Effective Health Care Program

Breathing Conditions
Subcutaneous and
Sublingual Immunotherapy

Subcutaneous and Sublingual Immunotherapy To Treat Allergic Rhinitis/Rhinoconjunctivitis and Asthma

Research Focus for Clinicians

A systematic review was undertaken to summarize the evidence regarding the efficacy, comparative effectiveness, and safety of subcutaneous and sublingual immunotherapy for adult and pediatric patients. All included studies are randomized controlled trials (RCTs) and were published from January 1967 to May 2012. There are 74 RCTs on the efficacy and safety of subcutaneous immunotherapy (SCIT), 60 RCTs on the efficacy and safety of sublingual immunotherapy (SLIT), and 8 RCTs on head-to-head comparisons between both forms of immunotherapy. This summary is provided to assist clinicians in decisionmaking along with a patient's values and preferences. Reviews of evidence should not be construed to represent clinical recommendations or guidelines. The HTML version of this clinician research summary provides links from findings in the Clinical Bottom Line and other tables to the full report for a more detailed discussion of the studies included in each analysis. The full report and the HTML version of this clinician research summary are available at *www.effectivehealthcare.ahrq.gov/allergy-asthma-immunotherapy.cfm*

Background

The medical management of patients with allergic rhinitis and allergic asthma includes allergen avoidance, pharmacotherapy, and immunotherapy. Daily use of pharmacotherapies for allergic rhinitis symptoms raises issues related to adherence, safety, and cost. Long-term use of inhaled steroids, long-acting bronchodilators, and leukotriene antagonists for asthma control have risks for moderate to severe adverse effects.

Allergen immunotherapy is typically used for patients whose allergic rhinoconjunctivitis and allergic asthma symptoms cannot be controlled by medication and environmental control, patients who cannot tolerate their medications, or patients who do not comply with chronic medication regimens. The U.S. Food and Drug Administration (FDA) has approved the use of allergen extracts for SCIT for treating allergic rhinitis and allergic asthma.

In the United States, a patient with allergies undergoing immunotherapy receives subcutaneous injections—in increasing doses—of an allergen-containing extract comprised of the relevant allergens to which he or she is sensitive in an attempt to suppress or eliminate allergy-related symptoms. There is considerable interest in using similar allergen extracts as SLIT as an alternative to SCIT. In the included studies, SLIT specifically refers to allergen extracts administered sublingually in the form of drops. Studies on sublingual tablets are not included here. Allergen extract drops are placed under the tongue for local absorption to desensitize the allergic individual over a period of months to years and to diminish allergic symptoms. SLIT is not currently FDA approved for use in the United States. However, some physicians are using subcutaneous formulations of allergens off-label for sublingual desensitization in the treatment of allergic respiratory conditions. This is largely based on products that have been researched for several years in the United States and Europe and are approved for use by European regulatory authorities.

Conclusions

- There is sufficient evidence to support the overall effectiveness and safety of both SCIT and SLIT for treating allergic rhinoconjunctivitis and asthma (Tables 1 and 2).
- However, there is not enough evidence to determine if either SCIT or SLIT is superior.
- SCIT and SLIT are usually safe, although local reactions are commonly reported regardless of the mode of delivery (Table 3).
- Serious, life-threatening reactions are rare, although they can occur (see SCIT, Table 3). SLIT studies mainly include patients with allergic rhinitis and/or mild asthma. Safety outcomes for SLIT should not be extrapolated to more severely affected patients.
- Most studies use a single allergen for immunotherapy (Table 4). It may be difficult to extrapolate these results to the use of multiple-allergen regimens, which are commonly used in clinical practice in the United States.
- Due to the wide variety of reported regimens, the target SLIT maintenance dose and the duration of therapy are unclear.

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Clinical Bottom Line

Table 1. Efficacy and Comparative Effectiveness of Subcutaneous and Sublingual Immunotherapy for Adult Patients*

Outcomes	SCIT vs. Placebo or vs. Standard Therapy (RCTs, No. of Patients) SOE	SLIT vs. Placebo or vs. Standard Therapy (RCTs, No. of Patients) SOE	SCIT vs. SLIT (RCTs, No. of Patients) SOE
Improves asthma symptom score	17–84% greater improvement vs. controls (16 RCTs, n = 1,178) ●●●	Significant improvement across all studies vs. controls (13 RCTs, n = 625) ●●●	SCIT may improve asthma symptoms more effectively than SLIT (4 RCTs, n = 171) ●○○
Decreases use of asthma medications	Decreased in 42% of studies vs. controls (12 RCTs, n = 1,062) ●●●	○○○	○○○
Improves combined asthma symptom and medication score	Significant improvement in 83% of studies vs. placebo (6 RCTs, n = 196) ●○○	○○○	○○○
Improves rhinitis/ rhinoconjunctivitis symptoms	Significant improvement in 73% of studies vs. controls (25 RCTs, n = 1,734) ●●●	Significant improvement in 56% of studies vs. controls (36 RCTs, n = 2,658) ●●○	SCIT is superior to SLIT for improving allergic nasal and/or eye symptoms (6 RCTs, n = 412) ●●○
Improves conjunctivitis symptoms	Significant improvement in 43% of studies vs. placebo (14 RCTs, n = 1,104) ●●●	Significant improvement in 46% of studies vs. placebo (13 RCTs, n = 1,074) ●●○	○○○
Decreases use of rhinitis/ rhinoconjunctivitis medications	Significantly decreased in 70% of studies vs. controls (10 RCTs, n = 564) ●●○	○○○	○○○
Improves combined symptoms (nasal, ocular, and bronchial)	Significant improvement in 67% of studies vs. placebo (6 RCTs, n = 591) ●●●	○○○	○○○
Improves combined rhinitis/ rhinoconjunctivitis symptom and medication score	Significant improvement in 83% of studies vs. controls (6 RCTs, n = 400) ●○○	○○○	○○○
Improves asthma plus rhinitis/ rhinoconjunctivitis symptoms	21–68% greater improvement vs. controls (5 RCTs, n = 175) ●●○	Significantly improved in 80% of studies vs. controls (5 RCTs, n = 308) ●●○	○○○
Decreases use of asthma plus rhinoconjunctivitis medications	14–83% greater reduction in asthma-based studies vs. controls (5 RCTs, n = 203); significantly decreased in 91% of rhinitis-based studies vs. controls (11 RCTs, n = 768) ●●●	Significant improvement in 47% of studies vs. controls (38 RCTs, n = 2,724) ●●○	There are no consistent differences between SCIT and SLIT (5 RCTs, n = 219) ●○○
Improves asthma plus rhinitis/ rhinoconjunctivitis symptom and medication score	○○○	Significant improvement in 68% of studies vs. controls (19 RCTs, n = 1,462) ●●○	SCIT is favored in 1 of 2 studies (2 RCTs, n = 65) ●○○
Improves disease-specific quality of life in patients with rhinitis/rhinoconjunctivitis	Significant improvement by the RQLQ or the SF-36® in 67% of studies vs. placebo (6 RCTs, n = 889) ●●●	Significant improvement by the RQLQ in 75% of studies vs. controls (8 RCTs, n = 819) ●●○	○○○

* Reported scales or scoring systems were not uniform across studies. Followup ranged from one pollen season to 6 years. Standard therapy varied across trials and could include environmental control and/or medications such as topical nasal corticosteroid or cromolyn preparations, oral antihistamines, decongestants, beta-agonists, oral steroids, bronchodilators, ocular corticosteroids, and montelukast.

RCT = randomized controlled trial; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SCIT = subcutaneous immunotherapy; SF-36® = Short Form (36) Health Survey; SLIT = sublingual immunotherapy; SOE = strength of evidence

Strength of Evidence Scale

High:	●●●	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate:	●●○	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low:	●○○	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient:	○○○	Evidence is either unavailable or does not permit a conclusion.

Clinical Bottom Line *(Continued)*

Table 2. Efficacy and Comparative Effectiveness of Subcutaneous and Sublingual Immunotherapy for Pediatric Patients*

Outcomes	SCIT vs. Placebo or vs. Standard Therapy (RCTs, No. of Patients) SOE	SLIT vs. Placebo or vs. Standard Therapy (RCTs, No. of Patients) SOE	SCIT vs. SLIT (RCTs, No. of Patients) SOE
Improves asthma symptom score	Significant improvement in 50% of studies vs. controls (6 RCTs, n = 550) ●●○	Significant improvement in all studies vs. controls (9 RCTs, n = 471) ●●●	SCIT is favored in 67% of studies vs. SLIT (3 RCTs, n = 135) ●○○
Decreases use of asthma medications	Significant reduction in 50% of studies (4 RCTs, n = 470) ●○○	○○○	○○○
Improves rhinitis/ rhinoconjunctivitis symptoms	Significant improvement in 67% of studies vs. placebo (3 RCTs, n = 285) ●●○	Significant improvement in 42% of studies vs. controls (12 RCTs, n = 1,065) ●●○	○○○
Improves conjunctivitis symptoms	Significant improvement in 67% of studies vs. placebo (3 RCTs, n = 285) ●○○	Significant improvement in 40% of studies vs. placebo (5 RCTs, n = 513) ●●○	○○○
Improves asthma plus rhinitis/ rhinoconjunctivitis symptoms	○○○	Significant improvement with high-dose and low-dose SLIT vs. placebo (1 RCT, n = 98) ●●○	SCIT may be favored over SLIT for reducing nasal and/or eye symptoms (3 RCTs, n = 135) ●○○
Decreases use of asthma plus rhinoconjunctivitis medications	Decreased in both studies vs. controls (2 RCTs, n = 80) ●○○	Significantly reduced in 42% of studies vs. controls (13 RCTs, n = 1,078) ●●○	SLIT may decrease medication use more than SCIT, but results are inconsistent (3 RCTs, n = 135) ●○○
Improves combined asthma or asthma plus rhinitis/ rhinoconjunctivitis symptom and medication score	Significant improvement in both studies vs. placebo (2 RCTs, n = 85) ●○○	Significant improvement in 50% of studies vs. controls (2 RCTs, n = 329) ●○○	○○○
Improves disease-specific quality of life in patients with rhinitis/rhinoconjunctivitis	Significant improvement measured by RQLQ in both studies vs. controls (2 RCTs, n = 350) ●○○	○○○	○○○

* Reported scales or scoring systems were not uniform across studies. Followup ranged from one pollen season to 6 years. Standard therapy varied across trials and could include environmental control and/or medications such as topical nasal corticosteroid or cromolyn preparations, oral antihistamines, decongestants, beta-agonists, oral steroids, bronchodilators, ocular corticosteroids, and montelukast.

RCT = randomized controlled trial; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy; SOE = strength of evidence

Table 3. Adverse Effects*

Study	Adults	Pediatric Patients
SCIT	■ Local reactions (such as redness, swelling, pruritus, or induration at injection site) were usually mild and occurred in 5 to 58 percent of patients and in 0.6 to 54 percent of injections and were more common than systemic reactions. ■ The most common systemic reactions were respiratory reactions, occurring in up to 46 percent of patients and in up to 3 percent of injections. ■ General symptoms (such as headache, fatigue, and arthritis) occurred in up to 44 percent of patients and were usually mild or unspecified. ■ Gastrointestinal reactions were reported in only one study. ■ Thirteen anaphylactic reactions were reported in four trials (n = 205 immunotherapy patients). No deaths were reported.	■ Local reactions were the most common adverse reactions in the pediatric population receiving SCIT. ■ There were no reports of anaphylaxis or deaths.
SLIT	■ Local reactions (such as irritation, itching, swelling, or pain in the oral cavity) were common and usually mild and occurred in 0.2 to 97 percent of patients receiving SLIT. ■ Systemic reactions occurred more frequently in the SLIT arm and included ocular, rhinitis/nasal, respiratory/asthma, cutaneous, gastrointestinal, and cardiovascular adverse effects. ■ No life-threatening reactions, anaphylaxis, or deaths were reported in the included trials.	■ Local reactions (such as irritation, itching, swelling, or pain in the oral cavity) were common but mild. ■ No life-threatening reactions, anaphylaxis, or deaths were reported in these trials. ■ The strength of evidence for all other adverse effects is insufficient.
SCIT vs. SLIT	■ The recording and reporting of the adverse events were neither uniform nor comparable across studies. ■ Local reactions were common and were all of mild or moderate severity. ■ There was one report of anaphylaxis with SCIT. ■ There were no reported deaths.	■ Local reactions were reported in both patient groups. ■ No systemic reactions were reported in patients receiving SLIT. ■ In the pediatric population taking SCIT, one anaphylaxis event and three respiratory systemic reactions were reported.

*Not all studies reported adverse effects; due to the lack of a consistent reporting system across studies, a meta-analysis of adverse effects was not possible.

SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy

Table 4. Included Studies by Type of Allergen for Subcutaneous Immunotherapy (SCIT), Sublingual Immunotherapy (SLIT), and SCIT Versus SLIT

Allergen	SCIT	SLIT	SCIT vs. SLIT
Dust mite[a]	21	14	6
Grass[b]	11	15	-
Weeds[c]	9	7	-
Cat	5	2	-
Dog	1	-	-
Mold[d]	6	2	-
Tree[e]	6	13	2
Multiple allergens	15	7	-

[a] Dust mites could include *Dermatophagoides pteronyssinus* or *D. farinae* or unspecified dust mites.

[b] Grass could include Bermuda grass, cocksfoot, meadow fescue, orchard grass, rye (*Secale cereale* or unspecified), Timothy grass, unspecified grass, or grass mix.

[c] Weeds could include English plantain, Kochia, mugwort, Parietaria, ragweed (short, Western, or unspecified), Russian thistle, or sagebrush.

[d] Mold could include *Alternaria, Aspergillus*, or *Cladosporium.*

[e] Tree could include American elm, bald cypress, birch, cottonwood, date sugar palm/wild date palm, Japanese cedar, London plane, maple, mountain cedar, olive, red/green ash, white birch, white oak, or tree mix.

Gaps in Knowledge

- Additional studies are needed on the efficacy and safety of multiple-allergen SCIT and SLIT
- The effectiveness of single-allergen versus multiple-allergen SCIT and SLIT for desensitization
- The efficacy and safety of SCIT and SLIT in specific subpopulations (pregnant women, monosensitized vs. polysensitized patients, patients with severe asthma, and urban vs. rural patients)
- Whether or not SCIT and SLIT can prevent or modify the atopic march in pediatric patients at high risk for allergic rhinitis and asthma, as well as the optimal age to initiate therapy
- Determining the target maintenance dose, dosing strategies, and the necessary durations of treatment for SCIT and SLIT
- Additional studies directly comparing SCIT to SLIT in pediatric and adult patients
- Optimizing allergen standardization for subcutaneous and sublingual regimens

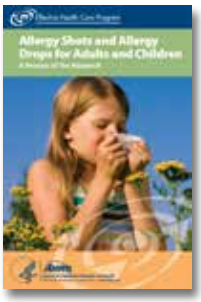
Ordering Information

For electronic copies of *Allergy Shots and Allergy Drops for Adults and Children, A Review of the Research*, this clinician research summary, and the full systematic review, visit *www.effectivehealthcare.ahrq.gov/allergy-asthma-immunotherapy.cfm*. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

What To Discuss With Your Patients

- The benefits and adverse effects of SCIT or SLIT for them or their child
- Any comorbid conditions that they or their child may have that would affect their ability to take SCIT or SLIT
- Other prescription or over-the-counter medications they are taking during SCIT or SLIT treatment
- What adverse effects to look for and when to call their doctor
- How often they should be taking SCIT or SLIT
- How long they can expect to take SCIT or SLIT
- The costs of SCIT and SLIT

Resource for Patients



Allergy Shots and Allergy Drops for Adults and Children, A Review of the Research is a free companion to this clinician research summary. It can help patients talk with their health care professionals about treatment options. It provides information about:

- Allergies in general
- How allergies are treated
- Allergy shots and allergy drops
- Benefits of allergy shots and allergy drops for adults and children
- Possible side effects of allergy shots and allergy drops for adults and children
- Questions to discuss with their doctor

Source

The information in this summary is based on *Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review,* Comparative Effectiveness Review No. 111, prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2007-10061-I for the Agency for Healthcare Research and Quality, March 2013. Available at *www.effectivehealthcare.ahrq.gov/allergy-asthma-immunotherapy.cfm*. This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, TX.

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