confounding* • All patients were recruited from the same population • Participants were randomized using an online computer program • Follow-up losses were taken into account *Conflict of Interest* • Authors declared competing financial conflicts of interest	• Study power was not calculated
Yukselen, 2013[20]	
Reporting • Explicitly stated the objective(s) in the introduction • Clearly described interventions, outcomes, and characteristics of included patients • Provided a list of confounders and described distribution: age, gender, exposure to allergen • Described main findings • There was a comprehensive attempt to report adverse events • Described characteristics of patients lost to follow-up • Reported probability values for main outcomes *External Validity* • Invited participants were representative of the population • Included participants were representative of the population • SLIT was self-administered at home, and SCIT was administered in a clinic *Internal Validity – Bias* • Patients and the outcome assessor were blinded to treatment allocation • There were no unplanned analyses • Follow-up time was two years • Used appropriate statistical tests to assess main outcomes • There was reliable compliance with the	*Reporting* • Did not assess random variability for main outcomes *Internal Validity – Bias* • Accuracy of main outcome measures was not discussed *Internal Validity – Confounding* • Ten patients had previously received placebo treatment for a year while the remainder of patients ha been on active treatment. • Randomization was not concealed • Multivariable analysis was not done *Power* • Study was not sufficiently powered *Conflict of Interest* • There was no conflict of interest statement

Table A7: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[12]

Strengths	Limitations
intervention *Internal Validity – Confounding* • Participants were randomized using a computer program • Follow-up losses were taken into account	
Yukselen, 2012[21]	
Reporting • Clearly stated the objective(s) in the introduction • Clearly described interventions, outcomes, and characteristics of included patients • Provided a list of confounders and described distribution: age, gender, exposure to allergen • Described main findings • There was a comprehensive attempt to report adverse events • Described characteristics of patients lost to follow-up • Reported probability values for main outcomes *External Validity* • Invited participants were representative of the population • Included participants were representative of the population • SLIT was self-administered at home, and SCIT was administered in a clinic *Internal Validity – Bias* • Patients and the outcome assessor were blinded to treatment allocation • There were no unplanned analyses • Follow-up time was one year • Used appropriate statistical tests to assess main outcomes • There was reliable compliance with the intervention *Internal Validity – Confounding* • Participants were randomized using a computer program • Follow-up losses were taken into account	*Reporting* • Did not assess estimates of random variability for main outcomes • Accuracy of main outcome measures was not discussed *Internal Validity – Confounding* • Multivariable analysis was not done *Power* • Study was not sufficiently powered *Conflict of Interest* • There was no conflict of interest statement
Marogna, 2011[2]	
Reporting • Clearly stated the objective(s) in the introduction • Clearly described interventions, outcomes, and characteristics of included patients • Provided a list of confounders and described distribution • Described main findings • No patients were lost to follow-up • Reported probability values for main outcomes	*Internal Validity – Bias* • Accuracy of main outcome measures was not discussed *Internal Validity – Confounding* • Randomization was not described • Did not state estimates of random variability for main outcomes • Safety was not assessed *External Validity* • Half of the participants were exposed to

Table A7: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[12]

Strengths	Limitations
Internal Validity – Bias • There were no unplanned analyses • Follow-up time was three years • Used appropriate statistical tests to assess main outcomes • There was reliable compliance with the intervention*Internal Validity – Confounding* • All patients were recruited from the same population • Logistic regression analysis was used to estimate the effect of the considered factors (age, sex, treatment and passive smoke exposure) on the main outcomes. • Follow-up losses were not relevant *Conflict of Interest* • Authors declared no competing financial conflict of interest	secondary smoking • The treatment environment was not described *Internal Validity – Bias* • Patients and the outcome assessor were not blinded to treatment allocation *Internal Validity – Confounding* • The randomization process was not described *Power* • Statistical power was not assessed
Mauro, 2011[22]	
Reporting • Clearly stated the objective(s) in the introduction • Clearly described interventions, outcomes, and characteristics of included patients • Provided a list of confounders and described distribution • Described main findings • Stated estimates of random variability for main outcomes • There was a comprehensive attempt to report adverse events • Described characteristics of patients lost to follow-up • Reported probability values for main outcome *External Validity* • Invited participants were representative of the population • Included participants were representative of the population *Internal Validity – Bias* • There were no unplanned analyses • Follow-up times were fixed • Used appropriate statistical tests to assess main outcomes • There was reliable compliance with the intervention *Internal Validity – Confounding* • All patients were recruited from the same population • Participants were randomized using a computer-generated list	*External Validity* • The representativeness of the facility could not be assessed *Internal Validity – Bias* • Patients and the outcome assessor were not blinded to treatment allocation • Accuracy of main outcome measures was not discussed *Internal Validity – Confounding* • Multivariable analysis to assess the potential influence of confounders was not done *Power* • Statistical power was not calculated

Table A7: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[12]	
Strengths	**Limitations**
• Follow-up losses were listed *Conflict of Interest* • Authors declared no competing financial conflict of interest	

Table A8: Strengths and Limitations of Economic Studies using Drummond[13]	
Strengths	**Limitations**
Verheggen, 2015[23]	
• Explicitly reported model design and inputs • Conducted sensitivity analysis • Discounted costs and benefits at a 3% rate • Explictly defined the outcome of interest (ICER) • Reported resources, unit costs, and disaggregated results • Provided details about the intervention and comparator (for example, components of SLIT tablet) • A 9 year time horizon was specified • Sources of efficacy data were a literature review and a meta-analysis • The payer perspective was taken • Costs were incorporated from the literature, consumer payments, and assumptions on treatment duration	• Limited generalizability to the Canadian setting

ICER = Incremental cost-effectiveness analysis; SLIT = Sublingual immunotherapy

Table A9: Strengths and Limitations of Guidelines using AGREE II[14]	
Strengths	**Limitations**
Seidman, 2015[24]	
Domain 1: Scope and Purpose	
• The overall objectives of the guideline are specifically described. • The health question covered by the guideline is specifically described. • The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described: Adults and children 2 years or older	• The guideline is not intended to be comprehensive
Domain 2: Stakeholder Involvement	
• The guideline development group includes individuals from all relevant professional groups. • The views and preferences of the target population were incorporated with the inclusion of consumer advocacy on the panel • The target users of the guideline are clearly defined.	

Table A9: Strengths and Limitations of Guidelines using AGREE II[14]

Strengths	Limitations
Domain 3: Rigour of Development	
• Systematic methods were used to search for evidence. • The criteria for selecting the evidence are clearly described. • The strengths and limitations of the body of evidence are clearly described. • The methods for formulating the recommendations are clearly described. • The health benefits, side effects, and risks have been considered in formulating the recommendations. • There is an explicit link between the recommendations and the supporting evidence. • The guideline has been externally reviewed by experts prior to its publication. • A procedure for updating the guideline is provided.	
Domain 4: Clarity of Presentation	
• The recommendations are specific and unambiguous • The different options for management of the condition or health issue are clearly presented. • Key recommendations are easily identifiable.	
Domain 5: Applicability	
• The guideline describes facilitators to its application. • The guideline provides advice and/or tools on how the recommendations can be put into practice. • The guideline presents monitoring and/or auditing criteria.	• The potential resource implications of applying the recommendations not discussed.
Domain 6: Editorial Independence	
• The views of the funding body have not influenced the content of the guideline. • Competing interests of guideline development group members have been recorded and addressed	

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A10: Summary of Findings of Included Systematic Reviews and Meta-Analyses

Outcome	Intervention Group	Comparator Group	Pooled Estimates of Effect or Narrative Findings of Primary Studies	Author's Conclusions or Interpretation
Nelson, 2015[15]				
Patients allergic to grass pollen only				
			Standardized mean difference[a]	
Symptom scores	SLIT drops	SCIT	0.189 (95% credible interval, 0.04 to 0.43)	"This analysis provided indirect evidence that commercially available treatments of SCIT and SLIT tablets for grass pollen allergy are similar in their efficacy. Neither SLIT tablets nor SCIT was significantly different from SLIT drops in symptom score reduction; however, point estimates showed smaller reductions for SLIT drops."[15] Page 265
	SLIT tablets		0.0145 (95% credible interval, 0.19 to 0.23)	
Medication scores	SLIT drops		-0.056 (95% credible interval, -0.50 to 0.40)	
	SLIT tablets		0.133 (95% credible interval, -0.31 to 0.57)	
Chelladurai, 2013[16]				
Patients allergic to dust mites only				
			Strength of evidence	
Asthma symptoms	SLIT	SCIT	Low strength evidence favouring SCIT over SLIT	"Low-grade evidence favors SCIT for reduction in allergic asthma symptoms and rhinitis symptom medication scores. Moderate-grade evidence also favors SCIT over SLIT for reduction in symptoms of allergic rhinitis/rhinoconjunctivitis. However, additional trials that directly compare SCIT with SLIT are needed to strengthen this evidence base."[16] Page 369
Increase in frequency of local reactions (%)	6.7%-56%	20%	NR	
Anaphylaxis (#)	0	1	NR	
Deaths (#)	0	0	NR	
Patients allergic to dust mites or birch tree pollen				
Rhinitis symptoms	SLIT	SCIT	Moderate strength evidence favouring SCIT over SLIT	
Medication use	SLIT	SCIT	Low strength evidence of equivalence favouring SCIT	
Combined symptom-	SLIT	SCIT	Low strength evidence	

Table A10: Summary of Findings of Included Systematic Reviews and Meta-Analyses

Outcome	Intervention Group	Comparator Group	Pooled Estimates of Effect or Narrative Findings of Primary Studies	Author's Conclusions or Interpretation
medication score			favouring SCIT over SLIT	
Lin, 2013[17]				
Patients allergic to dust mites only				
			Strength of evidence	
Asthma symptoms score	SLIT	SCIT	Low strength evidence favouring SCIT over SLIT	"The overall strength of evidence is low grade to support SCIT over SLIT for control of asthma symptoms and combined symptom-medication scores, and moderate grade for control of rhinitis and/or conjunctivitis symptoms. However there is insufficient evidence from head to head comparisons to determine the overall superiority of one form of specific immunotherapy over the other."[17] Page 102.
Increase in frequency of systemic reactions (%)	0%	17%	NR	
Increase in frequency of local reactions (%)	6.7%-56%	20%	NR	
Anaphylaxis (#)	0	1	NR	
Deaths (#)	0	0	NR	
Patients allergic to dust mites or birch tree pollen				
			Strength of evidence	
Rhinitis symptoms score	SLIT	SCIT	Moderate strength evidence favouring SCIT over SLIT	
Medication use score	SLIT	SCIT	Low strength evidence of equivalence	
Combined symptom-medication score	SLIT	SCIT	Low strength evidence favouring SCIT over SLIT	
Meadows, 2013[18]				
			Standardized score difference[a]	
Patients allergic to tree or grass pollen				
Symptom score	SLIT	SCIT	0.351; 95% credible interval, 0.127 to 0.586; Favours SCIT over SLIT	"I t is difficult to draw firm conclusions from [the] results as (1) they vary depending on which outcome measure is used and (2) they are associated in some instances with substantial

Table A10: Summary of Findings of Included Systematic Reviews and Meta-Analyses				
Outcome	**Intervention Group**	**Comparator Group**	**Pooled Estimates of Effect or Narrative Findings of Primary Studies**	**Author's Conclusions or Interpretation**
Medication use score			0.273; 95% credible interval, 0.027 to 0.529; Favours SCIT over SLIT	residual heterogeneity."[18] Page 60
Combined symptom-medication score			0.313; 95% credible interval, -195.80 to 194.10; No statistically significant difference	
Quality of life score			0.383; 95% credible interval, -0.042 to 0.804; No statistically significant difference	

NR = Not reported; SCIT = Subcutaneous immunotherapy; SLIT = Sublingual immunotherapy
[a] Based on indirect comparisons

Table A11: Summary of Findings of Included RCTs	
Main Study Findings	**Author's Conclusions**
Karakoc-Aydiner, 2015[19]	
<u>Children with mild to moderate asthma and/or rhinitis, allergic to dust mites</u> <u>At baseline</u> Median age±SD (years) SLIT (n=9): 10.14 ± 1.16 SCIT (n=12): 10.46 ±1.95 <u>Three years after treatment</u> Change in TSS relative to baseline SLIT (n = 9): -1.92 (*P* = 0.04) SCIT (n = 12): -2.3 (*P* = 0.007) Change in TMS relative to baseline SLIT (n = 9): -2.1 (*P* = 0.01) SCIT (n = 12): -2.2 (*P* = 0.01) Change in VAS relative to baseline SLIT (n = 9): -2.30 (*P* = 0.03) SCIT (n = 12): -3.34 (*P* < 0.01) Skin reactivity to *D.pteronyssinus*	• "HDM-sensitized children with asthma and/or rhinitis treated with either SCIT or SLIT showed improved clinical outcomes after 3 years of treatment compared with a pharmacotherapy only group. Further large clinical prospective studies with different extracts are needed to determine the sustained long-term effects after cessation of treatment in asthmatic children."[19] Page 341

Table A11: Summary of Findings of Included RCTs

Main Study Findings	Author's Conclusions
SLIT (n = 9): NR (*P* = 0.02) SCIT (n = 12): NR (*P* = 0.01*)* Skin reactivity to *D.farinae* SLIT (n = 9): NR (*P* = NS) SCIT (n = 12): NR (*P* < 0.01*)* Systemic reactions during build-up, other adverse events (%) SLIT (n = 9): 0, 0 SCIT (n = 12): 17, 0	
Aasbjerg, 2014[1]	
<u>Adults with history of rhinitis and hayfever symptoms, allergic to grass pollen</u> Mean age SLIT tablet: 31.5 (22–46) years SCIT: 34.6 (20–59) years Change in nasal challenge symptom score at 3 months SLIT tablet: -6.2 (95% CI: -28.5 to 15.7); *P* = NS SCIT: -55.1 (95% CI: -77.8 to 32.3); *P* < 0.05 Change in nasal challenge symptom score at 15 months SLIT tablet: -32.6 (95% CI: -55.1 to 10.1); *P* > 0.05 SCIT: -56.8 (95% CI: -81.7 to -31.9); *P* < 0.05	• "The observed difference in symptom score between SLIT tablet and SCIT is in contrast to the reported similarity in clinical effect, suggesting that the nasal challenge needs further optimization/validation to reflect the symptoms experienced after in vivo pollen exposure."[1] Page 426
Yukselen, 2013[20]	
<u>Children with perennial rhinitis and mild asthma, allergic to dust mites</u> At enrollment Mean age ± SD (years) SLIT (n=15): 1.8±2.5 SCIT (n=15): 11.5±3.0 *P*=0.58 Following 2 years of active treatment (relative to baseline) Median reduction in rhinitis symptom score (SLIT versus SCIT): 28% versus 64.5% ; *P* = 0.25 Median reduction in asthma symptom score (SLIT versus SCIT): 27.8% versus 100%; *P* = 0.03 Median reduction in rhinitis medication use score (SLIT versus SCIT): *P* = 0.19 Median reduction in asthma medication use score (SLIT versus SCIT): *P* = 0.02 Statistical significance of decrease in wheal diameter from skin-prick test (*D.pratense,*	• "…our study shows that although both clinical and immunologic improvement with SCIT begins from the first year of immunotherapy, it requires longer treatment with SLIT in HDM-sensitized children with rhinitis and asthma. [] More studies in children to address the long-term efficacy of these two most used modes of immunotherapy are needed in a larger population."[20] Page 240

Table A11: Summary of Findings of Included RCTs	
Main Study Findings	**Author's Conclusions**
D.farinae) SLIT: 0.01, 0.01 SCIT: 0.007, 0.006 Increase in tolerance to nasal provocation (SLIT versus SCIT): *P* = 0.53 Adverse events (systemic reactions, local reactions) (%) Not reported	
Yukselen, 2012[21]	
<u>Children with perennial rhinitis and mild asthma, allergic to dust mites</u> At baseline Mean age ± SD (years) SLIT (n=10): 9.2±3.4 SCIT (n=10): 10.9±3.2 *P*=0.51 Following 1 year of active treatment (relative to baseline) Median reduction in rhinitis symptom score (SLIT versus SCIT): 6.6% versus 31%; *P* = NR Median reduction in asthma symptom score (SLIT versus SCIT): 3.3% versus 100%; *P* = NR Statistical significance (*P)* of decrease in wheal diameter from skin-prick test (*D.pratense, D.farinae*) SLIT: 0.005, 0.001 SCIT: 0.008, 0.006 Statistical significance (*P)* of increase in tolerance to nasal provocation (SLIT versus SCIT): 0.01 versus 0.05; *P* = 0.31 Statistical significance (*P)* of increase in tolerance to HDM-specific bronchial provocation (SLIT versus SCIT): 0.56 versus 0.03; *P* = 0.91 Systemic adverse events None Local adverse events SLIT (itching or mild edema of the mouth and/or throat): 3 patients; 1 patient withdrew during induction phase due to side effects SCIT (injection site): 2 patients	• "We showed that both SCIT and SLIT had more clinical efficacy on the symptoms of both rhinitis and asthma compared to the baseline year…Further studies are needed to more precisely define doses and therapy duration, as well as the subgroups of patients who would be the ones to benefit more from the most appropriate type of immunotherapy"[21] Page 296
Marogna, 2011[2]	
<u>Children with perennial rhinitis and intermittent</u>	• "…this study shows that the exposure to

Table A11: Summary of Findings of Included RCTs

Main Study Findings	Author's Conclusions
<u>asthma, allergic to dust mites</u> Following 3 years of treatment Mean monthly symptom score difference (SLIT versus OA): *F* = 2.11; *P* = 0.152 Decrease in mean medication use without passive smoking (SLIT versus OA): 16.3 versus 3.4 Decrease in mean medication use with passive smoking (SLIT versus OA): 10.7 versus 8.9	passive smoke by children with respiratory allergy due to house dust mites lowers or nullifies the clinical response to standard drug therapy and, reduces the efficacy of sublingual immunotherapy which still exerts an overall positive significant clinical response."[2] Page 67
Mauro, 2011[22]	
<u>Adults with rhinitis and diagnoses with birch-apple syndrome</u> At baseline Mean age (years) SLIT (n=20): 38.7 SCIT (n=20): 36.9 After one year of treatment (n=34) Mean symptom-medication score SLIT (n=15): 3.63±1.08 SCIT (n=19): 4.77±1.41 *P* = NS Response to oral apple challenge (complete tolerance, increased tolerance) SLIT (n=7): 1, 2 SCIT (n=8): 2, 3 Adverse events (systemic reactions, serious) (%) SLIT (n=15): 0, 0 SCIT (n=19): 16, 0	• There is a "need of a much finer diagnostic work-up in selecting patients with birch-apple syndrome who are candidates to respond to birch pollen immunotherapy also concerning apple allergy. In particular, future studies should evaluate in single patients the apple strains responsible for clinical symptoms, and allergens expressed in such strains, in order to accurately investigate the factors underlying the positive or negative response to SIT."[22] Page 421

AUC = Area under the curve; MMS = Mean monthly symptoms; NR = Not reported; NS = Not statistically significant; OA = Oral antihistamine; SD = Standard deviation; SCIT = Subcutaneous immunotherapy; SLIT = Sublingual immunotherapy; SIT = Specific immunotherapy; TASS = Total asthma symptom score; TMS = Total medication score; TRSS = Total rhinitis symptom score; TSS = Total symptom score; VAS = Visual analog scale score

Table A12: Summary of Findings of Included Cost-effectiveness Study

Outcome	Intervention Group	Comparator Group	Discount rate	ICER	Author's Conclusions or Interpretation
Verheggen, 2015[23]					
Cost-effectiveness	SLIT tablets (Oralair®, 5-Grass)	Symptomatic treatment (loratadine and budesonide)	3%	€17,007 per QALY Sensitivity analysis range: €9,634 (societal perspective), €21,918 (shorter pollen season)	"…the 5-grass tablet results in a lower total number of incidental asthma patients compared to symptomatic treatment.[23] Page 5 "…since the cost of the 5-grass tablet is

Table A12: Summary of Findings of Included Cost-effectiveness Study

Outcome	Intervention Group	Comparator Group	Discount rate	ICER	Author's Conclusions or Interpretation
					dependent on a season's duration, incremental outcomes were sensitive to the length of the pollen season as well."[23] Page 8

QALY = Quality adjusted life years

Table A13: Summary of Findings of Included Evidence-Based Guidelines

Recommendation	Grade/Strength of Recommendation or Interpretation
Seidman, 2015[24]	
Clinicians should offer, or refer to a clinician who can offer, immunotherapy (sublingual or subcutaneous) for patients with AR who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls.	Recommendation. This means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (Grade B or C).[a] In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms. Grade B evidence includes RCTs; overwhelmingly consistent evidence from observational studies. Grade C evidence includes observational studies (case control and cohort design)

AR = Allergic rhinitis; RCTs = Randomized controlled trials

[a] Based on the American Academy of Pediatrics classification scheme

APPENDIX 5: Additional References of Potential Interest

Guidelines that Did Not Provide Evidence of a Systematic Review

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