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Practice Parameter

# Sublingual immunotherapy
## A focused allergen immunotherapy practice parameter update

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**Disclaimer:** The American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) have jointly accepted responsibility for establishing Sublingual Immunotherapy: A Practice Parameter. This is a complete and comprehensive document at the current time. The medical environment is changing, and not all recommendations will be appropriate or applicable to all patients. Because this document incorporated the efforts of many participants, no single individual, including members serving on the Joint Task Force on Practice Parameters (JTFPP), are authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information or interpretation of this practice parameter by the AAAAI or ACAAI should be directed to the executive offices of the AAAAI and the ACAAI. These parameters are not designed for use by the pharmaceutical industry in drug development or promotion. The JTFPP understands that the cost of diagnostic tests and therapeutic agents is an important concern that may appropriately influence the workup and treatment chosen for a given patient. The JTFPP recognizes that the emphasis of our primary recommendations regarding a medication may vary, for example, depending on third-party payer issues and product patent expiration dates. However, because a given test or agent's cost is so widely variable, and there is a paucity of pharmacoeconomic data, the JTFPP generally does not consider cost when formulating practice parameter recommendations. In extraordinary circumstances, when the cost benefit of an intervention is prohibitive as supported by pharmacoeconomic data, commentary may be provided. These parameters are not designed for use by pharmaceutical companies in drug promotion. The JTFPP is committed to ensuring that the Practice Parameters are based on the best scientific evidence that is free of commercial bias. To this end, the parameter development process includes multiple layers of rigorous review. These layers include the work group convened to draft the parameter, the task force reviewers, and peer review by members of each sponsoring society. Although the JTFPP has the final responsibility for the content of the documents submitted for publication, each reviewer comment will be discussed and reviewers will receive written responses to comments when appropriate. To preserve the greatest transparency regarding potential conflicts of interest, all members of the JTFPP and the practice parameters work groups will complete a standard potential conflict of interest disclosure form, which will be available for external review by the sponsoring organization and any other interested individual. In addition, before confirming the selection of a work group chairperson, the JTFPP will discuss and resolve all relevant potential conflicts of interest associated with this selection. Finally, all members of parameter work groups will be provided a written statement regarding the importance of ensuring that the parameter development process is free of commercial bias.

Previously published Practice Parameters of the Joint Task Force on Practice Parameters for Allergy & Immunology are available at http://www.AAAAI.org, http://www.ACAAI.org, or http://www.allergyparameters.org.

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## Classification of Recommendations and Evidence

*Recommendation Rating Scale*

| Statement | Definition | Implication |
|---|---|---|
| Strong recommendation (StrRec) | A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B).* In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms. | Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present. |
| Moderate (Mod) | A recommendation 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).* 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. | Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences. |
| Weak (Weak) | An option means that either the quality of evidence that exists is suspect (Grade D)* or that well-done studies (Grade A, B, or C)* show little clear advantage to one approach vs another. | Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role. |
| No recommendation (NoRec) | No recommendation means there is both a lack of pertinent evidence (Grade D)* and an unclear balance between benefits and harms. | Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit vs harm; patient preference should have a substantial influencing role. |

*See Strength of Recommendation definitions below.

*Category of Evidence*

Ia Evidence from meta-analysis of randomized controlled trials
Ib Evidence from at least one randomized controlled trial
IIa Evidence from at least one controlled study without randomization
IIb Evidence from at least one other type of quasi-experimental study
III Evidence from nonexperimental descriptive studies, such as comparative studies
IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

*Strength of Recommendation**

A Directly based on category I evidence
B Directly based on category II evidence or extrapolated recommendation from category I evidence
C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
LB Laboratory based
NR Not rated

## Methods and Overview of the Guideline Development Process

The sublingual immunotherapy (SLIT) practice parameters contain systematically developed statements with recommendations intended to optimize patient care and assist physicians and/or other health care practitioners and patients to make decisions regarding this therapy. This guideline is based on 2 published systematic reviews of the literature[1,2] and publications identified by the workgroup's comprehensive literature search and the US Food and Drug Administration (FDA)–approved SLIT tablets' product information.[3,4]

## Systematic Literature Review and Other Sources

Both the systematic reviews evaluated the efficacy and safety of SLIT and subcutaneous (SCIT) allergen immunotherapy.[2] Both

**Table 1**
Non-US Data Regarding Potential Investigational Indications for Liquid SLIT

| Condition | Data |
|---|---|
| Oral allergy syndrome | In a small study comparing SCIT and liquid SLIT for OAS, raw apple tolerance was achieved in 2 of 8 and 1 of 7 patients receiving apple SLIT and SCIT, respectively.[7] A trial of liquid SLIT for birch pollen allergy did not show efficacy for alleviating OAS symptoms, although this study used a relatively low maintenance dose of Bet v 1 (4.5 μg daily).[8] Liquid SLIT for OAS has also been studied with recombinant major apple allergen Mal d 1 and with a cross-reactive Bet v 1.[9] Two sublingual administrations of 50 μg of Mal d 1 were well tolerated and induced transient immune responses with decrease in Bet v 1 and Mal d 1 specific IgE and an increase in IL-10 and IFN-γ production from T cells. These results suggest that recombinant Mal d 1 might be a suitable allergen for potential future SLIT treatment of birch pollen–related apple allergy, but further research is needed. |
| Food allergy | There are multiple case reports of successful liquid SLIT for milk, peanut, hazelnut, kiwi, and peach allergy, and several clinical trials of SLIT involving these allergens.[10–16] Most of these trials are early phase 1 and 2 studies from the United States, and the quality of this evidence and study conduct is heterogeneous and not always subject to use of a control group, use of placebo, or prestudy oral food challenge to establish that participants were truly allergic and not naturally developing tolerance. There is no described routine clinical experience using liquid SLIT for approved treatment for food allergy in the United States or elsewhere, and this practice remains *highly* investigational and unproven in terms of potential dosing, safety, or efficacy. |
| Latex allergy | Clinical trials for liquid SLIT in the treatment of latex allergy in adults and children have had inconsistent results.[17–23] SCIT and liquid SLIT native latex immunotherapy were effective in reducing symptoms on latex exposure in a subset of latex allergic health care workers and children, although SLIT has a better safety profile comparatively. Mutated recombinant latex allergens are also being evaluated as a potential approach for latex immunotherapy.[24,25] Although standardized latex allergen extracts are commercially available in Europe, use of latex SLIT is limited research settings only. |
| Atopic dermatitis | In a single non-US study, 56 children 5–16 years old with atopic dermatitis, who were also monosensitized to dust mites and without food allergy or chronic asthma, were randomized 1:1 to SLIT with dust mites or placebo for 18 months. Significant improvement was noted in both SCORAD and medication use in mild-moderate disease in the active arm.[26] Adults (mean [SD] age, 27.3 [8.2] years) randomized to active dust mite SLIT and pharmacotherapy (n = 58) or to control pharmacotherapy only (n = 49) for 12 months noted significant reduction in daily drug scores and visual analog scores compared with the control group at 12-month follow-up. There is no current recommendation for any form of SLIT to treat atopic dermatitis, however. |
| Venom immunotherapy | Liquid SLIT with venom has been evaluated in 2 proof-of-concept studies that reported preliminary encouraging results with honeybee and vespula SLIT.[27,28] SLIT with venom was found to be safe and well tolerated, but there is both limited evidence of liquid venom SLIT and well-established efficacy of SCIT with venom. Currently, SLIT with venom is not recommended for treatment of venom allergy.[29] |

Abbreviations: IFN-γ, interferon γ; IL, interleukin; OAS, oral allergy syndrome; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

systematic reviews include evidence tables summarizing the included studies' strengths and weakness, which are referred to in this document and form the basis of the summary statement recommendations' strength. Given the recent publication of these reviews and lack of new data pertaining to FDA-approved SLIT formulations, the Agency for Healthcare Research and Quality (AHRQ) literature search was used for this review, and an independent search was not re-run. This decision was discussed and agreed on by the Joint Task Force on Practice Parameters (JTFPP) members in conjunction with the SLIT workgroup. The keywords for these searches have been published elsewhere.

The AHRQ systematic review (Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review) searched the databases of MEDLINE, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials through December 22, 2012.[1,5] English-language randomized clinical trials (RCTs) were included if they compared SLIT with placebo, pharmacotherapy, or other SLIT regimens and reported clinical outcomes. SLIT studies for which a related immunotherapy product was unavailable in the United States were excluded (eg, SLIT tablets). Paired reviewers selected articles and extracted the data. The strength of the evidence for each outcome was graded based on the risk of bias, consistency, magnitude of effect, and the directness of the evidence.

The systematic review by Meadows et al[2] sought to evaluate "the comparative clinical effectiveness and cost-effectiveness of SCIT and SLIT for seasonal allergic rhinitis by (1) undertaking a systematic review of RCTs in order to update the existing Cochrane reviews on the topic; (2) undertaking an indirect comparison of SCIT with SLIT; (3) undertaking a systematic review of existing economic evaluations (EEs); and (4) conducting an independent EE."

The databases of MEDLINE, EMBASE, The Cochrane Library, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, and Science Citation Index (Web of Knowledge) were searched through April of 2011 for RCTs of SCIT and/or SLIT compared with placebo and head-to-head comparisons (SCIT vs SLIT). Seventeen new RCTs of SCIT compared with placebo and 11 of SLIT compared with placebo were identified. The results presented were of the 11 SLIT trials published from last SLIT Cochrane review (2009 onward),[6] but all relevant studies were included in the meta-analyses. Fourteen economic evaluations were included; 5 studies compared SCIT with standard care, 6 studies compared SLIT with standard care, 2 studies compared both SCIT and SLIT with standard care, and 1 study compared different forms of SCIT to SLIT and standard care.

This guideline also includes publications identified through a comprehensive search of the literature conducted by the workgroup members using the MEDLINE database and the following search terms through April 2015: *immunotherapy*, *allergen immunotherapy*, *sublingual immunotherapy*, *subcutaneous immunotherapy*, *allergic rhinitis*, and *asthma*. Information and clinical trials included in the FDA-approved SLIT tablet product information was also considered in this document.

## Description of Methods Used to Formulate the Recommendations

The focus of the SLIT practice parameter is to provide guidance for effective, safe, and appropriate administration of the FDA-approved SLIT formulations. At the time of this writing, the FDA had approved 3 sublingual products, all of which are tablet formulations (short ragweed, Timothy pollen, and 5-grass pollen). This document also considered studies of other formulations, such as European SLIT extract solutions or off-label use of US-licensed SCIT allergen extracts for SLIT, in the context of addressing some clinical questions not addressed in the systematic reviews (eg, SLIT safety and efficacy in older adults or young children).

The workgroup evaluated the literature and formulated evidence-based recommendations. In the instances in which direct evidence was lacking, the recommendations represent broadly accepted consensus opinion as agreed on by a majority vote. The recommendations were graded on the strength and consistency of key findings from these systematic reviews, additional literature

**Table 2**
World Allergy Organization Grading System for SLIT Local Reactions[a]

| Symptom/sign | Grade 1: mild | Grade 2: moderate | Grade 3: severe | Unknown severity |
|---|---|---|---|---|
| Pruritus/swelling of mouth, tongue, or lip; throat irritation, nausea, abdominal pain, vomiting, diarrhea, heartburn, or uvular edema | • Not troublesome AND<br>• No symptomatic treatment required AND<br>• No discontinuation of SLIT because of local side effects | • Troublesome OR<br>• Requires symptomatic treatment AND<br>• No discontinuation of SLIT because of local side effects | • Grade 2 AND<br>• SLIT discontinued because of local side effects | Treatment is discontinued, but there is no subjective, objective, or both description of severity from the patient/physician. |

Each local AE can be early (<30 minutes) or delayed.

• Sec Table I for the MedDRA code that applies to exactly report and describe the AE.

[a]Reprinted with permission from reference [34].

search, and the recommendations in the FDA-approved SLIT product information to formulate evidence-linked recommendations for care.

The practice parameter development process involved several stages. The process began in June 2014 with the selection of workgroup chair, Michael Nelson, MD, PhD, and workgroup members, David Bernstein, MD, Hal Nelson, MD, Richard Lockey, MD, Phil Lieberman, MD, Anna Nowak-Wegrzyn, MD, Anju Peters, MD, and Charlotte Collins, JD, and ensued for 10 months. The workgroup began the process by developing a list of key clinical questions and topics to be addressed. At least 2 workgroup members were assigned to write each section, and the entire document was reviewed and revised through several rounds of electronic review and an in-person meetings. The document was then sent to the JTFPP for additional review and revision. Subsequently, it was sent to the sponsoring organizations (American Academy of Allergy, Asthma, and Immunology and American College of Allergy, Asthma, and Immunology). At this stage the document was reviewed by the sponsoring organizations' invited experts and posted to their website for membership comment. All comments were sent to the JTFPP and workgroup to consider for the final document.

## Benefits and Harms of Implementing the Guideline Recommendations Potential Benefits

The benefits and harms of a particular recommendation in the guideline was considered when the recommendation strength was assigned. The full-text guideline is available in English and can be accessed at http://www.allergyparameters.org.

## Executive Summary of FDA-Approved SLIT Products

The primary focus of the SLIT practice parameter is to provide guidance for effective, safe, and appropriate administration of the FDA-approved SLIT formulations. It is crucial that the practicing allergist separate the data on FDA reviewed products that have led to approval of these products (ie, grass and ragweed tablets) from the data in the literature with other allergens (eg, dust mites) and other formulations (eg, liquid formulations) that have not undergone the rigor of FDA review. Therefore, only the data supporting a statement on FDA-approved products is discussed in this document.

The age range in the product information of 3 FDA-approved sublingual tablets differs in terms of starting age (Grastek, ALK-Abello, Hørsholm, Denmark, 5 years; Ragwitek, ALK-Abello, Hørsholm, Denmark, 18 years; and Oralair, Stallergenes, Anthony, France, 10 years), but all list 65 years of age as the upper limit (Table 1). These age range recommendations reflect the ages included in the clinical trials that were considered during the SLIT tablet approval process. Both the Timothy grass SLIT tablet and the 5-grass tablet have demonstrated clinical benefits beginning in the first year of a 3-year treatment.[30,31] Significant improvement in the combined symptom and medication scores over placebo were observed through 2 additional grass pollen seasons after discontinuation of 3 years of continuous treatment with the Timothy grass SLIT tablet and throughout 3 years of precoseasonal treatment with the 5-grass SLIT tablet. There are insufficient studies that directly compare SCIT and SLIT, precluding a definitive statement regarding efficacy comparison of these forms of immunotherapy.

All FDA-approved studies of SLIT have used a single allergen SLIT use. Because no studies found efficacy of multiple allergens administered as a mixture, there is a need for further investigations to determine efficacy and optimal formulations and regimens for multiallergen SLIT. The prescribing information for the short ragweed pollen allergen extract tablet (Ragwitek) in adults 18 to 65 years old, the Timothy grass pollen allergen extract tablet (Grastek) in children 5 years old up to adults 65.9 years old, and the 5-grass pollen allergen extract tablet (Oralair) for those 18 to 65 years old calls for administration of the maintenance dose tablet without build-up (Table 1).[3,4] The FDA-approved prescribing information for the 5-grass tablet (Oralair) recommends a 3-day up-dosing of 100IR, 200IR, and 300IR for children 10 to 17 years old. This up-dosing recommendation reflects the the 5-grass tablet (Oralair) pediatric clinical trial protocol rather than documented safety issues with a no up-dosing protocol in this age group. SLIT should be initiated at least 12 to 16 weeks before the relevant season for

**Table 3**
Description of Local Adverse Effects Related to SLIT (MedDRA 14.1)[a]

| Local Adverse Effect | MedDRA preferred term | MedDRA code | MedDRA low-level term |
|---|---|---|---|
| Mouth and ear | | | |
| Altered taste perception | Dysgeusia | 10013911 | Taste alteration |
| Itching of lips | Oral pruritus | 10052894 | Itching of mouth |
| Swelling of lips | Swelling of lips | 10024570 | Swelling of lips |
| Itching of oral mucosa | Oral pruritus | 10052894 | Itching of mouth |
| Swelling of oral mucosa | Mucosal edema | 10030111 | Mucosal swelling |
| Itching of ears | Ear pruritus | 10052138 | Ear pruritus |
| Swelling of tongue | Swollen tongue | 10042727 | Swelling of tongue, nonspecific |
| Glossodynia | Glossodynia | 10018388 | Glossodynia |
| Mouth ulcer | Mouth ulceration | 10028034 | Mouth ulcer |
| Tongue ulcer | Tongue ulceration | 10043991 | Tongue ulceration |
| Throat irritation | Throat irritation | 10043521 | Throat irritation |
| Uvular edema | Pharyngeal edema | 10034829 | Pharyngeal edema |
| Upper gastrointestinal tract | | | |
| Nausea | Nausea | 10028813 | Nausea |
| Stomach ache | Abdominal pain, upper | 10000087 | Stomach ache |
| Vomiting | Vomiting | 10047700 | Vomiting |
| Lower gastrointestinal tract | | | |
| Abdominal pain | Abdominal pain | 10000081 | Abdominal pain |
| Diarrhea | Diarrhea | 10012735 | Diarrhea |

Abbreviation: MedDRA, Medical Dictionary for Regulatory Activities.
[a]Adapted from reference [34].

preseasonal and coseasonal therapy to achieve optimal efficacy. Localized symptoms (eg, oromucosal itching and swelling) are common during the first week of SLIT treatment, whereas systemic allergic reactions can occur but are rare. The JTFPP recognizes that there will be many questions regarding the use of SLIT in clinical practice for which there are insufficient evidence-based answers. eTable 1 was developed by the JTFPP, using the Delphi method, to answer some of the most frequently asked questions.

**Summary Statement 1:** Only use FDA-approved SLIT products for the treatment of allergic rhinitis/rhinoconjunctivitis and not for any other related or unrelated condition. (Strength of Recommendation: Strong; Evidence: A/B)

There are no FDA-approved study indications for SLIT for the treatment of oral allergy syndrome, food allergy, latex allergy, atopic dermatitis, or venom allergy. Studies evaluating indications for these conditions are ongoing.

In RCTs, SLIT has been associated with oral pharyngeal adverse effects and systemic allergic reactions. Most SLIT adverse events are local reactions (oral, pharyngeal, or gastrointestinal symptoms).[3,4,32]

Most SLIT adverse reactions occur outside the medical-supervised setting; therefore, these reports are dependent on patient recall and appropriate recognition of symptoms associated with a localized or systemic reaction.[33] Thus, systemic allergic reactions to SLIT may be underreported and mischaracterized given different postadministration procedures compared with SCIT (Tables 2 and 3).

**Summary Statement 2:** The physician should be aware that SLIT may not be suitable in patients with certain medical conditions, particularly those that may reduce the patient's ability to survive a systemic reaction or the resultant treatment of the systemic reaction. (Strength of Recommendation: Strong; Evidence: D)

The FDA-approved SLIT tablet prescribing information lists the following contraindications: severe, unstable, or uncontrolled asthma; any history of a severe systemic reaction to any form of immunotherapy; a history of any severe local reaction to SLIT; a history of eosinophilic esophagitis (EoE); or hypersensitivity to any of the inactive ingredients of the preparation. SLIT may not be suitable in patients with medical conditions that may reduce their ability to survive a serious systemic reaction or increase the risk of adverse reactions after epinephrine administration. Examples of these medical conditions include but are not limited to markedly compromised lung function (either chronic or acute), unstable angina, recent myocardial infarction, significant arrhythmia, or uncontrolled hypertension. SLIT may not be suitable for patients who are taking medications that could potentiate or inhibit the effect of epinephrine should it be required.

Although the SLIT tablets have not been studied in patients with severe, unstable, or uncontrolled asthma, these are known risks for severe and even fatal reactions to SCIT and are relative contraindications for initiating or continuing allergen immunotherapy, including SLIT. There is no published basis for withholding SLIT to patients with a history of a severe systemic reaction to agents other than allergen immunotherapy, but was an exclusion criteria used in the studies of the Timothy grass, 5-grass pollen, and short ragweed SLIT tablets. There are also no published data that indicate that a patient who has had a severe SLIT local reaction to one allergen is at increased risk for a severe local or systemic reaction to another allergen. The inactive ingredients of the FDA-approved SLIT tablets have rarely been associated with anaphylaxis or other significant adverse effects.[35,36]

Any history of EoE, past or currently active, is a stated contraindication to initiation of treatment in the FDA-approved SLIT tablets' product prescribing information.[3,4] Development of EoE while taking SLIT is also a potential risk. It is not well established whether SLIT can exacerbate already present EoE in a patient initiating SLIT, although it is presumed that this is of potential risk to occur. There is, however, a case report of a patient who twice developed retrosternal pain and dysphagia accompanied by eosinophilia on esophageal biopsy while taking Timothy grass SLIT tablets, with both symptoms and EoE clearing once the tablets were no longer taken.[37]

European guidelines recommend and the FDA-approved SLIT tablet product information inserts mandate that, in cases of oral inflammation, such as mouth ulcers, lichen planus, or dental extractions, administration of SLIT be temporarily discontinued until there is "complete healing of the oral cavity."[3,4] However, further data are needed to better substantiate the degree to which this is a risk.

**Summary Statement 3:** Use FDA-approved SLIT products very cautiously in the pregnant or breastfeeding patient because there are insufficient data regarding the safety of initiating or continuing SLIT during either pregnancy or breastfeeding. (Strength of Recommendation: Weak; Evidence: C)

There are few data on the safety or efficacy of allergen immunotherapy (SLIT or SCIT) continued (but not initiated) during pregnancy. Although it is a distinctly different therapy, observational retrospective SCIT studies and case reports provide some reassurance as to its safety, but similar data are not available for SLIT tablets. Therefore, although the current allergen immunotherapy practice parameters state that subcutaneous allergen immunotherapy "can be continued but is usually not initiated in the pregnant patient," at this time there are insufficient data regarding experience with initiating or continuing SLIT during pregnancy to make any comment.[33]

The 5-grass pollen and the Timothy grass SLIT tablets are assigned a category B pregnancy rating (eg, animal reproduction studies have failed to demonstrate a risk to the fetus, but there are no adequate and well-controlled studies in pregnant women). The FDA product information for these products states, "Because systemic and local adverse reactions with immunotherapy may be poorly tolerated during pregnancy, Oralair®/Grastek® should be used during pregnancy only if clearly needed." The ragweed tablet (Ragwitek) is assigned a category C rating (eg, animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks), which is the pregnancy rating status of all of the US-licensed allergen extracts.[38]

It is not known whether any of the FDA-approved SLIT products are secreted in breast milk. Given this paucity of data, no specific recommendations can be made about the safety of SLIT tablets used during breastfeeding.

**Summary Statement 4:** Do not assume dosing equivalence between SLIT tablets and extracts of the same allergen. There are no direct comparisons between the same allergen extract administered as a SLIT tablet vs as an aqueous SLIT extract, and it is unknown whether equal efficacy and/or safety exists when using similar doses of the 2 preparations. Each formulation has to have its own safety profile established. (Strength of Recommendation: Weak; Evidence: C)

There are no FDA-approved SLIT aqueous formulations and thus no basis for comparison. The effective doses with grass[39,40] and ragweed SLIT tablets[41] have been carefully defined in large, multidose studies. Because no studies have revealed efficacy of multiple allergens administered as a mixture, there is a need for further investigations to determine efficacy and optimal formulations and regimens for multiallergen SLIT.

**Summary Statement 5:** Administer the patient's first dose of SLIT in a medical facility under the supervision of a physician or other health care professional with experience in the diagnosis and treatment of anaphylaxis. The patient should be observed in the clinic or medical facility for 30 minutes after the administration of the SLIT dose. (Strength of Recommendation: Strong; Evidence: D)

The FDA-approved SLIT tablets' product information inserts that the first SLIT dose be administered in a medically supervised setting and is the general practice in Europe. In phase 3 studies of SLIT tablets, most systemic allergic reactions (albeit very rare) and administrations of epinephrine have been with the first dose.[3,4,32] With SCIT, all doses are always administered in a medically supervised setting.[33] SLIT is a different product than SCIT. This recommendation for the initial SLIT tablet dose, although based mainly on expert opinion of where one can most safely accomplish introduction of any new allergen in immunotherapy, also reflects that the safety of first dose initiation of SLIT at home has not been studied to determine whether this may be feasible. Future studies are needed to demonstrate this is a safe practice before the present recommendation could be changed.

**Summary Statement 6:** Prescribe epinephrine (either an autoinjector or other form for self-injection) to patients receiving SLIT tablets. Patients should be trained how to use the device, instructed on how to recognize and manage adverse reactions and missed doses, and advised on when to contact their physician or other health care professional. Recommendations for when to withhold the SLIT tablet dose to avoid potential situations when systemic allergic reactions may be more likely should also be provided. (Strength of Recommendation: Strong; Evidence: D)

Following the first dose in the physician's office, SLIT is administered at home without direct medical supervision. Patients should be given specific written instructions about how to manage adverse local or systemic reaction, missed doses, and the clinical situations that indicate they should withhold SLIT. They should also be instructed on when to contact their physician or other health care professional regarding SLIT adverse reactions, treatment gaps, or other events that may affect treatment (eg, new medication or illness). As indicated in the FDA-approved SLIT tablet product information, patients should not receive SLIT treatments if their asthma is not well controlled. Treatment discontinuation should be considered if there are repeated asthma exacerbations or other significant adverse events. Treatment instructions should include information about oral lesions that require a temporary discontinuation of use of SLIT tablets (eg, oral lichen planus, mouth ulcers, thrush, or wounds) after oral surgery or dental extraction.[3,4,31] Although there have been no fatalities attributable to SLIT use recorded to date in the European Union, where it is not the usual practice to prescribe autoinjectable epinephrine for SLIT patients, the FDA has directed that autoinjectable epinephrine be prescribed for all patients receiving SLIT and that they be instructed in its use. Local reactions to SLIT are common, and physicians should describe local reactions and systemic allergic reactions. Patients also should be instructed on the clinical signs and symptoms of a systemic allergic reaction and when to administer epinephrine if such an event occurs.

**Summary Statement 7:** Reduce a patient's SLIT dose if they have missed treatment for more than 7 days. (Strength of Recommendation: Weak; Evidence: D)

There is little evidence to guide how long discontinuation of treatment with SLIT tablets can be tolerated before the risk of a local or systemic allergic reaction increases. No controlled trials have examined the safety of resuming SLIT treatment after missed doses. The FDA-approved patient labeling (Medication Guide) for all 3 SLIT tablet recommends contacting the health care practitioner if more than one dose is missed: "Take (Oralair® and 7 days for Grastek® and Ragwitek®) as prescribed by your doctor until the end of the treatment course. If you forget to … do not take a double dose. Take the next dose at your normal scheduled time the next day. If you miss more than one dose … contact your healthcare provider before restarting."[3,4,32] The 3 products' clinical trial protocols differed in the length of a treatment gap allowed before the patient was required to contact the study investigator: 1 day for the 5-grass tablet (Oralair®) and 7 days for the Timothy grass tablet (Grastek) and the ragweed tablet (Ragwitek). However, the 5-grass tablet (Oralair) and the Timothy grass tablet (Grastek) had similar safety profiles in trials with no up-dosing or discontinuous (precoseasonal) protocols, suggesting that recommendations for treatment gaps should be the same. Data regarding the safety resuming the ragweed tablet (Ragwitek) after treatment interruptions are limited because all the pivotal clinical trials were conducted during a single season. In the clinical trials, treatment interruptions for up to 7 days were allowed.

**Summary Statement 8:** Schedule patients receiving SLIT therapy for regular follow-up care with a specialist trained in the evaluation of patients with allergic conditions to monitor efficacy and safety and as a strategy for optimizing adherence. (Strength of Recommendation: Moderate; Evidence: D)

Patients receiving SLIT therapy will benefit from regularly scheduled care with a health care professional skilled in the assessment and management of patients with allergic conditions, as is the case with SCIT.[33] This is to assess for issues with symptom control and overall efficacy with SLIT tablet use, and to ensure adherence. There are no studies or practitioner experience to date describing follow-up care with FDA-approved SLIT formulations, but this recommendation follows common sense clinical practices that should be followed with prescribing any form of immune-modulating therapy, in particular therapy where the FDA strongly recommends such patients be prescribed autoinjectable epinephrine.

**Summary Statement 9:** Currently, the only FDA-approved products for SLIT in the United States are the 5-grass (Oralair), Timothy grass (Grastek), and ragweek (Ragwitek) tablets, indicated for the treatment of allergic rhinitis. Although alternative regimens and preparations for SLIT have been proposed and may be used off-label in the United States (eg, use of liquid SCIT extract for sublingual delivery or use of specific sublingual drops or other sublingual tablets), these products and formulations do not have FDA approval at present and have not been systematically studied in a rigorous manner in US populations. Use of such products or formulations as prescribed SLIT therapy is currently off-label, at a practitioner's discretion and liability, and is without recommendation for any current particular indication in the US populations. Therefore, off-label use of aqueous SLIT extracts or any other non–FDA-approved SLIT formulation is not endorsed. (Strength of Recommendation: Strong; Evidence: D)

There are 84 randomized, double-blind, placebo-controlled studies in non-US patients evaluating aqueous SLIT drop formulations for the treatment of allergic rhinitis or rhinoconjunctivitis and asthma, of which 60 have been conducted using grass, ragweed, and dust mite extracts.[42] The reported effective dose ranges for aqueous SLIT are very broad, unlike in SCIT.[43] Furthermore, the effective dose may vary for a particular allergen, depending on how it is formulated (eg, tablet vs extract solution).[44,45] Many allergens have not been formally evaluated in an RCT or open aqueous SLIT clinical trial, and effective aqueous SLIT dose ranges cannot be extrapolated from the collective literature. Each particular aqueous SLIT formulation must independently demonstrate a safe and effective dosing regimen for a particular indication. Despite a lack of FDA-approved aqueous SLIT formulations in the United States, an American Academy of Allergy, Asthma, and Immunology survey suggests US aqueous SLIT prescriptions among respondents increased from 5.9%[46] to 11.4% between 2007 and 2011, and 86% of respondents reported prescribing commercially available SCIT extracts for off-label use as SLIT.[47] This notwithstanding, further comprehensive study of aqueous SLIT forms and other non–FDA-approved forms of SLIT is necessary to provide data regarding indications for therapy, effective dose ranges for aqueous SLIT extracts, and the overall safety and efficacy of such preparations before formal guideline recommendations can be made.

## Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.anai.2016.12.009.

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## Supplementary Data

**eTable 1**
Suggested Guidelines for the Practicing Allergist Regarding the Use of FDA-Approved SLIT Products

| Question no. | Question or concern | Expert suggestion and rationale |
|---|---|---|
| 1 | Late administration: missed days 1–7 | Based on the experience obtained with the SLIT trials, the lack of dose escalation, in general, and the experience with SCIT, no dose reduction is recommended. |
| 2 | Late administration: missed days 8–14 | Follow the above guidelines except for those SLIT products that have a dose escalation. For products with a dose escalation, it is recommended to restart from dose 1 and escalate as indicated in the package insert. |
| 3 | Late administration: missed days >14 | It is suggested that the patient return to the physician's office for the next dose to be administered under supervision. |
| 4 | Delay in the administration of epinephrine by the patient | Although local and GI symptoms are very common adverse effects, the patient should be educated to have a low threshold for use of their epinephrine autoinjector and for calling 911 when experiencing a systemic reaction. Consider the use of epinephrine for the rapid onset (<15 minutes) of any of the following: (1) symptoms beyond the local oral and mild GI symptoms, (2) moderate to severe tongue or throat swelling, (3) wheezing or respiratory distress, (4) generalized urticaria and/or angioedema, and (5) any serious, potentially life-threatening symptom.[1,2] |
| 5 | After the administration of epinephrine for SLIT-induced anaphylaxis, it is strongly suggested to discontinue treatment | The patient should discontinue SLIT and schedule an office visit with the prescribing allergist. Once the allergist has confirmed that the patient experienced anaphylaxis, most patients should be advised to permanently discontinue SLIT when administered in a medically nonsupervised setting (eg, at home). The final decision must be made on a case-by-case basis, balancing the potential for benefit with the potential for harm and involving the patient in the decision-making process. |
| 6 | After professional dental cleaning | It is suggested to resume SLIT 24 hours after a dental cleaning procedure.[a] |
| 7 | After brushing and flossing of teeth | No caution is usually advised for brushing teeth. Because flossing and gum hygiene can be associated with gum bleeding, it is recommended that the patient delay the administration of SLIT for a few hours after the cessation of gum bleeding.[a] |
| 8 | After dental extraction and gum surgery | The FDA advises waiting for complete healing. Although adequate healing will usually occur after 10–14 days (eg, when stiches are often removed), it is advised to discuss with the dentist when adequate healing will occur.[a,3] |
| 9 | Aphthous stomatitis, herpes, oral lichen planus | The FDA advises waiting for complete healing. Recovery can vary from days to longer than 1 week. If longer than 2 weeks, return to office for examination and SLIT tablet administration under supervision.[4] |
| 10 | High degree of specific IgE allergen sensitivity | Although there is no firm answer, some studies suggest no increased risk.[4] However, because increased allergen sensitivity is known to be a risk factor for SCIT and anaphylaxis, in general,[2,4,5] caution is advised, especially for former SCIT patients who have experienced anaphylaxis from SCIT. |
| 11 | Administration of SLIT during active allergen season | Although no change in schedule is advised, patients should be advised to contact their allergist if seasonal allergy symptoms are significantly increased.[1,3,6] |
| 12 | Use of SLIT in a patient who has been diagnosed to have asthma | SLIT is currently not approved for patients with severe, unstable, or uncontrolled asthma. Patients with controlled mild to moderate asthma may be given SLIT when the patient and physician have determined that the benefits of treatment outweigh the potential risks.[1,2,5,7] |
| 13 | Symptomatic asthma or an asthma exacerbation | Because of a possible increased risk of anaphylaxis, the patient should discontinue SLIT until they have discussed their increase in asthma symptoms with their physician.[1,2,3,5,7] |
| 14 | Increased symptoms of AR, AC, atopic dermatitis | There are no reported increased risks associated with the administration of SLIT when a worsening of symptoms occurs; however, patients should contact their physicians if they are unable to bring their symptoms under control.[1,2,5] |
| 15 | Overdosing errors with SLIT | SLIT case reports have reported an increased risk.[3,8,9] Patients should withhold SLIT until they have contacted their allergist for advice. |
| 16 | Administration in conjunction with SCIT (using different allergens, eg, perennial allergens) | Although using multiple allergens in SCIT has not been associated with increased risks, combining SCIT and SLIT has not been well studied. |
| 17 | Increased risks of SLIT when using multiple allergen, multiple tablet treatment | The limited studies on SLIT are mixed, with some studies demonstrating no increased risk,[10] but one case study indicating increased risk.[11] Reduced efficacy has also been a concern with the use of multiple SLIT tablets. |
| 18 | Use of concurrent thyroid medication, first-generation antihistamines, tricyclics, á-adrenergic blockers, and/or cardiac glycosides or diuretics | The FDA indicates that it may not be suitable to start SLIT in a patient taking one of these medications, in that, were anaphylaxis to occur, these medications could potentiate or inhibit the effect of epinephrine. On the basis largely of the favorable experience with SCIT, it is recommended that the patient and physician determine, before initiating SLIT, whether the benefits of treatment outweigh the risks. |
| 19 | Must use of monoamine oxidase inhibitors be stopped? | The risk of adverse effects of epinephrine administration is theoretically greater if the patient is taking a monamine oxidase inhibitor. Therefore, the allergist should discuss an alternative medication with the prescribing physician. Consider monoamine oxidase inhibitors a relative contraindication to the use of SLIT. |
| 20 | Must use of $\beta$-blockers be stopped? | A patient taking a $\beta$-blocker may be less responsive to the beneficial effect of epinephrine when this drug is administered for the treatment of anaphylaxis. Therefore, the concomitant use of $\beta$-blockers and allergen immunotherapy should be carefully considered from an individualized risk-benefit standpoint, and the patient's preferences should be incorporated into the medical decision-making process.[1,2,4,5,7] |
| 21 | Must use of angiotensin-converting enzyme inhibitors be stopped? | Although there is a theoretical risk of more severe or unresponsive anaphylaxis when the patient is taking an ACE inhibitor, there is no evidence that ACE inhibitors infer any increased risk for inhalant immunotherapy. Therefore, we see no reason to stop using these medications when SLIT is initiated.[2,5] |
| 22 | Does use of NSAIDS need to be stopped? | It is not advised that use of NSAIDs needs to be stopped for SLIT. |
| 23 | Do antihistamines help with GI symptoms attributable to SLIT? | There is no known benefit of antihistamines for reducing the GI symptoms that develop with SLIT. |
| 24 | Can antihistamines be taken before SLIT administration? Will this help with oral symptoms of SLIT? | Use of antihistamines does not need to be stopped and may reduce local oral symptoms. On the other hand, intermittent use of antihistamines potentially increases the risk of adverse reactions in SCIT.[1,2,5] |
| 25 | Concurrent GI infection and the administration of SLIT | Although there are limited published data[6] on risks associated with GI infections, for moderate to severe GI infections, we recommend that SLIT be discontinued until improvement occurs.[2,5] |

(*continued on next page*)

**eTable 1** (*continued*)

| Question no. | Question or concern | Expert suggestion and rationale |
|---|---|---|
| 26 | Risk with a history of food-induced anaphylaxis | To date there has not been any reported increased risk of administering SLIT to patients who report systemic reactions to foods.[2] Although the product information indicates that there is a contraindication for any systemic allergic reaction (which could include food-induced anaphylaxis), there are no data indicating that these patients should be excluded from treatment using inhalant SLIT tablets. |
| 27 | Risk with a history of oral allergy syndrome | Although studies are limited, the benefit of SLIT seems to outweigh any potential risk when treating patients with the oral allergy syndrome.[12] |
| 28 | After a recent moderate to severe allergic reaction to a food or medication | Hold SLIT and contact the allergist within 72 hours of the reaction for further instruction. |

Abbreviations: AC, allergic conjunctivitis; ACE, angiotensin-converting enzyme; AIT, allergen immunotherapy; AR, allergic rhinitis; FDA, US Food and Drug Administration; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.
[a]This is based solely on expert opinion as there is no published evidence to offer guidance.

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